Inclusion, appraisal and summary of evidence for the National evidence-based guideline for the management of absolute cardiovascular disease risk

An initiative of the National Vascular Disease Prevention Alliance

The NVDPA is a group of four leading and well-known Australian charities: Kidney Health Australia, Diabetes Australia, the National Heart Foundation of Australia and the National Stroke Foundation. It was established in 2000 and aims to reduce cardiovascular disease in Australia. Links to the full guidelines can be found on NVDPA member websites: **www.strokefoundation.com.au, www.kidney.org.au, www.diabetesaustralia.com.au and www.heartfoundation.org.au.**

The NVDPA would like to acknowledge the international Centre for Allied Health Evidence (iCAHE), University of South Australia for their work in developing this report.

Contents

1. Background

The *international* Centre for Allied Health Evidence (iCAHE) was engaged by the National Stroke Foundation (NSF) on behalf of the National Vascular Disease Prevention Alliance (NVDPA) to conduct the systematic search and appraisal for the development of these guidelines. The paradigm to be adopted *a priori* was one of absolute risk. Wherever possible the protocol followed that of the Scottish Intercollegiate Guidelines Network (SIGN) Guideline 97 (Risk estimation and the prevention of cardiovascular disease) to enable efficiencies. The original SIGN protocol was adapted to:

- reflect the absolute risk approach;
- update the searches to June 2010 (SIGN searches were conducted in August 2004- June 2005);
- comply with NHMRC guideline procedures;
- reflect the questions modified/rewritten from the original SIGN questions by the NVDPA Expert Working Group and to incorporate subgroups where appropriate.

A further update search for the Australian CVD Absolute Risk Assessment Guidelines was also conducted in particular to cover absolute risk assessment for the under 45 and over 75 age groups. The search and appraisal process for these questions followed the protocol reported by the guideline developers (NVDPA Technical report 2006).

2. Methods

Literature review

The clinical questions and literature review methodology is outlined in appendix 2: Guidelines development process report, in the full guidelines document. In short, 26 clinical questions were developed to guide the literature search. As noted above the current guideline development process built on two existing guidelines: The Guidelines for the assessment of absolute cardiovascular disease risk (2009) and the SIGN Risk estimation and the prevention of cardiovascular disease (2007). As such search dates updated those used in these two guidelines. Where possible the highest level of evidence was selected (high quality, Level I studies). Where possible studies focussed specifically on the primary prevention of CVD were selected however often there was a mix of primary and secondary prevention. Where possible this is noted. Prespecified subgroups were used for specific questions. These included one or more of the following:

a. Those deemed clinically high risk as outlined in the assessment guidelines (those with SBP >180 or DBP>110mmHg, diabetes >60yrs, diabetes with microalbuminuria, CKD [see levels below], familial hypercholesterolaemia, cholesterol >7.5mmol/L)
b. Those with atrial fibrillation
c. High, medium and low absolute risk of CVD
d. Abnormal BP and normal BP
e. Hypercholesterol and normal cholesterol
f. Diabetes and no diabetes
g. Chronic kidney disease and no chronic kidney disease (break down into GFR <45 ml/min, GFR 45-60 ml/min and GFR >60 ml/min)

The primary outcomes for each question were **cardiovascular events** and **all cause mortality**. The secondary outcomes of interest were surrogate outcomes as specified in the individual questions (e.g. BP control).

The search was undertaken in two phases based on the PICO questions. Initally the literature was searched based on the population and intervention for each of the broad topics. Each study outcome and comparison was then evaluated before the final section of included studies made relevant to each specific question

Evidence Tables and quality checks
Included studies had data abstracted into tables for each question including evidence summary, citation, study type, evidence level (as per NHMRC), patient number and characteristics, intervention, comparison, length of follow-up, outcome measure, effect size and funding source (as appropriate).

Two reviewers independently assessed the methodological quality of each included trial and resolved disagreements by consensus, with reference to a third reviewer if necessary. This appraisal was included in the evidence table. Methodological quality of included systematic reviews (SRs) was assessed using the SIGN *Methodology checklist for systematic reviews and meta-analyses or* the NSF *Methodological Checklist for systematic reviews (modified SIGN checklist with Guidelines-International-Network template)*; included randomised controlled trials (RCTs) were assessed using the NSF *Methodological Checklist for randomised controlled trials (modified SIGN checklist with Guidelines-International-Network template)*; included cohort studies were assessed using the SIGN *Methodology checklist for cohort studies*.

For Questions 1-5 the Monash group had applied critical appraisal questions related to diagnostic studies – this practice was continued for the update for consistency, though it should be noted the studies retrieved were methodologically more related to prognostic or screening designs.

Formulation of recommendations – FORM framework

To assist in the formulation of recommendations, where a body of evidence existed for each question, the NMHRC *FORM* process was applied. This resulted in a preliminary Evidence Statement used by the expert working group in their final recommendations and is supported by a 'strength of recommendation' grade (based on the NHMRC Body of Evidence matrix).

The application of a grade to a recommendation is based on an assessment of all the included studies for that recommendation (the 'body of evidence').

Table 1 Body of evidence assessment matrix

Component	A	B	C	D
	Excellent	**Good**	**Satisfactory**	**Poor**
Volume of evidence	Several level I or II studies with low risk of bias	One or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias	Level III studies with low risk of bias, or level I or II studies with moderate risk of bias	Level IV studies, or level I to III studies with high risk of bias
Consistency	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted

Generalisability	Population/s studied in body of evidence are the same as the target population for these guidelines	Population/s studied in the body of evidence are similar to the target population for these guidelines	Population/s studied in body of evidence are different to the target population for these guidelines, but it is clinically sensible to apply this evidence to the target	Population/s studied in body of evidence are different to the target population and it is hard to judge whether it is sensible to generalise to the target population
Applicability	Directly applicable to the Australian healthcare context	Applicable to the Australian healthcare context, with few caveats	Probably applicable to the Australian healthcare context, with some caveats	Not applicable to the Australian healthcare context

Source: NHMRC additional levels of evidence and grades for recommendations for developers of guidelines PILOT PROGRAM 2005 – 2007.

Table 2 Overall grade of evidence based recommendation

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Source: BMC Med Res Methodol. 2011 Feb 28;11:23.

Additional guidance

CBR	Consensus-based recommendations (CBR) developed by the guidelines expert working group when a systematic review of the evidence found either an absence of direct evidence which answered the clinical question or poor quality evidence, which was deemed not to be strong enough to formulate an evidence based recommendation.
PP	Practice points (PP) developed by the guidelines expert working group where a systematic review had not been conducted but there was a need to provide practical guidance to support the implementation of the evidence based and/or consensus based recommendations.

Important consideration

The current guidelines take an absolute risk approach to the management of CVD risk which has posed some challenges in formulation of the recommendations. This is because although there is robust and compelling evidence in the published literature which clearly shows that pharmacotherapy reduces the levels of individual risk factors (blood pressure and lipids) with consequent reduction in CVD mortality or CVD events, this evidence is based on a single risk factor/relative risk approach. Therefore the expert panel carefully considered the literature before making and grading the recommendations in an absolute risk paradigm. When examining the evidence, special consideration was given to any heterogeneity found between subgroups and the generalisability of the findings. In general, the final grading of these recommendations was downgraded to account for the uncertainty of applying evidence from a relative risk approach to an absolute risk paradigm.

3. Absolute risk assessment (Q1-5)

Search results

The following table summarises the results of the search.

Sources	Dates	Total hits	Retrieval list	Final inclusions
Questions 1-5: Absolute risk assessment				
Databases: Medline; Embase; Cinahl; PsychINFO; Pubmed; Cochrane Library, including CENTRAL Cochrane Controlled Trial Register (CCTR) **Other sources:** see protocol for details of guideline and internet sites; pearling; expert working group.	**2006-2010**	**287**	**31 +3 + 5**	**15** Aspelund 2007 Bineau 2009 Chanman 2009 Chow 2009 D'Agostino 2008 De Bacquer 2009 Dhaliwal 2009 Grover 2006 Hippisley –Cox 2008 Loucks 2009 Marques-Vidal 2008 May 2006 Pencina 2009 Ruppert 2007 Van der Heijden 2009
Search terms: as per Monash then adapted	CVD or cardiovascular disease OR coronary disease OR heart attack OR stroke Absolute risk assessment OR Global risk assessment OR Multivariate risk assessment OR Framingham OR PROCAM			
Outcomes:	Measures of predictive accuracy; odds ratios, relative risk and risk of observed CVD events (including CVD mortality, MI, CHD, stroke, and peripheral vascular disease).			

NOTE: The current systematic review forms the basis to make recommendations for adults under and over the age ranges recommended in the Assessment guidelines. Although the search strategy for development of the new assessment recommendations in these guidelines was essentially the same as that used for the Guidelines for the Assessment of Absolute Risk, the evidence for the 45 to 74 (35 to 74 for A&TSI) age range was not reviewed and the Guidelines for the Assessment of Absolute Risk were not updated.

Literature included

Included studies: Assessment of predictive ability of an absolute CVD risk assessment method					
Study citation	**Study design**	**Participants**	**Level of evidence**	**Intervention / outcomes**	**Results**
Aspelund et al 2007.	Prospective study	Total 15 832, aged 36-64 years, mean age=51 y.o; 7555 men; 8277 women	II	Intervention: Compares SCORE risk charts with Iceland data Outcomes: End-points: fatal or non-fatal CHD and noncoronary artherosclerotic CVD Participant defined as having CHD event if MI, CABG or PCI had occurred.	**Fatal CHD events** N=1,549, **Fatal non-CHD CVD events** N=687 **CHD morbidity risk in Iceland** Total 3309 CHD events recorded Cumulative rate of 18.4% for men and 3.7% for women **Comparison of baseline risk between Iceland and SCORE for fatal events** Men=baseline risk is closer to low-risk SCORE function, though diverges towards higher risk SCORE function with increased age Women = Baseline risk almost identical to low-risk SCORE function **Cumulative CVD death rate before 65 years in Iceland** Men = 6.41% (intermediate compared to European cohort) Women = 1.66% (low compared to European cohort) **CHD death as percentage of all CVD deaths** Men=88%, Women=72% - both men and women, highest deaths compared to SCORE cohort **Hazard ratio estimates for CHD events in Iceland** Smoker (current) hazard ratio=1.72 [95% CI 1.60-1.84] Cholesterol hazard ratio=1.32 [95% CI 1.28-1.36] Systolic blood pressure hazard ratio = 1.12 [95% CI 1.10-1.14] **Fatal CVD risk and CHD morbidity risk** Men = 5% fatal CVD risk corresponds to 13% CHD risk Women = 5% fatal CVD risk corresponds to 8% CHD risk Spearman's rank correlation between CHD score and fatal CVD score = 0.96. **Comparison between Iceland population and SCORE project** Comparison of relative risk estimates show remarkable similarity between estimates from Iceland and those from other European countries.

					aROC (95% CI), sensitivity-specificity Iceland risk chart: 0.80 (0.78-0.82) 64-81 sens-spec at 4% risk threshold for CVD SCORE low risk chart: 0.80(0.77-0.82) 54-86 sens-spec at 4% risk threshold for CVD These data from Iceland externally validate the SCORE project risk predictions. The low-risk version of the SCORE chart can be applied to risk evaluation in Iceland. However, as the data are available, the Iceland version should be used in Iceland to give a better prediction of absolute risk, especially in men.
Bineau et al 2009.	Prospective, population based cohort study	Total N=6913 cohort of French people aged 65 to 85 years; Participants did not have history of stroke	II	Intervention: FRE stroke risk function compared with current cohort 3C Outcomes :Incident stroke	RR for 3C 1. Age: men RR=2.29 [95% CI 1.29-4.07], women RR=3.51 [95% CI 1.90-6.50]; SBP: men RR=1.14 [95% CI 1.10-1.29], women RR=1.22 [95% CI 1.08-1.36]; Atrial fibrillation: men RR=2.60 [95% CI 1.17-5.78], women: RR=2.91 [95% CI 1.03-8.21] was independently associated with stroke risk. 2. Diabetes, smoking & history of cardiovascular disease were not significantly associated with stroke risk. 3. 10 year age increase associated with higher increase in stroke risk among 3C participants than Framingham participants. (Men: RR3C=2.29 versus RRF=1.63, P=0.27; Women: RR3C=3.51 versus RRF=2.01, P=0.09) 4. For most risk factors, RR did not differ significantly between 2 cohorts except for age in women. Calibration analysis Original Framingham stroke risk function overestimated the 6-year expected stroke rate in 3C by a factor of 3.70 [95% CI, 2.84-4.80] for men and factor of 4.35 [95% CI 3.34-5.67] for women. Recalibrated Framingham risk function did not overestimate expected stroke rates among 3C men (1.17 [95% CI 0.90-1.52] and women (0.85 [95% CI 0.65-1.11]. The 3C stroke risk function did not overestimate stroke rates observed among 3C men (1.13 [95% CI, 0.87-1.47] and women (0.97 [95% CI 0.75-1.26] The recalibrated Framingham risk function gave reliable and accurate prediction, which was not further improved by “local” 3C stroke risk prediction.

Chanman et al 2009	Systematic review (13 studies) but no meta-analysis possible due to heterogenous studies and inconsistent study quality	Various diabetic cohorts	I	Intervention: Predictive performance of 17 different risk assessment tools Outcomes: Fatal or non fatal CVD, CHD stroke	The predictive ability of CVD risk scores, which were developed mainly for White populations, varies considerably between different populations. There is little evidence to suggest that using risk scores developed in individuals with diabetes will help to estimate CVD risk among diabetic patients more accurately than use of those developed in the general population. The inconsistency in methods used to evaluate CVD risk scores makes it difficult to compare or summarise the predictive ability of different risk scores. Overall, CVD risk scores rank individuals reasonably accurately and are therefore useful in the management of diabetes with regard to targeting therapy to patients at highest risk.
Chow et al 2009	n/a	Random sample of 4535 adults from over 20 Indian villages as collected under the APRHI study in 2005	II	Intervention: Framingham (model 1) compared to • Model 2. Used a recalibration of the FRE with local data from rural Indian population. Specific data on risk factor levels and CHD rates were taken from Andhra Pradesh Rural Health Initiative (APRHI) • Model 3. Also used a recalibration of the FRE using local risk factor level data from the specified rural Indian population but used CHD published national India data. Outcomes: Fatal and non-fatal CHD incidence; 10 year CHD-free survival rates	Baseline mean 10-year probability of CHD: Model 1. Men= 10.4% (9.6-11.1%); Women = 5.3% (4.9-5.7%) Model 2. Men = 10.7% (9.9-11.5%); Women = 4.2% (3.9-4.5%) Model 3. Men = 18.9% (17.7 to 20.1%); Women = 8.2 (7.6-8.8%) The proportions of the population at estimated high (>20%), intermediate (10-20%) and low (<10%) 10-year CHD risk derived using the three models showed a similar pattern. The national recalibration model (model 3) produced risk estimates that were substantially higher. Recalibration of the Framingham risk tool is a practical approach to estimation of cardiovascular risk in countries such as India but the reliability and applicability of the data used for recalibration is of key importance. In India, equations re-calibrated to national summary data are unlikely to be relevant to all regions of India.
D'Agostino et al	Prospective cohort study	Data from participants in the original Framingham	II	Intervention: Used a Cox proportional-hazards	Over 12 years of follow-up, 1174 participants (456 women) developed a first CVD event. All traditional risk factors evaluated predicted CVD

2008	(ongoing)	Heart Study and the Framingham Offspring Study. Participants aged between 30 to 74; Total n=8491, women = 4522		regression to evaluate the risk of developing a first CVD event. Sex-specific multivariable risk functions ("general CVD" algorithms) were derived that incorporated age, total and high-density lipoprotein cholesterol, systolic blood pressure, treatment for hypertension, smoking, and diabetes status. Outcomes: Coronary heart disease, stroke, peripheral artery disease, or heart failure	risk (multivariable-adjusted P_0.0001). The general CVD algorithm demonstrated good discrimination (C statistic, 0.763 [men] and 0.793 [women]) and calibration. Simple adjustments to the general CVD risk algorithms allowed estimation of the risks of each CVD component. A sex-specific multivariable risk factor algorithm can be conveniently used to assess general CVD risk and risk of individual CVD events (coronary, cerebrovascular, and peripheral arterial disease and heart failure). The estimated absolute CVD event rates can be used to quantify risk and to guide preventive care.
De Bacquer 2009	Secondary analysis of prospective data	Total N=6212 (men = 3179, and women = 3033) free of CHD	II	Intervention: SCORE risk assessment tool Outcomes: Agreement between numbers of predicted and observed CVD deaths across the entire spread of risk	During the period of 10 years, 274 CVD deaths were observed while the recalibrated risk chart predicted 263 events. The SCORE Belgium risk chart showed very good accuracy over the complete range of predicted risk (Hosmer–Lemeshow: P = 0.14). ROC analysis revealed excellent discriminatory power in labelling future cases of fatal cardiovascular disease with a c-statistic of 0.86. The 5% threshold for the probability of 10-year cardiovascular death yielded an optimal balance of sensitivity and specificity. The SCORE Belgium risk chart proves to be well suited as an accurate and precise estimation tool for the assessment of cardiovascular risk in Belgium.
Dhaliwal et al 2009	Prospective cohort study	Representative Australian adults: Men = 4175, women = 4487; data collected in National Heart Foundation Risk Factor Prevalence Survey 1989.	II	Intervention: Development of a parsimonious model to predict coronary heart disease (CHD) and cardiovascular disease (CVD) deaths using individual components of the Framingham risk score plus measures of central	Smoking status, high density lipoprotein cholesterol (HDL-C) and the total cholesterol (TC) to HDL-C ratio were significant univariate predictors of CHD deaths. These together with systolic blood pressure were significant predictors of CVD deaths. The obesity measures of WC and WHR were significant univariate predictors but BMI was not. In multivariable analyses, only smoking status and waist to hip ratio were identified as key independent risk factors for CHD and CVD deaths, although TC to HDL-C ratio contributed minimally to CHD deaths. Receiver operator characteristic (ROC) curves for the Framingham risk score in comparison to the WHR plus smoking model were virtually

				obesity. Outcomes: Coronary heart disease (CHD) and cardiovascular disease (CVD) deaths in 15 year follow up	identical, with no added effect of the lipid ratio. The preferred model for predicting CHD and CVD deaths uses central obesity plus smoking with no added influence of measured lipids or blood pressure. A public health focus on identifying and modifying central obesity is at least as important as the measurement and treatment of lipids and hypertension.
Grover et al 2006	Prospective , comparative	1173 Canadian participants, aged between 30 and 67 years old used in the assessment of FRE and CLEM models.	II	Intervention: FRE and CLEM models Outcome: CHD death	The Framingham and CLEM models demonstrated very similar results despite being developed on two independent cohorts. The area under the receiver operating characteristic curves for the Framingham and CLEM models were 0.80 (95% CI 0.78 to 0.83) and 0.81 (95% CI 0.78 to 0.83), respectively, indicating reasonably good discriminating ability for both models. Model calibration based on the observed 10-year incidence rate of coronary deaths versus the predicted rate was also reasonably accurate.
Hippisley-Cox et al 2008	Prospective open cohort study	1.07 million patients, aged between 35-74 years registered at THIN practices between 1995 and 2006; men=54 709 0.61 million patients from QRESEARCH validation cohort.	II	Intervention: QRISK evaluation tool Outcomes: CVD	Characteristics of both cohorts were similar, except that THIN patients were from slightly more affluent areas and had lower recording of family history of CHD. QRISK performed better than Framingham for every discrimination and calibration statistic in both cohorts. Framingham overpredicted risk by 23% in the THIN cohort, while QRISK underpredicted risk by 12%. QRISK is better calibrated to the UK population than Framingham and has better discrimination. The results suggest that QRISK is likely to provide more appropriate risk estimates than Framingham to help identify patients at high risk of CVD in the UK.
Loucks et al 2009	Observational cohort study	1835 participants. Mean age 35.0 years at baseline, 52.4% were women.	II	Intervention: Association between cumulative life-course SEP and CHD Outcomes: Myocardial infarction, coronary insufficiency, and coronary death	Cox proportional hazards analyses indicated that cumulative SEP was associated with incident CHD after adjustment for age and sex (hazard ratio ¼ 1.82, 95% confidence interval: 1.17, 2.85 for low vs. high cumulative SEP score). Adjustment for CHD risk factors reduced that magnitude of association (hazard ratio ¼ 1.29, 95% confidence interval: 0.78, 2.13). These findings underscore the potential importance of CHD prevention and treatment efforts for those whose backgrounds include low SEP throughout life.
Marques-Vida 2008	Cross-sectional, population-based study	35% of Lausanne inhabitants (total inhabitants = 56694) aged 35-75years randomly selected. 5773 participants	II	Intervention: SCORE risk assessment tool Outcomes: CVD death	According to the original and calibrated functions, 16.3 and 15.8% of men and 8.2 and 8.9% of women, respectively, had a 10-year CVD risk ≥5%. Concordance correlation coefficient between the two functions was 0.951 for men and 0.948 for women, both P<0.001. Both risk

		(3074 women and 2699 men)			functions adequately predicted the 10-year cumulative number of CVD deaths: in men, 71 (original) and 74 (calibrated) deaths for 73 deaths when using the CVD mortality rates; in women, 44 (original), 45 (calibrated) and 45 (CVD mortality rates), respectively. Compared to the original function, the calibrated function classified more women and fewer men at high-risk. Moreover, the calibrated function gave better risk estimates among participants aged over 65 years. The original SCORE function adequately predicts CVD death in Switzerland, particularly for individuals aged less than 65 years. The calibrated function provides more reliable estimates for older individuals
May et al 2006	Prospective cohort study	3582 women aged 60 to 79 years who were free of coronary heart disease (CHD) at entry into the British Women's Heart and Health Study	II	Intervention: Framingham and General practice (GP) model: includes standard risk factors of age, systolic blood pressure and smoking status but not cholesterol ratio, diabetes, and left ventricular hypertrophy, because these require laboratory tests/ECG. Included alternative risk factors- BMI/waist measurement and self rate health) Outcomes: CHD and CVD	Framingham CHD: predicted risk 5.7%; Observed risk 5.5% - therefore over-prediction of 3%. Under predicted in the low-risk fifths Over predicted in the highest-risk fifths. Discrimination – 0.59 (classified by fifths of risk) 0.63 (classified by ranked risk) CVD: predicted risk 10.5%; observed risk 6.8%- therefore over-prediction of 54%. Over-prediction was greatest in the two highest-risk fifths. Discrimination – 0.62 (classified by fifths of risk) 0.64 (classified by ranked risk) Addition of C-reactive protein or fibrinogen did not improve the performance of the Framingham equation. Over predicted risk, particularly for CVD, in higher risk fifths. Sensitivity and specificity – not well calibrated to this population 30% CVD risk threshold – 38%/79% 15% CVD risk threshold - 85%/30% GP model BMI was not an independent predictor of CHD or CVD. Self-rated health was a particularly strong predictor of events with a hazard ratio for "poor" compared to "excellent" of 9.6 (95% CI 4.1 to 22.9) Discrimination appears to be marginally better with GP model , but CIs for comparison against Framingham overlap. GP model superior and more feasible but needs testing on other

					populations (applicability)
NIPPON DATA80 Research Group 2006	Follow-up study	Aged 30 years and older, 9353 participants (4098 men, mean age 50.3 yrs; 5255 women, mean age 50.8 year)	II	Intervention: Construction of risk assessment charts Outcomes: death from coronary heart disease (CHD), stroke, and all cardiovascular disease (CVD)	The original charts based on the findings from NIPPON DATA80 are suitable for assessing CHD, stroke, and all CVD death risk in the general Japanese population.
Pencina et al 2009	Prospective	Subjects from this cohort, between 20 and 60 years old, free of cancer and CVD at baseline, had a complete risk factor profile	II	Intervention: Assessment of a 30 year risk prediction function Outcomes: Coronary death, myocardial infarction, stroke	The 30-year hard CVD event rates adjusted for the competing risk of death were 7.6% for women and 18.3% for men. Standard risk factors (male sex, systolic blood pressure, antihypertensive treatment, total and high-density lipoprotein cholesterol, smoking, and diabetes mellitus), measured at baseline, were significantly related to the incidence of hard CVD and remained significant when updated regularly on follow-up. Body mass index was associated positively with 30-year risk of hard CVD only in models that did not update risk factors. Model performance was excellent as indicated by cross-validated discrimination C =0.803 and calibration X^2 =4.25 (P 0.894). In contrast, 30-year risk predictions based on different applications of 10-year functions proved inadequate. Standard risk factors remain strong predictors of hard CVD over extended follow-up. Thirty-year risk prediction functions offer additional risk burden information that complements that of 10-year functions
Ruppert et al 2007	Prospective cohort study	658 coronary heart disease (CHD) free subjects, with childhood (<17 years old) onset T1D, epidemiologically representation of T1D cases in Allegheny County, Pennsylvania. Final dataset consisted of 552 subjects, 49% male and 98% were Caucasian, mean age at entry into the study was 27 yo and duration of diabetes	II	Intervention: Assessment of FRE Outcomes: (CHD) (MI, CHD death, or Q-waves)	Expected and observed events were compared and demonstrated poor prediction. Risk factors previously found to be associated with CHD in T1D other than those in the Framingham risk function (age, smoking, cholesterol/HDLc, systolic blood pressure) were compared within the highest risk deciles. In men, elevated fibrinogen (p=0.007), white blood cell count (WBC) (p=0.037), albumin excretion rate (AER) (p=0.0001), and lower HDLc (p=0.048) were predictive. In females, higher Beck Depression Inventory (p=0.008), HbA1 (p=0.008), AER (p=0.01), LDLc (p=0.007), fibrinogen (p=0.006), WBC (p=0.005), non-HDLc (p=0.0005), WHR (p=0.003), and estimated glucose disposal rate (p=0.002) were associated. Risk factors not considered by the Framingham risk equation may account for the lack of fit and should be

		prior to study entry was 18 years.			examined further.
Van der Heijden et al 2009	Prospective, population based Study	Dutch, Caucasian men and women, 50-75 years of age, with normal glucose tolerance (NGT), intermediate hyperglycemia and type 2 diabetes. 1125 individuals with NGT, 232 individuals with intermediate hyperglycemia, and 125 individuals with diabetes, individuals were assigned these levels according to WHO criteria of 2006 after oral glucose tolerance test.	II	Intervention: To test the validity of the Framingham, Systematic Coronary Risk Evaluation (SCORE), and UK Prospective Diabetes Study (UKPDS) risk function in the prediction of risk of coronary heart disease (CHD) Outcomes: CHD events	During 10 years of follow-up, a total of 197 CHD events, of which 43 were fatal, were observed in this population, with the highest percentage of first CHD events in the diabetic group. The Framingham and UKPDS prediction models overestimated the risk of first CHD event in all glucose tolerance groups. Overall, the prediction models had a low to moderate discriminatory capacity. The SCORE risk function was the best predictor of fatal CHD events in the group with NGT (area under the receiver operating characteristic curve 0.79 [95% CI 0.70–0.87]), whereas the UKPDS performed better in the intermediate hyperglycaemia group (0.84 [0.74–0.94]) in the estimation of fatal CHD risk. After exclusion of known diabetic patients, all prediction models had a higher discriminatory ability in the group with diabetes. The use of the Framingham function for prediction of the first CHD event is likely to overestimate an individual's absolute CHD risk. In CHD prevention, application of the SCORE and UKPDS functions might be useful in the absence of a more valid tool.

Evidence details

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method					
Characteristics of study:					
Study citation	Aspelund, T., Thorgerisson, G., Sigurdsson, G., & Gudnason, V. Estimation of 10-year risk of fatal cardiovascular disease and coronary heart disease in Iceland with results comparable with those of the Systematic Coronary Risk Evaluation project. European Journal of Cardiovascular Prevention & Rehabilitation 2007; 14(6):761-8				
Study		**Study design**	Prospective study	**N (total)**	15 832
Setting	Reykjavik study - large scale epidemiological study of cardiovascular and other chronic disease conducted in Iceland in stages between 1967 and 1991. All inhabitants in greater Reykjavik area born between 1907 and 1935 were invited to participate (=19000 people participated, 71% participation rate). For this study				
Participants	Total 15 832, aged 36-64 years, mean age=51 y.o; 7555 men; 8277 women				
Intervention	Compares SCORE risk charts with Iceland data				
Comparison	Total fatal CVD risk and CHD morbidity				

Outcomes	End-points: fatal or non-fatal CHD and noncoronary artherosclerotic CVD Participant defined as having CHD event if MI, CABG or PCI had occurred.		
Quality of study			
Quality criteria		**Met?**	**Comments**
Specified inclusion/exclusion criteria		yes	Excluded based on coronary event before introduction to the study, elevated cholesterol levels, high systolic blood pressure and age of 65 years or more.
Explicit description of participants		Yes	
Appropriate spectrum of consecutively selected participants		Yes	All inhabitants
Prospective selection of participants		Yes	
Test is compared with an appropriate reference (gold) standard		Yes	
Test is compared with the reference standard in all participants		yes	71% participation rate
Blinded assessment of test and reference standard results		Yes	assumed
Test and reference standard undertaken prior to any interventions		unclear	Not stated
Level of evidence	II	**Risk of bias**	Very low
Results of study (event rates, sensitivity, specificity, area under ROC curve)			
Fatal CHD events **Fatal non-CHD CVD events**	N=1549 N=687		
CHD morbidity risk in Iceland	Total 3309 CHD events recorded Cumulative rate of 18.4% for men and 3.7% for women.		
Comparison of baseline risk between Iceland and SCORE for fatal events	Men=baseline risk is closer to low-risk SCORE function, though diverges towards higher risk SCORE function with increased age Women = Baseline risk almost identical to low-risk SCORE function.		
Cumulative CVD death rate before 65 years in Iceland	Men = 6.41% (intermediate compared to European cohort) Women = 1.66% (low compared to European cohort)		
CHD death as percentage of all CVD deaths	Men=88% Women=72% - both men and women, highest deaths compared to SCORE cohort		
Hazard ratio estimates for CHD events in Iceland	Smoker (current) hazard ratio=1.72 [95% CI 1.60-1.84] Cholesterol hazard ratio=1.32 [95% CI 1.28-1.36] Systolic blood pressure hazard ratio = 1.12 [95% CI 1.10-1.14]		

Fatal CVD risk and CHD morbidity risk	Men = 5% fatal CVD risk corresponds to 13% CHD risk Women = 5% fatal CVD risk corresponds to 8% CHD risk Spearman's rank correlation between CHD score and fatal CVD score = 0.96.	
Comparison between Iceland population and SCORE project	Comparison of relative risk estimates show remarkable similarity between estimates from Iceland and those from other European countries.	
aROC (95% CI), sensitivity-specificity	Iceland risk chart	SCORE low risk chart
	0.80 (0.78-0.82) 64-81 sens-spec at 4% risk threshold for CVD	0.80(0.77-0.82) 54-86 sens-spec at 4% risk threshold for CVD
Notes	These data from Iceland externally validate the SCORE project risk predictions. The low-risk version of the SCORE chart can be applied to risk evaluation in Iceland. However, as the data are available, the Iceland version should be used in Iceland to give a better prediction of absolute risk, especially in men.	

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method					
Characteristics of study:					
Study citation	Bineau, S., Dufouil, C., Helmer, C., Ritchie, K., Empana, J., Ducimetiere, P., Alperovitch, A., Bousser, M. G., Tzourio, C. Framingham Stroke Risk Function in a Large Population-Based Cohort of Elderly People: The 3C Study. *Stroke* 2009; 40; p1564-70				
Study		**Study design**	Prospective, population based cohort study	**N (total)**	6913
Setting	Eligible participants on the French electoral rolls, with acceptance rate of 37%. Participants had follow-up examination at 2, 4 and 6 years after enrollment.				
Participants	**Total N=6913** cohort of French people aged 65 to 85 years; Participants did not have history of stroke				
Intervention	Framingham stroke risk function				
Comparison	Current cohort (3C) local stroke risk functions compared with Framingham risk function and recalibrated Framingham risk function.				
Outcomes	Incident stroke				
Quality of study					
Quality criteria		**Met?**	**Comments**		
Specified inclusion/exclusion criteria		yes	Invited, age, no history of stroke, missing co-variates		
Explicit description of participants		Yes			
Appropriate spectrum of consecutively selected participants		yes			
Prospective selection of participants		yes			

Test is compared with an appropriate reference (gold) standard	yes	Three way comparison	
Test is compared with the reference standard in all participants	yes	795 drop outs acknowledged	
Blinded assessment of test and reference standard results	yes	Assumed. End point adjudication committee	
Test and reference standard undertaken prior to any interventions	unclear	Not stated	
Level of evidence	II	**Risk of bias**	Very low
Results of study (event rates, sensitivity, specificity, area under ROC curve)			
Multivariate-adjusted relative risk factors for 3C cohort	1. Age: men RR=2.29 [95% CI 1.29-4.07], women RR=3.51 [95% CI 1.90-6.50]; SBP: men RR=1.14 [95% CI 1.10-1.29], women RR=1.22 [95% CI 1.08-1.36]; Atrial fibrillation: men RR=2.60 [95% CI 1.17-5.78], women: RR=2.91 [95% CI 1.03-8.21] was independently associated with stroke risk. 2. Diabetes, smoking & history of cardiovascular disease were not significantly associated with stroke risk. 3. 10 year age increase associated with higher increase in stroke risk among 3C participants than Framingham participants. (Men: RR_{3C}=2.29 versus RR_F=1.63, *P*=0.27; Women: RR_{3C}=3.51 versus RR_F=2.01, *P*=0.09) 4. For most risk factors, RR did not differ significantly between 2 cohorts except for age in women.		
Calibration analysis	Original Framingham stroke risk function overestimated the 6-year expected stroke rate in 3C by a factor of 3.70 [95% CI, 2.84-4.80] for men and factor of 4.35 [95% CI 3.34-5.67] for women. Recalibrated Framingham risk function did not overestimate expected stroke rates among 3C men (1.17 [95% CI 0.90-1.52] and women (0.85 [95% CI 0.65-1.11]. The 3C stroke risk function did not overestimate stroke rates observed among 3C men (1.13 [95% CI, 0.87-1.47] and women (0.97 [95% CI 0.75-1.26].		
Notes	Recalibrated Framingham risk function used mean values of risk factors and average incidence rates derived from 3C data. The recalibrated Framingham risk function gave reliable and accurate prediction, which was not further improved by "local" 3C stroke risk prediction.		

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method: diabetic population	
Characteristics of study:	
Study citation	Chanman P, Simmons RK, Sharp SJ, Griffin SJ, Wareham NJ. Cardiovascular risk assessment scores for people with diabetes: a systematic review. Diabetologia, 2009. 52: 2001-14

Study		Study design	Systematic review	N (total)	
Search strategy	Comprehensive search strategy in Medline, Web of Science, Cochrane reviews from database inception to 30 June 2008. Included key concepts of CVD, type 2 diabetes, risk assessment/score/prediction, names of known risk scores.				
Selection criteria	Included: 13 studies (5 published 2006+)prospective cohort studies or RCT; evaluated in diabetic population; reported a measure of the performance of the risk score; primary outcome fatal/non fatal CVD, fatal/non-fatal CHD, fatal/non-fatal cerebrovascular disease/stroke				
Intervention	8 risk scores originally devised in populations with diabetes (included diabetes-specific risk factors such as age at diagnosis, duration of diabetes, measure of glycaemic control) 9 risk scores developed in general population and subsequently evaluated in diabetic cohort (contained dichotomous variable for diabetes yes/no).				
Comparison	Some compare with Framingham.				
Outcomes	Most risk scores developed in the general population underestimated CVD risk in diabetic patients. There is little evidence that using risk scores developed in individuals with diabetes will help to estimate CVD risk among diabetic patients more accurately than using those developed in the general population				

Quality of study		
Quality criteria (SIGN)	**Met?**	**Comments**
Study addresses an appropriate and clearly focused question	yes	
Description of the methodology used is included	yes	Narrative review only, meta-analysis not possible due to study heterogeneity.
The literature search was sufficiently rigorous to identify all the relevant studies	yes	Medline, Web of Science, Cochrane reviews from database inception to 30 June 2008. Included key concepts of CVD, type 2 diabetes, risk assessment/score/prediction, names of known risk scores.
Study quality was addressed and taken into account?	no	Narrative description of size and origin of validation cohort, recruitment sources, definition of diabetes included (3 studies); clear definitions of CVD endpoints (missing in 4 studies)
There were enough similarities between the studies to justify combining them.	no	Each study had different inclusion criteria, follow up, ascertainment methods, statistical methods. Thus difficult to compare the predictive ability between risk scores
Determine the methodological quality of the study according to this ranking, based on responses above.		++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
	+	+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
Level of evidence SR but no meta-analysis possible due to heterogenous studies and inconsistent study quality		

Results of study (event rates, sensitivity, specificity, area under ROC curve)			

SECTION 3 asks you to identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.

Notes	In post 2006 studies:				
		Validation population	Diabetes definition	Outcome (n=no of events)	result
	Simmons 2009 Oxford risk engine=UKPDS risk engine version 3	1410 men and women 40-75 years on placebo arm of CARDS study	1985 WHO criteria	CVD events (n=189) (fatal/non fatal MI, sudden cardiac death, other IHD, fatal/non fatal stroke, fatal PVD)	Underestimated by 10.6% (189 observed vs 169 predicted events) over 3.9 years
	Donnan 2006 Diabetes audit and research in Tayside, Scotlands (DARTS)	Salford Diabetes Information System, f/u 5 years	Treatment with diet or oral hypoglycaemic agents, >35 years	CHD determined by hospital episode statistics (n=N/A))	c-statistic=0.69 (95% CI 0.58, 0.79), graph shown only
	Cederholm 2008 Swedish national diabetes register	5823 men and women aged 18-70years with diabetes, f/u 5.6 years	From Swedish national diabetes register	Fatal and non-fatal CVD (n=N/A)	c-statistic= 0.69 good calibration observed/predicted CVD rate ratio = 0.998
	Yang 2008 Hong Kong Diabetes Registry	3546 Chinese men and women, median age 56 yrs. Median f/u 5.6 yrs	Type 2 diabetes referred from GP/clinics/hospital discharge	CHD: MI or IHD (n=170)	Overall aROC=0.704 (95% CI 0.675 – 0.733) Adjusted aROC=0.737 Good calibration (HL χ^2=14.05, p>0.05) 5 year CVD risk>5.2% sensitivity=67.6; specificity=68.5
	Yang 2007 Hong Kong Diabetes Registry for Stroke	3541 Chinese diabetic patients without previous stroke, median f/u=5.37 years	Type 2 diabetes referred from GP/clinics/hospital discharge	Physician confirmed stroke diagnosis at hospital dischange (n=182)	Adjusted aROC haemorrhagic stroke=0.770 Ischaemic stroke=0.785 5 year risk of stroke>6.1% sensitivity=65.7, specificity=74.9

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method					
Characteristics of study:					
Study citation	Chow, C. K., Joshi, R., Celermajer, D. S., Patel, A., Neal, B. C. Recalibration of a Framingham risk equation for a rural population in India. *J. Epidemiology Community Health* 2009; 63; p. 379-85				
Study		**Study design**		**N (total)**	4535

Setting	Estimated the proportion of rural Indian population at high risk of coronary heart disease using three CHD risk prediction models based on the Framingham risk equation (FRE). Local risk factor data was obtained from the APRHI study conducted in 2005.
Participants	Random sample of 4535 adults from over 20 Indian villages as collected under the APRHI study in 2005
Intervention	Framingham (model 1)
Comparison	Model 2. Used a recalibration of the FRE with local data from rural Indian population. Specific data on risk factor levels and CHD rates were taken from Andhra Pradesh Rural Health Initiative (APRHI) Model 3. Also used a recalibration of the FRE using local risk factor level data from the specified rural Indian population but used CHD published national India data.
Outcomes	Fatal and non-fatal CHD incidence; 10 year CHD-free survival rates.

Quality of study		
Quality criteria	**Met?**	**Comments**
Specified inclusion/exclusion criteria	yes	Stratified random sampling, selected villages
Explicit description of participants	Yes	Described elsewhere
Appropriate spectrum of consecutively selected participants	unclear	
Prospective selection of participants	yes	
Test is compared with an appropriate reference (gold) standard	yes	
Test is compared with the reference standard in all participants	yes	Though not clearly stated
Blinded assessment of test and reference standard results	yes	assumed
Test and reference standard undertaken prior to any interventions	unclear	Not stated

Level of evidence	II	**Risk of bias**	low

Results of study (event rates, sensitivity, specificity, area under ROC curve)	
Baseline mean 10-year probability of CHD: Model 1. Model 2. Model 3.	 Men= 10.4% (9.6-11.1%); Women = 5.3% (4.9-5.7%) Men = 10.7% (9.9-11.5%); Women = 4.2% (3.9-4.5%) Men = 18.9% (17.7 to 20.1%); Women = 8.2 (7.6-8.8%)
	The proportions of the population at estimated high (>20%), intermediate (10-20%) and low (<10%) 10-year CHD risk derived using the three models showed a similar pattern.

Notes	The national recalibration model (model 3) produced risk estimates that were substantially higher. Recalibration of the Framingham risk tool is a practical approach to estimation of cardiovascular risk in countries such as India but the reliability and applicability of the data used for recalibration is of key importance. In India, equations re-calibrated to national summary data are unlikely to be relevant to all regions of India.

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method					
Characteristics of study:					
Study citation	D'Agostino, R., Vasan, R., Pencina, M., Wolf, P., Cobain, M., Massaro, J., Kannel, W., General Cardiovascular Risk Profile for Use in Primary Care: The Framingham Heart Study. *Journal of the American Heart Association* 2008; 117; p. 743-53				
Study		**Study design**	Prospective cohort study (ongoing)	**N (total)**	8491
Setting	Secondary analysis of Framingham Study, US. Presents a single multivariate risk function that predicts risk of developing a first CVD event in participants in the Framingham study.				
Participants	Data from participants in the original Framingham Heart Study and the Framingham Offspring Study Participants aged between 30 to 74; Total n=8491, women = 4522				
Intervention	Framingham model				
Comparison	Updated Framingham				
Outcomes	CVD as composite of CHD (coronary death, myocardial infarction, coronary insufficiency and angina), cerebrovascular events (including ischemic and haemorrhagic stroke, transient ischemic attack); peripheral artery disease (intermittent claudication) and heart failure.				
Quality of study					
Quality criteria		**Met?**	**Comments**		
Specified inclusion/exclusion criteria		Yes	Free of prevalent CVD, no missing covariate data		
Explicit description of participants		Yes	Described elsewhere (Framingham original and offspring cohorts)		
Appropriate spectrum of consecutively selected participants		yes			
Prospective selection of participants		yes			
Test is compared with an appropriate reference (gold) standard		Yes			
Test is compared with the reference standard in all participants		Yes			
Blinded assessment of test and		yes	Committee also adjudicated, multidisciplinary.		

reference standard results			
Test and reference standard undertaken prior to any interventions	unclear	Not stated	
Level of evidence	II	**Risk of bias**	Very low
Results of study (event rates, sensitivity, specificity, area under ROC curve)			
	Multivariate-adjusted regression found highly significant relations of all risks factors evaluated (age, cholesterol, SBP, smoking, diabetes) and incident CVD.		
Sex-specific CVD functions c statistics for risk function	Men = 0.763 [95% CI 0.746-0.780] Women = 0.793 [95% CI 0.772 – 0.814]		
c statistics for Framingham CHD risk function	Men = 0.756 [95% CI, 0.739 – 0.773] significantly lower than model used in current study, P=0.051 Women = 0.778 [95% CI 0.756-0.799]; difference compared with new model P=0.003		
Net reclassification improvement from using new model	Men = 6.65% (P<.001) Women =7.95% (P=0.003)		
Notes	This study presents an updated, general risk prediction instrument, based on traditional risk factors, for prediction of CVD. This general CVD risk function demonstrates very good discrimination and calibration both for predicting CVD, and for predicting risk of individual CVD components (ie. coronary, cerebrovascular, and peripheral arterial disease and heart failure), comparable to disease specific algorithms.		

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method					
Characteristics of study:					
Study citation	De Bacquer, D., De Backer, G. Predictive ability of the SCORE Belgium risk chart for cardiovascular mortality. *International Journal of Cardiology* 2009;				
Study		**Study design**	Secondary analysis of prospective data	**N (total)**	6212
Setting	Prospective cohort study conducted in the eighties by the Belgian Interuniversity Research on Nutrition and Health. The absolute 10-year probability of developing a fatal cardiovascular event was calculated by Systematic Coronary Risk Evaluation (SCORE) risk chart and compared to national mortality statistics.				
Participants	Total N=6212 (men = 3179, and women = 3033) free of CHD				
Intervention	SCORE				
Comparison	National mortality statistics				
Outcomes	CVD mortality				
Quality of study					
Quality criteria		**Met?**	**Comments**		
Specified inclusion/exclusion criteria		yes	Random, stratified sampling from voting list, exuded if covariates missing		

Explicit description of participants	yes	Described elsewhere		
Appropriate spectrum of consecutively selected participants	yes			
Prospective selection of participants	yes	10 year follow up		
Test is compared with an appropriate reference (gold) standard	yes	Score versus national mortality statistics		
Test is compared with the reference standard in all participants	yes	99%complete		
Blinded assessment of test and reference standard results	yes	Assumed		
Test and reference standard undertaken prior to any interventions	unclear	Not stated		
Level of evidence	II	**Risk of bias**	Very low	
Results of study (event rates, sensitivity, specificity, area under ROC curve)				
Actual CVD deaths over 10 year follow-up: SCORE risk chart predicted:	274 263			
Hosmer-Lemeshow statistic across several risk categories	Demonstrated acceptable goodness-of-fit between observed and expected events (χ^2=8.31, P=0.14)			
ROC analysis	c-statistic = 0.86; men=0.82; women=0.88			
Notes	The SCORE Belgium risk chart showed very good accuracy for predicting the 10-year probability of CVD mortality (274 CVD deaths were observed while the recalibrated risk chart predicted 263 events). Prediction was good across the range of predicted risk, with high discrimination and balance of sensitivity/specificity.			

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method					
Characteristics of study:					
Study citation	Dhaliwal, S., Welborn, T. Central obesity and cigarette smoking are key determinants of cardiovascular disease deaths in Australia: A public health perspective. *Preventive Medicine* 2009; 49; p. 153-57				
Study		**Study design**	Prospective cohort study	**N (total)**	8862
Setting	Australian study developing a model to predict coronary heart disease and cardiovascular disease using individual components of the Framingham risk score and measures of central obesity.				
Participants	Representative Australian adults: Men = 4175, women = 4487; data collected in National Heart Foundation Risk Factor				

	Prevalence Survey 1989.		
Intervention	Framingham Risk variables		
Comparison	Smoking and central obesity variables (BMI, WC, WHR)		
Outcomes	Cardiovascular disease mortality		
Quality of study			
Quality criteria	**Met?**	**Comments**	
Specified inclusion/exclusion criteria	yes	Excludes those with baseline history of heart disease, stroke, diabetes	
Explicit description of participants	yes	Described elsewhere - Registered voter – age/ex stratified sample	
Appropriate spectrum of consecutively selected participants	yes		
Prospective selection of participants	yes	15 year follow-up	
Test is compared with an appropriate reference (gold) standard	yes	FRE with alternate variables	
Test is compared with the reference standard in all participants	unclear		
Blinded assessment of test and reference standard results	yes	assumed	
Test and reference standard undertaken prior to any interventions	unclear	Not stated	
Level of evidence	II	**Risk of bias**	Very low
Results of study (event rates, sensitivity, specificity, area under ROC curve)			
Deaths during 15 year follow-up	Total deaths = 610 Due to CVD = 126 Due to CHD = 85		
Significant univariate predictors of risk for CHD and CVD after adjustment for age and sex	Smoking status HDL-C WC WHR		
Significant univariate predictor of risk for CVD after adjustment for age and sex	Systolic blood pressure		
Multivariate significant independent predictors of both CHD and CVD	Smoking status: CHD deaths = 2.24 (95% CI 1.39-3.59) p=0.001; CVD deaths = 1.88 (95% CI 1.26-2.83) p=0.002 WHR: CHD deaths = 1.42 (95% CI 1.12-1.80) p=0.004; CVD deaths = 1.46 (95% CI 1.21-1.77) p<0.0005		

Framingham predicted risk model	Area under ROC curve for CHD = 0.875 (0.841-0.909) Area under ROC curve for CVD =0.866 (0.836-0.897)
Obesity and smoking model	Area under ROC curve for CHD = 0.876 (0.84-0.912) Area under ROC curve for CVD = 0.872 (0.843-0.902)
Notes	The various models were not significantly different in terms of sensitivity and specificity in the discrimination of CHD and CVD deaths. Authors prefer obesity and smoking as public health predictors.

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method					
Characteristics of study:					
Study citation	Grover, S., Hemmelgarn, B., Joseph, L., Milot, A., Trembaly, G. The role of global risk assessment in hypertension therapy. *Canadian Journal of Cardiology* 2006;22(7); p. 606-13				
Study		**Study design**	Prospective , comparative	**N (total)**	1173
Setting	Review of cardiovascular risk assessment models and their applications to Canadians. Models included: Framingham heart Study risk equation and the Cardiovascular Life Expectancy Model (CLEM). Canadian data from the lipid research clinics follow-up cohort. 10-year risk from each model were calculated and then compared with observed outcomes in a small Canadian cohort. Other models examined but not applied to Canadian cohort were the United Kingdom Prospective Diabetes Study and the Systematic COronary Risk Evaluation (SCORE) model.				
Participants	1173 Canadian participants, aged between 30 and 67 years old used in the assessment of FRE and CLEM models.				
Intervention	FRE and CLEM models				
Comparison	Observed fatal coronary events				
Outcomes	Fatal coronary events				
Quality of study					
Quality criteria		**Met?**	**Comments**		
Specified inclusion/exclusion criteria		yes	Described elsewhere		
Explicit description of participants		yes	LRC Follow-up Cohort		
Appropriate spectrum of consecutively selected participants		yes	Small cohort		
Prospective selection of participants		yes	10 year follow-up		
Test is compared with an appropriate reference (gold) standard		yes	FRE and CLEM with observed rates		
Test is compared with the reference standard in all participants		unclear	Drop outs and participation rate not reported		
Blinded assessment of test and		yes	Assumed		

reference standard results			
Test and reference standard undertaken prior to any interventions	unclear	Not stated	
Level of evidence	II	**Risk of bias**	Low (small numbers)
Results of study (event rates, sensitivity, specificity, area under ROC curve)			
Risk factors common to all models	Age, sex, smoking habits, total cholesterol, systolic blood pressure. Presence of diabetes is a common independent risk factor in all models except for SCORE		
FRE model CLEM model	Area under ROC curve = 0.80 (95% CI 0.78 to 0.83) Area under ROC curve = 0.81 (95% CI 0.78 to 0.83)		
Notes	Small number of cardiac deaths in the Canadian cohort provided limited data on which to validate risk models.		

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method					
Characteristics of study:					
Study citation	Hippisley-Cox, J., Coupland, C., Vinogradova, Y. Performance of the QRISK cardiovascular risk prediction algorithm in an independent UK sample of patients from general practice: a validation study. *Heart* 2008; 94; p. 34-39				
Study		**Study design**	Prospective open cohort study	**N (total)**	1.68 million
Setting	Assessed the performance of the QRISK score for predicting CVD in a UK sample in comparison with Framingham score.				
Participants	1.07 million patients, aged between 35-74 years registered at THIN practices between 1995 and 2006; men=54 709 0.61 million patients from QRESEARCH validation cohort.				
Intervention	QRISK				
Comparison	Framingham score.				
Outcomes	first diagnosis of CVD (MI, CHD, stroke, TIA)				
Quality of study					
Quality criteria		**Met?**	**Comments**		
Specified inclusion/exclusion criteria		yes	Random sample of GP practices; excludes diabetics, on statins with CVD		
Explicit description of participants		yes	Described elsewhere		
Appropriate spectrum of consecutively selected participants		yes			
Prospective selection of participants		yes	10+ year follow-up		
Test is compared with an appropriate reference (gold) standard		yes	QRISK versus FRE		

Test is compared with the reference standard in all participants	yes	Variable	
Blinded assessment of test and reference standard results	yes	assumed	
Test and reference standard undertaken prior to any interventions	unclear	Not stated	
Level of evidence	II	**Risk of bias**	Very low
Results of study (event rates, sensitivity, specificity, area under ROC curve)			
Framingham	Framingham over-predicted by 23% in THIN cohort while QRISK under-predicted by 12%. QRISK had better discrimination and calibration statistics in both THIN and QRESEARCH validation cohorts than Framingham.		
THIN cohort:	• 132 076 patients classified as high risk (more than 20% risk of CVD over 10 years) using Framingham, 53.6% would be reclassified as low risk on QRISK. For these patients, the observed 10-year risk was 17.4% (95% CI 16.8% to 17.9%) • 14 245 patients classified as low risk on Framingham but high risk on QRISK had an observed 10-year risk of 23.7% (95% CI 22.4% to 25%)		
QRESEARCH cohort	• 46 785 patients (7.7% of total) would be reclassified from high to low risk or vice versa using QRISK compared to Framingham • Of the 76 748 patients classified as high risk using Framingham, 48.8% would be reclassified as low risk on QRISK. The observed 10 year risk was 16.7% (95% CI 16.2% to 17.2%) • 9306 patients classified as low risk on Framingham but high risk on QRISK had observed 10 year risk of 24.4% (95% CI 23.2% to 25.6%).		
Notes	QRISK outperformed FRE in these UK populations		

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method					
Characteristics of study:					
Study citation	Loucks, E., Lynch, J., Pilote, L., Fuhrer, R., Almeida, N., Richard, H., Agha, G., Murabito, J., & Benjamin, E. (2009) Life-course socioeconomic position and incidence of coronary heart disease, The Framingham Offspring Study. *American Journal of Epidemiology*, 169:829-36.				
Study		**Study design**	Observational cohort study	**N (total)**	1835

Setting	The Framingham Offspring Study (US) began in 1971 recruiting offspring (or offspring's spouses) of the participants of the Framingham Heart Study.			
Participants	1835 participants. Mean age 35.0 years at baseline, 52.4% were women.			
Intervention	"Accumulation-of-risk " socioeconomic position (cumulative SEP) (total amount of exposure to socioeconomic disadvantage over every phase of a participants life – childhood SEP and adulthood SEP)			
Comparison	CHD incidence			
Outcomes	CHD events (myocardial infarction, coronary insufficiency, and coronary death).			
Quality of study				
Quality criteria		**Met?**	**Comments**	
Specified inclusion/exclusion criteria		yes	Excluded 2136 due to no father in original study, 937 due to missing variables, participants ≥28 years at time their own educational attainment and occupation were measured, 21 due to borderline Coronary heart disease events.	
Explicit description of participants		Yes	Described elsewhere – Framingham Offspring study	
Appropriate spectrum of consecutively selected participants		yes		
Prospective selection of participants		yes		
Test is compared with an appropriate reference (gold) standard		yes		
Test is compared with the reference standard in all participants		Yes		
Blinded assessment of test and reference standard results		yes	Assumed	
Test and reference standard undertaken prior to any interventions		unclear	Not stated	
Level of evidence	II		**Risk of bias**	Low (small numbers)
Results of study (event rates, sensitivity, specificity, area under ROC curve)				
Childhood SEP: father's education	Inversely associated with CHD risk factors (smoking, BMI, systolic blood pressure HDL:total cholesterol, fasting glucose. Inversely associated with CHD incidence after adjusting for age and sex (Hazard Ratio= 1.65, 95% CI 1.02,2.66 for father's education < high school vs. > high school)			
Adulthood SEP: own education	Inversely associated with smoking, systolic blood pressure, and HDL:total cholesterol ratio. Inversely associated with CHD incidence after adjusting for age and sex (Hazard Ratio= 1.85, 95% CI 1.05, 3.27 for own education ≤ 12 years vs. ≥ 17 years)			
Adulthood SEP: own occupation	Inversely related to smoking and BMI.			

	Not associated with CHD incidence
Accumulative SEP	Inversely associated with CHD incidence (HR = 1.82, 95% CI:1.17, 2.85 for low vs. high cumulative SEP score)
Notes	Secondary analyses were conducted using cardiovascular disease instead of CHD as an outcome, which resulted in similar findings compared to CHD. Both outcomes support an inverse association of cumulative life-course SEP with CHD incidence. Adjustment for CHD risk factors reduced the magnitude of association. We included as considered several SEP factors within the final cumulative SEP.

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method					
Characteristics of study:					
Study citation	Marques-Vidal, P., Rodondi, N., Bochud, M., Pecoud, A., Hayoz, D., Paccaud, F., Mooser, V., Waeber, G., & Vollenweider, P (2008) Predicitve accuracy and usefulness of calibration of the ESC SCORE in Switzerland. *European Journal of Cardiovascular Prevention & Rehabilitation* 15(4): 402-8.				
Study		**Study design**	Cross-sectional, population-based study	**N (total)**	5773
Setting	Low CVD risk country, Switzerland. Data collected as part of the CoLaus study.				
Participants	35% of Lausanne inhabitants (total inhabitants = 56694) aged 35-75years randomly selected. 5773 participants (3074 women and 2699 men)				
Intervention	Original SCORE and Calibrated SCORE (based on Swiss CVD mortality rates)				
Comparison	10-year CVD mortality data				
Outcomes	CVD mortality				
Quality of study					
Quality criteria		**Met?**	**Comments**		
Specified inclusion/exclusion criteria		yes	Exclusions if presented with any personal history of CVD at baseline and for missing data for the calculation of the CHD risk scores.		
Explicit description of participants		yes	Caucasian Swiss; CoLaus study cohort		
Appropriate spectrum of consecutively selected participants		yes			
Prospective selection of participants		unclear	Follow-up not stated		
Test is compared with an appropriate reference (gold) standard		yes			
Test is compared with the reference		yes	Assumed, not stated		

standard in all participants			
Blinded assessment of test and reference standard results	yes	Assumed	
Test and reference standard undertaken prior to any interventions	unclear	Not stated	

Level of evidence	II	**Risk of bias**	Very low

Results of study (event rates, sensitivity, specificity, area under ROC curve)	
Risk factor combinations	Participants with a CVD risk ≥5% was similar for both original (n=753) and calibrated (n=749) functions. The agreement between scores as determined by Lin's concordance correlation coefficient was 0.951 for men and 0.948 for women (p<0.001).
Women	Calibrated SCORE overestimated participants at high-risk
Men	Calibrated SCORE underestimated participants at high-risk
Age	Older age group: calibrated function provide more accurate estimates compared to CVD mortality data
Notes	Participants that were identified as at risk using calibrated SCORE were significantly older and had lower levels of SBP and total cholesterol and lower smoking frequency. Original SCORE adequately predicts CVD death in Switzerland especially for individuals aged ≤65 years. The Calibrated SCORE provides more reliable estimates for older individuals.

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method					
Characteristics of study:					
Study citation	May, M., Lawlor, D., Brindle, P., Patel, R., & Ebrahim S (2006) Cardiovascular disease risk assessment in older women: can we improve on Framingham? British Women's Heart and Health prospective cohort study.				
Study		**Study design**	Prospective cohort study	**N (total)**	3582
Setting	23 towns in the United Kingdom				
Participants	3582 women aged 60 to 709 years who were free of coronary heart disease (CHD) at entry into the British Women's Heart and Health Study				
Intervention	Framingham and General practice (GP) model: includes standard risk factors of age, systolic blood pressure and smoking status but not cholesterol ratio, diabetes, and left ventricular hypertrophy, because these require laboratory tests/ECG. Included alternative risk factors- BMI/waist measurement and self rate health)				
Comparison	observed incidence of CHD and CVD events (NHS Central Register, mortality data), plus 2 yearly review of medical records				
Outcomes	CHD and cardiovascular disease (CVD)				
Quality of study					

Quality criteria	Met?	Comments
Specified inclusion/exclusion criteria	yes	Women, randomly selected from English towns, free of CHD
Explicit description of participants	yes	Described elsewhere (British Women's Heart and Health study)
Appropriate spectrum of consecutively selected participants	yes	But only women
Prospective selection of participants	Yes	5 year follow-up
Test is compared with an appropriate reference (gold) standard	Yes	
Test is compared with the reference standard in all participants	yes	11% were imputed
Blinded assessment of test and reference standard results	`yes	Assumed
Test and reference standard undertaken prior to any interventions	unclear	Not stated

Level of evidence	II	**Risk of bias**	Very low

Results of study (event rates, sensitivity, specificity, area under ROC curve)	
Framingham	CHD: predicted risk 5.7%; Observed risk 5.5% - therefore over-prediction of 3%. Under predicted in the low-risk fifths Over predicted in the highest-risk fifths. Discrimination – 0.59 (classified by fifths of risk) 0.63 (classified by ranked risk) CVD: predicted risk 10.5%; observed risk 6.8%- therefore over-prediction of 54%. Over-prediction was greatest in the two highest-risk fifths. Discrimination – 0.62 (classified by fifths of risk) 0.64 (classified by ranked risk) Addition of C-reactive protein or fibrinogen did not improve the performance of the Framingham equation. Over predicted risk, particularly for CVD, in higher risk fifths. Sensitivity and specificity – not well calibrated to this population 30% CVD risk threshold – 38%/79% 15% CVD risk threshold - 85%/30%
GP model	BMI was not an independent predictor of CHD or CVD. Self-rated health was a particularly strong predictor of events with a hazard ratio for "poor" compared to "excellent" of 9.6 (95% CI 4.1 to 22.9) Discrimination appears to be marginally better with GP model , but CIs for comparison against Framingham overlap.
Notes	GP model superior and more feasible but needs testing on other populations (applicability)

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method			
Characteristics of study:			
Study citation	Pencina, M., D'Agostino, R., Larson, M., Massaro, J., Vasan, R. Predicting the 30-year risk of cardiovascular disease. The Framingham heart study. *Circulation* 2009; 119: 3078-84.		
Study design	Prospective	**N (total)**	4506
Setting	Based on the Framingham Offspring Cohort (enrolled from 1971) in the United States. Had continuous CVD monitoring for a median of 32 years (max=35 years)		
Participants	Subjects from this cohort, between 20 and 60 years old, free of cancer and CVD at baseline, had a complete risk factor profile		
Intervention	Framingham 30 year risk profile developed and evaluated (5 fold validation accounted for using the same data for development and evaluation).		
Comparison	Different applications of 10 year risk		
Outcomes	Primary outcome=Risk of "hard CVD" (coronary death, myocardial infarction and stroke[fatal or non-fatal]) Secondary outcome=risk of "full CVD" (hard CVD plus coronary insufficiency and angina pectoris, stroke plus TIA, intermittent claudication and congestive heart failure).		

Quality of study		
Quality criteria	**Met?**	**Comments**
Specified inclusion/exclusion criteria	yes	
Explicit description of participants	yes	
Appropriate spectrum of consecutively selected participants	yes	
Prospective selection of participants	yes	
Test is compared with an appropriate reference (gold) standard	yes	Compared with alternative versions of "tripling" 10 year risk, including a time-dependent updating
Test is compared with the reference standard in all participants	yes	
Blinded assessment of test and reference standard results	unknown	but likely
Test and reference standard undertaken prior to any interventions	yes	No therapeutic interventions included in this study

Level of evidence	II	**Risk of bias**	Low-very low
Results of study (event rates, sensitivity, specificity, area under ROC curve)			

Hazard ratios with 95% CIs for 30 year risk of hard CVD (per 1-SD increase in the natural logarithm)	**Variable**	**HR (CI) main model**
	Male sex	1.73 (1.45, 2.07)
	Age	2.09(1.88, 2.31)
	SBP	1.29 (1.19, 1.39)
	Antihypertensive treatment	1.48 (1.10, 2.00)
	Smoking	2.01 (1.72, 2.35)
	Diabetes mellitus	2.49 (1.82, 3.41)
	Total cholesterol	1.33 (1.23, 1.44)
	HDL cholesterol	0.78 (0.72, 0.84)
Model performance:	C-statistic (aROC)= 0.803 (good discrimination) Modified Hosmer-Lemeshow χ^2 statistic= 4.25 (p=0.894) (good calibration)	
Notes	30 year risk very close to incidence rates. Good discrimination indicated by C-statistic. 30 year risk cannot be adequately replaced by different combinations of 10 year risk estimates. Cohort were white Americans, limits generalisability The effects of BMI were mediated through other risk factors. BMI .."is present in the 30-year risk model when the follow-up is extended for a long period from the baseline, but then it affects the individual risk factors, and after we control for this impact in time-updated models, BMI loses its significance" p 3081	

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method					
Characteristics of study:					
Study citation	Ruppert, K., Roberts, M., Orchard, T., & Zgibor, J (2007) Cardiovascular disease risk prediction in type 1 diabetes: accounting for the differences. *Diabetes Research and Clinical Practice*. 78: 234-7.				
Study		**Study design**	Prospective cohort study	**N (total)**	552
Setting	Pittsburgh Epidemiology of Diabetes Complications Study – a prospective study of subjects with childhood type 1 diabetes (T1D) diagnosed between 1950 and 1980.				
Participants	658 coronary heart disease (CHD) free subjects, with childhood (<17 years old) onset T1D, epidemiologically representation of T1D cases in Allegheny County, Pennsylvania. Final dataset consisted of 552 subjects, 49% male and 98% were Caucasian, mean age at entry into the study was 27 yo and duration of diabetes prior to study entry was 18 years.				
Intervention	Framingham risk equation				
Comparison	Observed CHD events				
Outcomes	CHD events (MI, CHD death, or Q-waves)				
Quality of study					

Quality criteria	Met?	Comments
Specified inclusion/exclusion criteria	Yes	Exclusions from analysis were those that had prevalent CHD (n-52), unknown CHD history (n=3), incomplete follow up (n=26) or died from unrelated causes (n=25). Participants who suffered a CHD event after year 10 were censored at the time.
Explicit description of participants	yes	Clinic based but representative, biannually assessed
Appropriate spectrum of consecutively selected participants	yes	
Prospective selection of participants	yes	
Test is compared with an appropriate reference (gold) standard	yes	
Test is compared with the reference standard in all participants	yes	Stated loss to follow-up
Blinded assessment of test and reference standard results	yes	Assumed
Test and reference standard undertaken prior to any interventions	assumed	Rx for T1D ongoing

Level of evidence	II	**Risk of bias**	Low

Results of study (event rates, sensitivity, specificity, area under ROC curve)	
Female	Risk scores in deciles 7-10 (n=111) (previous work has shown that females experience he majority of event in deciles 7-10), 14% had an CHD event. The following baseline values were found to be predictive of an event; BDI (p = 0.008), A1c (p = 0.008), AER (p = 0.01), LDLc (p = 0.007), fibrinogen (p = 0.006), WBC (p = 0.005), non-HDLc (p = 0.0005), and WHR (p = 0.003), eGDR (p = 0.002). significant. No events were noted in deciles 1–3 or 6. Two women in deciles 4 and 5 experienced a cardiac event. One was a fatal MI at year 10 and the other was a non-fatal MI at year 8.
Male	Risk scores in deciles 6-10 (n=138) (previous work has shown that males experience most event in deciles 6-10), 16% had an CVD event. Baseline risk factors that were found to be predictors of CHD within 10 yrs included elevated fibrinogen (p=0.007), WBC (p = 0.037), and AER (p = 0.0001), and lower HDL (p = 0.048). In deciles 1 and 2, there was one event in each (no events in deciles 3–5). One subject experience Q-waves at 7.8 years into the study and the other experienced a non-fatal MI at 4.3 years.
Notes	Using this model may underestimate the risk and may mis-specify the importance of various risk factors and the potential effects of risk factor modification. Reasons for underestimations may not be the same risk factors for each gender. Authors strongly recommend development of alternative risk prediction method in Type 1 diabetes.

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method					
Characteristics of study:					
Study citation	Van der Heijden, A., Ortegon, M., Niessen, L., Nijpels, G., & Dekker, J. (2009). Prediction of coronary heart disease risk in general, pre-diabetic, and diabetic population during 10 years of follow-up: accuracy of the Framingham, SCORE, and UKPDS Risk Functions: The Hoorn Study. *Diabetes Care*, 32(11): 2094-8.				
Study		**Study design**	Prospective, population based Study	**N (total)**	1125
Setting	The Hoorn Study- The Netherlands, a population based cohort study (n=2484). Participants were selected from this larger cohort study.				
Participants	Dutch, Caucasian men and women, 50-75 years of age, with normal glucose tolerance (NGT), intermediate hyperglycemia and type 2 diabetes. 1125 individuals with NGT, 232 individuals with intermediate hyperglycemia, and 125 individuals with diabetes, individuals were assigned these levels according to WHO criteria of 2006 after oral glucose tolerance test.				
Intervention	Framingham, SCORE, UKPDS				
Comparison	Observed fatal/non-fatal CHD events (medical records) – defined as fatal and non-fatal ischemic heart disease and sudden death				
Outcomes	non fatal and/or fatal CHD events				
Quality of study					
Quality criteria		**Met?**	**Comments**		
Specified inclusion/exclusion criteria		yes	Patients were excluded if previous history of CVD (n=470), missing values for any predictor values (n=21) or outcome variables (n=496).		
Explicit description of participants		Yes	Hoorn Study – described elsewhere		
Appropriate spectrum of consecutively selected participants		Yes			
Prospective selection of participants		Yes	10 year follow-up		
Test is compared with an appropriate reference (gold) standard		Yes			
Test is compared with the reference standard in all participants		Yes			
Blinded assessment of test and reference standard results		Yes	Assumed		
Test and reference standard undertaken		unclear	Diabetic were being treated		

prior to any interventions			
Level of evidence	II	**Risk of bias**	Very low
Results of study (event rates, sensitivity, specificity, area under ROC curve)			
Framingham	-Overestimated risk of CHD risk when compared to observed CHD incidence rate in all three subgroups. - Risk of first CHD. Low ability to discriminate in all subgroups except for the type 2 diabetes subgroup – whom the discriminatory ability was moderate.		
SCORE	-Estimated fatal CHD fair in both NGT and intermediate hyperglycemia subgroups, but less precise in diabetic subgroup. - Prediction of fatal CHD- moderate ability		
UKPDS	-Overestimated risk of CHD risk when compared to observed CHD incidence rate in all three subgroups. - Moderate ability to identify those with high risk for first CHD event in NGT and intermediate hyperglycemia subgroups, and low ability in type 2 diabetes subgroup - Highest discriminatory ability for intermediate hyperglycemia sub group for fatal CHD		
Notes	-All prediction models showed better discrimination when a fatal CHD event was used as the predicted outcome. -The addition of family history of myocardial infarction slightly improved most risk algorithms in prediction of the risk of a first CHD event, although changes were not statistically significant. -Although Framingham and UKPDS were designed to estimate first CHD in the general population and diabetic population, respectively. Both functions performed better in estimating fatal CHD than the SCORE. - Framingham function in prediction of first CHD event in all subgroups was likely to overestimate individual's absolute CHD risk. -Application of SCORE risk function in diabetic population to aid in CHD prevention - Application of SCORE and UKPDS in NGT & intermediate hyperglycaemic populations to aid in CHD prevention		

FORM framework Question 1

Key question(s): 1. Which absolute risk assessment method is most predictive of future CVD events in a mixed adult (aged >18) population not known to have CVD or diabetes?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Several studies: - level II (assessed using levels of Prognostic studies), - low to very low risk of bias (retained Diagnostic studies criteria from original guidelines so some questions not applicable)	A	**One or more level I studies with a low risk of bias or several level II studies with a low risk of bias**
	B	**One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias**
	C	**One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias**
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
High heterogeneity of study questions with many multi-risk prediction tools evaluated and/or compared: Framingham original and recalibrated versions, SCORE, CLEM, QRISK, locally generated models (eg 3C, GP, Indian, NIPPON, public health models). Consistent finding is that tool must be locally calibrated even if based on original framework.	A	**All studies consistent**
	B	**Most studies consistent and inconsistency can be explained**
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
	NA	**Not applicable (one study only)**
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Evidence applies to a large patient population, is associated with potential benefits via changed treatment, but no harms reported and has significant resource and organisational implications.	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Large amount of data related to adult Caucasian, however as noted above there are consistent findings that CVD risk and risk factor effects are variable across several domains and need to be locally validated.	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to**
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Only one new study in the Australian population – investigated different risk factors to those from FRE (central obesity and smoking as public health model)	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

There has been a natural evolution in research evaluating models to assess absolute risk – comparing new and locally produced models with the original Framingham or to recalibrate the FRE using local data. Therefore the original recommendation to adopt the Framingham is now tempered by issues of applicability. This is compounded by only one new study in an Australian population and still no studies directly reporting absolute risk assessment for indigenous populations. Entry into most studies included those who were 30 years although some were younger. The validity of using FRE for those under 30 is untested. Likewise very limited data for those >75 years.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1.Evidence base	A	High quality, low risk studies: large populations, 10+ year follow up
2.Consistency	C	Clinical heterogeneity leads to difficulty pooling findings; all studies comparing new models against FRE found new to be more appropriate
3.Clinical impact	A	Remains high
4. Generalisability	B	Findings support a locally calibrated risk assessment model
5. Applicability	C	Remains questionable in culturally diverse population

Evidence statement

Original evidence supports the use of the Framingham Risk Evaluation. However there is consistent emerging evidence (>2006) across countries, that strongly suggests the Framingham risk evaluation model requires calibration to local populations. Cultural and racial factors appear to influence the impact of traditional risk factors. Thirty year risk modeling is also available, which demonstrates the impact of adverse risk factors in young adults over a long term.

RECOMMENDATION (in addition to those already provided in the assessment guideline)	GRADE OF RECOMMENDATION	

a) In adults aged 18–29 years who are not known to have CVD or to be at clinically determined high risk, and who present with one or more CVD risk factors (e.g. elevated blood pressure or lipids, family history of premature CVD) the Framingham Risk Equation may be used to project estimated risk by assuming an age of 30 years. Results should be interpreted with the understanding that the score is an extrapolation of risk and therefore likely to overestimate five year risk. (Consensus based recommendation)

b) In adults aged 30 to 44 years who are not known to have CVD or to be at clinically determined high risk, the Framingham Risk Equation may be used to estimate CVD risk over the next 5 years. (Grade B)

c) In adults aged over 74, who are not known to have CVD or to be at clinically determined high risk, absolute cardiovascular risk over the next five years should be assessed using the Framingham Risk Equation. Calculation should be performed using the age of 74 years. Although the Framingham Risk Equation might underestimate risk in this population, available evidence suggests that this approach will provide an estimate of minimum cardiovascular risk. (Consensus based recommendation)

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up*	
The original guideline evidence tables used Diagnostic Levels and quality criteria related to Diagnostic studies. We believe the studies should be evaluated as Prognostic studies as they do not establish point in time diagnoses but rather evaluate the relative accuracy of risk assessments in predicting the occurrence of CVD events. As such the quality criteria do not seem appropriate. Nevertheless, this update of the evidence has reproduced the original methodology. The implications for this recommendation are significant in that the FRE has been questioned in the international literature.	
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	**Yes** – FRE may not be used much for those <45 years
Are there any resource implications associated with implementing this recommendation?	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	**YES** –if assessment to be considered by practice nurses
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**YES –**clinical knowledge/behaviour

FORM framework Question 2

Key question(s): Which absolute risk assessment method is most predictive of future CVD events in a mixed adult (aged >18) population not known to have CVD and who have diabetes?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
1 systematic review (Chanman et al): no meta-analysis due to heterogeneous studies and inconsistent quality 2 individual studies (Ruppert et al and Van der Heijden et al): - level II (assessed using levels of Prognostic studies), - low risk of bias (retained Diagnostic studies criteria from original guidelines	A	**One or more level I studies with a low risk of bias or several level II studies with a low risk of bias**
	B	**One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias**
	C	**One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias**
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
SR- Most risk scores developed in the general population underestimated risk in diabetic populations, but there is little evidence that risk scores developed in diabetic populations provide better estimates. Studies from 2005-current cited in SR have developed risk scores in one half of a cohort, then validated them in the other half, and have reported better predictive ability, however need to be validated more widely. Both individual studies found FRE to be inaccurate: one in T1D compared to observed events where Framingham underestimates, and one in T2D comparing FRE with SCORE and UKPDS finding FRE overestimates.	A	**All studies consistent**
	B	**Most studies consistent and inconsistency can be explained**
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Evidence applies to a large patient population, is associated with potential benefits via changed treatment, but no harms reported and has significant resource and organisational implications.	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Data related to adult Caucasian (Dutch and UK). Two post 2005 studies cited in SR in Chinese population.	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to**
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
No clear data on influence of race or culture to guide.	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**

	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

One study compared FRE with observed events in people with T1D and found the FRE was a poor predictor – identified other factors not in the FRE. Evidence suggests T1D is different factors to T2D.
One study compared FRE, SCORE and UKPDS in adults (diabetic, prediabetic and normal) and in diabetic population reported FRE to overestimate, therefore supported use of SCORE and UKPDS for CHD prevention.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	High quality, low risk studies: smaller populations, 10 year follow-up
2. Consistency	B	Neither individual study supported FRE
3. Clinical impact	A	Remains high
4. Generalisability	B	Most studies adult Caucasian
5. Applicability	C	Remains questionable in culturally diverse population

Evidence statement

In adults with type 1 or 2 diabetes, not known to have CVD, use of the FRE to predict absolute cardiovascular risk over 5 or 10 years is likely to be inaccurate. However there is insufficient evidence that risk scores developed in diabetic populations will better predict CVD risk in diabetic patients. Some positive predictive risk-engines developed in local populations (eg Chinese, Swedish, Scottish) need to be validated more widely. Consideration of the SCORE or UKPDS tools is recommended, with additional non-traditional factors to be investigated as a matter of urgency, however, these specific risk scores need to be validated in other populations before they are widely adopted.

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE OF RECOMMENDATION**	

No additional recommendation made to existing guidelines.

UNRESOLVED ISSUES

If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up

The original guideline evidence tables used Diagnostic Levels and quality criteria related to Diagnostic studies. We believe the studies should be evaluated as Prognostic studies as they do not establish point in time diagnoses but rather evaluate the relative accuracy of risk assessments in predicting the occurrence of CVD events. As such the quality criteria do not seem appropriate. This update of the evidence has reproduced the original methodology in applying these criteria. The implications for this recommendation are significant in that the FRE has been questioned in the international literature. This needs to be considered by the clinical and research community.	
IMPLEMENTATION OF RECOMMENDATION *No additional recommendation was considered necessary so not relevant.*	

Questions 3-5

For the following three questions no further trials were located therefore refer to previous technical report for the Assessment of absolute CVD risk guideline.

Q3. Which absolute risk assessment method is most predictive of future CVD events in a mixed adult (aged >18) population not known to have CVD and who are overweight (defined as BMI within the range 25.0–29.9 kg/m2) or obese (BMI ≥30kg/m2)?

For interest only: Wilson 2008: Does not compare different absolute risk score methods in an overweight/obese population, thus does not answer the question. This study examines data from the Framingham Offspring study population sample (n=4780) to estimate the effect, or contribution, of BMI on risk of CVD. In a simple prediction model of CVD that included age, sex, and smoking, a 1-SD unit (4.33kg/m^2) of BMI imparted a 28% effect on risk of initial CVD events. After full adjustment with traditional (Framingham) CVD prediction factors, the effect of a SD of BMI remained statistically significant, but declined to 10%. It was estimated that 67% of the BMI effects appear to operate through ratio of cholesterol to HDL cholesterol, systolic BP and diabetes mellitus. Thus a considerable proportion of the adverse effects of BMI are exerted through traditional risk factors. Long term follow up of middle aged adults was required to fully identify these effects.

This is consistent with evidence from Pencina 2009, where the effects of BMI were mediated through other risk factors. BMI .."is present in the 30-year risk model when the follow-up is extended for a long period from the baseline, but then it affects the individual risk factors, and after we control for this impact in time-updated models, BMI loses its significance" p 3081

Q4. Which absolute risk assessment method is most predictive of future CVD events in adult (aged >18) Aboriginal and Torres Strait Islander peoples not known to have CVD?

No further studies located. One high quality previous study found FRE underestimated risk in this population (see Assessment Guideline). Given the importance to provide guidelines for this group the EWG developed consensus based recommendations for all age groups >18 years (in addition to the established recommendation provided by the assessment guidelines). Relevant experts in the field and some unpublished data was used to develop these recommendations:

a) In Aboriginal and Torres Strait Islander adults aged 18–29 years who are not known to have CVD or to be at clinically determined high risk, and who present with one or more CVD risk factors (e.g. elevated BP or lipids, family history of premature CVD) the Framingham Risk Equation may be used to project estimated risk by assuming an age of 30 years. As the equation has not been validated in this population, the calculated risk score should be interpreted with caution. (CBR)
b) In Aboriginal and Torres Strait Islander adults aged 30–34 years who are not known to have CVD or to be at clinically determined high risk, the Framingham Risk Equation may be used to estimate CVD risk over the next five years. Although the Framingham Risk Equation might underestimate risk in this population, available evidence suggests that this approach will provide an estimate of minimum cardiovascular risk. (CBR)
c) Aboriginal and Torres Strait Islander adults aged over 74 years should be considered as being at high CVD risk. (CBR)

Q5. Which absolute risk assessment method is most predictive of future CVD events in adult (aged >18) people with chronic kidney disease (eGFR <45ml/min1.73 m^2) not known to have CVD?

No further studies located. Nil previous studies identified.

4. Aims of treatment, monitoring and follow up (Q6-8)

Search results

The following table summarises the results of the search.

Sources	Dates	Total hits	Retrieval list	Final inclusions
Databases: Medline; Embase ; Cinahl; PsychINFO Cochrane Library, including CENTRAL Cochrane Controlled Trial Register (CCTR) **Other sources:** pearling; expert working group.	**2002-2010**	**138**	**31**	**(Q6) 18** **(Q7 and 8) 13** (note this was a narrative review from a systematic search)
Search terms:	multiple intervention, single intervention/treatment, monitor, cardiovascular, primary prevention, risk factors, compliance, adherence, absolute risk, side effects.			

Question 6 Summary

Question: Is there evidence that multiple risk intervention is more effective in reducing CVD events and all cause mortality than intervention on single risk factors?
NOTE: evidence to be systematically identified but used in narrative review (rather than comprehensive critical appraisal and summary process) to form important part of main body of guidelines
Two main areas in the literature were identified that address this question:

1. **Lifestyle change approaches** which use education/ counselling/intensive intervention to seek to change behaviours regarding diet, exercise, smoking and weight, and to a lesser extent, compliance with hypertension and dyslipidaemia medication regimes: low effectiveness on CVD/all cause mortality, small effect on risk factors
2. **Pharmacological approaches** that address lipid lowering and hypertension risk factors simultaneously: high effectiveness (BP and lipid goals, Framingham risk reduction). But results limited by short term trials, with no information on CVD or all cause mortality.

SECTION 1: Effectiveness of lifestyle change interventions which address multiple risk factors

This has been examined in a Cochrane review (Ebrahim 2006), which examined 39 RCTs published up to 2001. The interventions under investigation were educational /counseling based, with or without pharmacological treatments, which aimed to reduce more than one cardiovascular risk factor (i.e. blood pressure, smoking, total

blood cholesterol, physical activity, diet). Trials duration was at least 6 months. The study population included adults > 40 years of age without evidence of cardiovascular disease.
Risk of bias: allocation methods not reported in smaller trials. Outcome measures often assessed with knowledge of allocation. Few trials provided sufficient detail for interventions to be replicated. No intention to treat analyses.
Large heterogeneity between trials due to differences in the use of both antihypertensive and cholesterol-lowering drugs, and the populations studied.

Outcomes:
total mortality (results from 10 trials) pooled odds ratio of 0.96 (95% CI 0.92 to 1.01) favouring intervention. Trials in hypertensive patients were significant contributors to this result
coronary disease mortality (results from 10 trials) 0.96 (95% CI 0.89 to 1.04) favouring intervention
blood pressure: (38 interventions)Systolic blood pressure change, weighted mean difference between intervention and control was -3.6 mm Hg (95% CI -3.9 to -3.3) in fixed effect analysis. For diastolic blood pressure the weighted mean difference was -2.8 mm Hg (95% CI -2.9 to -2.6).
blood cholesterol: Difference -0.07 mmol/L, 95% CI -0.08 to -0.06 mmol/L. Likely reflects increased use of cholesterol lowering medication.
Smoking prevalence: overall net reduction of 24%. However, most were self reports of smoking status, validated objectively in only 3 trials.

Summary: These interventions were ineffective in improving all cause or CVD mortality. Changes in risk factors (blood pressure, cholesterol, smoking) were modest, and likely overestimated due to lack of intention to treat analysis and self report assessment (smoking).

The authors suggest that individual/family based counseling/educational interventions to the general population/people at low risk of CVD are ineffective. They suggest a more effective approach may be “health protection” using fiscal and legislative change to reduce smoking, dietary consumption of fats, “hidden” salt and calories, and increase facilities and opportunities for exercise. They especially caution against exporting a “health promotion” approach supported by insufficient evidence to developing countries where a “health protection” approach may be better indicated. However, no evidence is provided to support this argument.

NOTE: this Cochrane review was updated and published in 2011. This summary was added by the NSF project team. Sixteen additional trials were included (total of 55). Fourteen trials (139,256 participants) with reported clinical event endpoints, the pooled ORs for total and CHD mortality were 1.00 (95% CI 0.96 to 1.05) and 0.99 (95% CI 0.92 to 1.07), respectively. Total mortality and combined fatal and non-fatal cardiovascular events showed benefits from intervention when confined to trials involving people with hypertension (16 trials) and diabetes (5 trials): OR 0.78 (95% CI 0.68 to 0.89) and OR 0.71 (95% CI 0.61 to 0.83), respectively. Marked heterogeneity (I2 > 85%) for all risk factor analyses was found.

Authors' conclusions
“Interventions using counselling and education aimed at behaviour change do not reduce total or CHD mortality or clinical events in general populations but may be effective in reducing mortality in high-risk hypertensive and diabetic populations. Risk factor declines were modest but owing to marked unexplained heterogeneity between trials, the pooled estimates are of dubious validity. Evidence suggests that health promotion interventions have limited use in general populations.”

Three more recent RCTs were identified. Two were intensive group based interventions to address lifestyle factors (Folta 2009 and Erikson 2009), while the other used motivational interviewing based on an absolute risk profile (Wister 2007). While the latter study demonstrated a small difference compared with control in Framingham 10 year risk profile, effects on risk factors (BP, cholesterol, smoking) were generally modest where they occurred at all.

study	population	outcomes: Intervention v control risk factors	outcomes: absolute risk, mortality
Strong Women, Healthy Hearts Folta 2009	Rural, sedentary, overweighty/obese women N=96, Intervention=61 Control=35 Lost to follow up =11 12 week intervention	**body weight** (-2.1 kg; 95% CI =-3.2, -1.0) **waist circumference** (-2.3 in; 95%CI =-4.2, -0.5) **energy intake** (-390 kcal/day; 95% CI=-598, -183) **increase in activity** (+1637 steps/day; 95% CI =712, 2562)	None reported
Intervention: 2x1 hour classes/week for 12 weeks. 30 mins mod-vig physical activity. Behaviour change strategies to promote physical activity. Didactic, hands-on and behavior change strategies to improve intake and weight			

study	population	outcomes: Intervention v control risk factors	outcomes: absolute risk, mortality
Simon Fraser Heart Health Report Card System Wister 2007	Primary prevention group (Fram 10 year risk 10% or less) n=315 45-64 years old intervention (157) control (158) groups. 1 year outcomes in n=278 **1 year intervention**	Significant differences between intervention and control in **systolic BP** intervention: –7.49 (–9.97 to –5.01) control: –3.58 (–6.08 to –1.08) **total cholesterol** (mmol/L) intervention: –0.41 (–0.59 to –0.23) control: –0.14 (–0.32 to 0.04	**Framingham 10 year risk:** significantly greater change baseline-1 year in intervention –3.10, 95% CI –3.98 to –2.22 than control –1.30, 95% CI –2.18 to –0.42 (adjusted for covariates)
Intervention: uses Framingham risk scoring methodology to measure global cardiovascular risk levels and to identify targets, which are then distributed in an annual report card to participants and their physicians. Coupled with evidence-based prevention knowledge aimed at motivating participants to change their risk factors through a Telehealth counselling approach(motivational interviewing). Initial telehealth counselling occurred within 10 days of the patient receiving the annual report card and every 6 months thereafter for approximately 30 minutes per session. Smokers prepared to quit received additional 20- to 30-minute sessions at 2, 4, 8 and 12 weeks.			

study	population	outcomes: Intervention v control risk factors	outcomes: absolute risk, mortality
Bjorknas study Erikson 2009	N=151 Intervention (75)	Differences between intervention and control: **waist circumference**(-2.2 cm), waist-hip ratio (-0.02)	Not assessed

	control(76) Moderate-high risk of CVD 120(80%) completed 3 year follow-up **3 year intervention**	**systolic BP** (24.9 mmHg), and diastolic BP (21.6 mmHg) **smoking cessation**: proportion of individuals who quit smoking in the intervention group was greater than in the control group	
Intervention: The first three months of the intervention included three sessions per week of supervised progressive exercise training and diet counselling on a total of five occasions. Small group (10-13) sessions in a primary care setting. Participants subsequently invited to attend sessions 6x in first year, 4x in 2nd year and 2x in 3rd year. These sessions to encourage behavior change (stages of change and social support).			

None of the lifestyle interventions which addressed multiple risk factors compared results with addressing a single risk factor only, so no direct information was found to address this question.

SECTION 2: Pharmacological approaches that address lipid lowering and hypertension risk factors simultaneously

Co-administration of antihypertensive and lipid lowering therapy

There is robust evidence on the efficacy of using medication to reduce both blood pressure and cholesterol to target levels.

Studies have evaluated the co-administration of amlodipine and atorvastatin, and found the same or better effectiveness from simultaneously administering both drugs, compared with a single drug only.

The AVALON trial (Messerli 2006) compared co-administration of amlodipine and atorvastatin, with the single drug therapy, and placebo. At Week 8 (n=847 patients), 45% of the patients receiving amlodipine 5 mg and atorvastatin 10 mg reached both their blood pressure and low-density lipoprotein cholesterol goals, compared with 8.3% with amlodipine ($p < 0.001$), 28.6% with atorvastatin ($p < 0.001$), and 3.5% with placebo. At 28 weeks, 67.1% of patients coadministered amlodipine and atorvastatin (mean doses, 7.6 mg and 28.4 mg, respectively) achieved both targets. Framingham estimated 10-year risk of coronary heart disease declined from baseline levels of 15.1% to 6.9% at Week 28 in this group.

In the RESPOND trial (Preston 2007) of hypertensive patients with dyslipidaemia, the use of amlodipine and atorvastatin together did not differ from the efficacy achieved with each medication alone. Framingham risk with combination therapy declined from baseline values of 15.8-18.0% to 7.3%-10.7% .

In the ASCOT-LLA study (Sever 2006), patients who had received atorvastatin(10mg once daily) or placebo in addition to their antihypertensive routine over 3.3 years. The relative risk of non-fatal MI and fatal CHD was reduced by 36% in the group receiving combination drug therapy, compared with the group receiving placebo plus antihypertensive therapy.

Single pill combination of amlodipine and atorvastatin

However, control of hypertension and dyslipidaemia reported to be poor; in a population of 154,235 patients managed care patients, 90% were not meeting target guidelines for both criteria (Petitt 2003). The issues of non-adherence with poly pharmacy routines might be lessened with the use of a single pill.

Clinical trials (comparative and non-comparative) have been conducted to evaluate the effectiveness of a single pill which combines the antihypertensive amlodipine with the cholesterol lowering drug atorvastatin. Included patient populations had hypertension and high LDL at baseline.

study	population	Size and duration	intervention	Patients achieving both BP and LDL-C goals	Framingham 10 year CHD risk score reduction
GEMINI Blank 2005	US. Hypertension and concurrent dyslipidaemia	N=1220 14 weeks	amlodipine–atorvastatin vs placebo	57.7%	Not assessed
GEMINI AALA Erdine 2009	27 countries in Asia, Africa, Middle east, Latin America	N=1649 14 weeks	amlodipine–atorvastatin vs placebo	55.2%	51.6%
JEWEL I JEWEL II Hobbs 2006	UK, Canada European countries	N=2245 16 weeks	amlodipine–atorvastatin vs placebo	55.5%	29-52%
CAPABLE Flack 2008	African Americans	N=499 20 weeks	amlodipine–atorvastatin vs placebo	48.3%	50%

Adverse effect s or side effects of the combination pill appear to be similar in nature, severity and frequency to those seen with amlodipine or atorvastatin administered alone. The combined medication was well tolerated during these clinical trials in patients with hypertension and dyslipidaemia (Devabhaktuni 2009).

References

Blank R, LaSalle J, Reeves R, Maroni J, Tarasenko L, Sun F. Single-pill therapy in the treatment of concomitant hypertension and dyslipidemia (the amlodipine/atorvastatin gemini study). *J Clin Hypertens (Greenwich)*. 2005;7(5):264–273.

Devabhaktuni M, Bangalore S.Fixed combination of amlodipine and atorvastatin in cardiovascular risk management: patient perspectives. Vasc Health Risk Manag. 2009;5(1):377-87

Ebrahim S, Beswick A, BurkeM,Davey Smith G. Multiple risk factor interventions for primary prevention of coronary heart disease. *Cochrane Database of Systematic Reviews* 2006, Issue 4. Art. No.: CD001561. DOI: 10.1002/14651858.CD001561.pub2.

Erdine S, Ro YM, Tse HF, et al; Gemini-AALA Investigators. Singlepill amlodipine/atorvastatin helps patients of diverse ethnicity attain recommended goals for blood pressure and lipids (the Gemini-AALA study). *J Hum Hypertens*. 2009;23(3):196–210.

Eriksson MK, Franks PW, Eliasson M. A 3-year randomized trial of lifestyle intervention for cardiovascular risk reduction in the primary care setting: the Swedish Björknäs study. PLoS One. 2009;4(4):e5195. Epub 2009 Apr 14.

Flack JM, Victor R, Watson K, et al. Improved attainment of blood pressure and cholesterol goals using single-pill amlodipine/atorvastatin in African Americans: the CAPABLE trial. *Mayo Clin Proc*. 2008;83(1):35–45.

Folta, Sara C.. Lichtenstein, Alice H.. Seguin, Rebecca A.. Goldberg, Jeanne P.. Kuder, Julia F.. Nelson, Miriam E The StrongWomen-Healthy Hearts Program: Reducing Cardiovascular Disease Risk Factors in Rural Sedentary, Overweight, and Obese Midlife and Older Women American Journal of Public Health. Jul 2009. Vol. 99, No. 7. p. 1271-1277

Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*.2002;360(9326):7–22.

Hobbs FD, Gensini G, Mancini GB, et al. Can combining different risk interventions into a single formulation contribute to improved cardiovascular disease risk reduction? Rationale and design for an international, open-label program to assess the effectiveness of a single pill (amlodipine/atorvastatin) to attain recommended target levels for blood pressure and lipids (The JEWEL Program). *Int J Cardiol*. 2006;110(2):242–250.

Messerli FH, Bakris GL, Ferrera D, et al. Efficacy and safety of coadministered amlodipine and atorvastatin in patients with hypertension and dyslipidemia: results of the AVALON trial. *J Clin Hypertens (Greenwich)*. 2006;8(8):571–581; quiz 582–583.

Pettitt D, Karter AJ, Peng TY, et al. The impact of concurrent dyslipidemia and diabetes on hypertension management and goal attainment. Vancouver, Canada: Poster presentation at the 26th Annual Meeting of the Society of General Internal Medicine; 2003.
Preston RA, Harvey P, Herfert O, et al. A randomized, placebo-controlled trial to evaluate the efficacy, safety, and pharmacodynamic interaction of coadministered amlodipine and atorvastatin in 1660 patients with concomitant hypertension and dyslipidemia: the respond trial. *J Clin Pharmacol*. 2007;47(12):1555–1569.

Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*. 2003;361(9364): 1149–1158.

Sever P, Dahlof B, Poulter N, et al. Potential synergy between lipid-lowering and blood-pressure-lowering in the Anglo-Scandinavian Cardiac Outcomes Trial. *Eur Heart J*. 2006;27(24):2982–2988.

Turnbull F. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet*. 2003;362(9395):1527–1535.

Wister A, Loewen N, Kennedy-Symonds H, McGowan B, McCoy B, Singer J One-year follow-up of a therapeutic lifestyle intervention targeting cardiovascular disease risk. CMAJ. 2007 Oct 9;177(8):859-65.

Question 7 & 8 Summary

Question 7. What evidence exists to support the benefit of monitoring treatment effects? Report evidence for secondary outcomes defined as:

- **AR levels**
- **Individual risk factor levels**
- **Side effects**
- **Compliance with treatment.**

Question 8. Do strategies to promote concordance with medication reduce the risk of CVD?

NOTE: as for Q6 evidence to be systematically identified but used in narrative review to form important part of main body of guidelines. These two questions were considered together.

Summary

There is some evidence to support the use of monitoring – particularly for individual risk factors and for compliance. The literature to support the promotion of concordance with medication is by and large the same and either reports better effects for individual risk factors or in some instances reduced overall CVD risk.

The literature reports several methods for monitoring adherence and compliance with pharmacological interventions in terms of effect (eg BP or lipid levels) – methods include self-monitoring, tele-monitoring, individualised and longitudinal care, education, risk checks, counselling, simplified regimens, reminder systems. Other studies report the negative health results of poor compliance (either by the practitioner in not following guideline targets or the person being treated) – one systematic review confirms that NOT monitoring contributes to poor adherence and worse outcomes.

References	Summary
McManus RJ, Mant J, Bray EP, Holder R, Jones MI, Greenfield S, Kaambwa B, Banting M, Bryan S, Little P, Williams B, Hobbs FR. *Telemonitoring and self-management in the control of hypertension (TASMINH2): a randomised controlled trial*. Lancet. 2010 Jul 17;376(9736):163-172. Epub 2010 Jul 8 Primary Care Clinical Sciences, University of Birmingham and National Institute for Health Research (NIHR) National School for Primary Care Research, Birmingham, UK.	RCT Intervention: Combination of self and tele-monitoring of BP (self-monitoring of blood pressure and self-titration of antihypertensive drugs, combined with tele-monitoring of home blood pressure measurements versus usual care) Results: Greater reduction in BP levels compared to usual care, no difference in side effects
Bates TR, Connaughton VM, Watts GF. *Non-adherence to statin therapy: a major challenge for preventive cardiology*. Expert Opin Pharmacother. 2009 Dec;10(18):2973-85. University of Western Australia, Royal Perth Hospital, Lipid Disorders Clinic, Department of Internal Medicine, Australia.	SR Results: Lack of monitoring and other factors contribute to poor adherence to statin therapy and therefore worse outcomes (lipid levels and CVD events)
Berra K, Ma J, Klieman L, Hyde S, Monti V, Guardado A, Rivera S, Stafford RS. *Implementing cardiac risk-factor case management: lessons learned in a county health system.* Crit Pathw Cardiol. 2007 Dec;6(4):173-9 Program on Prevention Outcomes and Practices, Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, CA 94305-5705, USA.	RCT Results: Case-management (CM) can positively influence chronic disease care (including cardiovascular risk reduction) by facilitating guideline-concordant interventions that improve outcomes through intensive, individualized, longitudinal care.
García-Ortiz L, Gómez-Marcos MA, González-Elena LJ, Maderuelo-Fernández JA,Ramos-Delgado E, Torrecilla-Garcia M. *Cardiovascular risk of hypertensive people with long-range monitoring. The effect of aging (Ciclo Risk Study)* Rev Esp Salud Publica. 2007 Jul-Aug;81(4):365-73.	Longitudinal study Results: Ageing may mask the effect achieved by health care in the absolute cardiovascular risk check. The relative risk could be an alternative for monitoring the follow-up.
Green BB, Ralston JD, Fishman PA, Catz SL, Cook A, Carlson J, Tyll L, Carrell D, Thompson RS. *Electronic communications and home blood pressure monitoring (e-BP) study: design, delivery, and evaluation framework*. Contemp Clin Trials. 2008 May;29(3):376-95. Epub 2007 Sep 26. Group Health Permanente, Seattle, WA, USA. green.b@ghc.org	RCT . Electronic communications and home blood pressure monitoring (e-BP) study: design, delivery, and evaluation framework. Results: Not available
Leal Hernández M, Abellán Alemán J, Ríos Cano EJ, Martínez Crespo J, Sebastián Vicente B, Vicente Martínez R. *Information on cardiovascular risk in hypertense patients*	Clinical trial Results: Informing people of their CVD risk and following up had

monitored in primary care. Does it improve our efficacy? Aten Primaria. 2006 Jun 30;38(2):102-6. Universidad Católica de Murcia, España. mlealh@papps.org	significant benefits in reducing their FRE if they were in the high risk group – the effect was not significant in the low and medium risk groups
Ogedegbe G, Schoenthaler A. *A systematic review of the effects of home blood pressure monitoring on medication adherence.* J Clin Hypertens (Greenwich). 2006 Mar;8(3):174-80. Behavioral Cardiovascular Health and Hypertension Program, Columbia University College of Physicians and Surgeons, New York, NY 10032, USA. goo1@columbia.edu	SR, 11 RCTs, Intervention: Effects of home blood pressure monitoring on medication adherence. Results: Six of the 11 randomized controlled trials reported statistically significant improvement in medication adherence; 84% of these were complex interventions involving the use of HBPM in combination with other adherence-enhancing strategies such as patient counselling by nurses, pharmacists, or a telephone-linked system; patient education; and the use of timed medication reminders. Interventions conducted in primary care settings were not effective compared with those that occurred in hospital-based clinics or nonclinical settings.
Greenlund KJ, Denny CH, Mokdad AH, Watkins N, Croft JB, Mensah GA. *Using behavioral risk factor surveillance data for heart disease and stroke prevention programs.* Am J Prev Med. 2005 Dec;29(5 Suppl 1):81-7. Cardiovascular Health Branch, Division of Adult and Community Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia 30341, USA. keg9@cdc.gov	Used behavioural risk factor surveillance data for heart disease and stroke prevention programs. Results: Not available
Rabinowitz I, Tamir A. *The SaM (Screening and Monitoring) approach to cardiovascular risk-reduction in primary care--cyclic monitoring and individual treatment of patients at cardiovascular risk using the electronic medical record.* Eur J Cardiovasc Prev Rehabil. 2005 Feb;12(1):56-62. Clalit Heath Services and the Department of Family Medicine, Haifa, Israel. Raly@netvision.net.il	Observational study Intervention: Screening and Monitoring approach to cardiovascular risk-reduction in primary care--cyclic monitoring and individual treatment of patients at cardiovascular risk using the electronic medical record. Results: Reduced risk factors significantly
Schroeder K, Fahey T, Ebrahim S. *Interventions for improving adherence to treatment in patients with high blood pressure in ambulatory settings.* Cochrane Database of Systematic Reviews 2004, Issue 3. Art. No.: CD004804. DOI: 10.1002/14651858. CD004804. Schedlbauer A, Davies P, Fahey T. *Interventions to improve adherence to lipid lowering medication.* Cochrane Database of Systematic Reviews 2010, Issue 3. Art. No.: CD004731. DOI: 10.1002/14651858. CD004371.pub3.	Cochrane reviews Results: Reminders, simplifying regimens, education all improve adherence to BP and lipid lowering medication and therefore treatment effects.
Van Ganse E. Souchet T. Laforest L. Moulin P. Bertrand M. Le Jeunne P. Chretin S. Yin D. Alemao E. de Pouvourville G. *Long-term achievement of the therapeutic objectives of lipid-lowering agents in primary prevention patients and cardiovascular outcomes: an observational study*. Ovid MEDLINE(R) Atherosclerosis. 185(1):58-64, 2006 Mar. [Comparative Study. Journal Article. Randomized Controlled Trial. Research Support, Non-U.S. Gov't] UI: 16038912	Observational study Results: Failure to attain therapeutic objectives in lipid management increased the risk of CVD events

Gumbs P.D., Verschuren, V.M, Mantel-Teeuwisse, A.K., de Wit, A.G., Hofman, A., Trienekens, P.H., Stricker, B, de Boer, A., and Klungel, O.H. *Drug Costs Associated with Non-Adherence to Cholesterol Management Guidelines for Primary Prevention of Cardiovascular Disease in an Elderly Population – The Rotterdam Study*. Drugs Aging, 2006; 23 (9_: 733-741 1170-229X/06.0009-0733.	Report the costs of under treatment in lipid control in the Netherlands (ie not treating to guidelines)

5. Blood pressure lowering (Q9-13)

Search results

Sources	Dates	Total hits	Retrieval list	Final inclusions
Databases: Medline; Embase ; Cinahl; PsychINFO Cochrane Library, including CENTRAL Cochrane Controlled Trial Register (CCTR) **Other sources:** pearling; expert working group.	**2002-2010**	**3090**	**42+4**	**21** Agarwal 2009 Arguedas 2009 Bramlage 2009 Chalmers 2004 Heerspink 2009 Howard 2008 Kojada 2008 Law 2009 Musini 2009 Ostergrem 2008 Ruilope 2004 Staessen 2004 Strippoli 2005 Strippoli 2006 Turnbull 2005, 2008 Wang 2005 Webb 2010 Weber 2010 Wright 2009 Zanchetti 2009
Search terms:	Blood Pressure; Antihypertensive Agents; Adrenergic beta-Antagonists; DIURETICS; Angiotensin-Converting Enzyme Inhibitors Receptors, Angiotensin; Angiotensin II Type 1 Receptor Blockers Calcium Channel Blockers; lower$ adj2 blood pressure$;centrally acting agents; alpha blockers			

Literature included

Question 9. Does pharmacological blood pressure lowering reduce CVD events and all cause mortality?	
References	**Comments / Quality**
Agarwal R, Sinha AD. Cardiovascular protection with antihypertensive drugs in dialysis patients: systematic review and meta-analysis. *Hypertension*. 2009; 53: 860-6.	Moderate quality SR. CKD patients on dialysis.
Blood pressure trialists Collaboration; Turnbull F et al. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet*. 2003; 362: 1527-35.	High quality SR. Individual patient data. Mix of primary and secondary prevention. Included in SIGN.
Blood pressure trialists Collaboration; Turnbull F, Neal B, Algert C, Chalmers J, Chapman N, Cutler J*, et al.* Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Arch Intern Med*. 2005; 165: 1410-9.	Good quality SR. Mix of primary and secondary prevention.
Blood pressure trialists Collaboration; Turnbull F, Neal B, Ninomiya T, Algert C, Arima H, Barzi F*, et al.* Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *BMJ*. 2008; 336: 1121-3.	Good quality SR. Mix of primary and secondary prevention.
Heerspink H.J.L. Ninomiya T. Zoungas S. de Zeeuw D. Grobbee D.E. Jardine M.J. Gallagher M. Roberts M.A. Cass A. Neal B. Perkovic V. Effect of lowering blood pressure on cardiovascular events and mortality in patients on dialysis: a systematic review and meta-analysis of randomised controlled trials. The Lancet. 2009. 373(9668) (pp 1009-1015).	High quality SR. People with CKD
Law, M., Morris, J., Wald, N. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ (2009); 338; 1245-1261.	High quality SR. Included primary and secondary trials and cohort studies.
Strippoli GF, Craig M, Craig JC. Antihypertensive agents for preventing diabetic kidney disease. Cochrane Database Syst Rev. 2005: CD004136.	High quality SR.
Strippoli GF, Bonifati C, Craig M, Navaneethan SD, Craig JC. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. Cochrane Database Syst Rev. 2006: CD006257.	High quality SR.
Wang, J., Staessen, S., Franklin, S., Fagard, R., Gueyffier, F. Systolic and Diastolic Blood Pressure Lowering as Determinants of Cardiovascular Outcome. Hypertension, 2005; 45(5); 907-913.	Good quality SR. Does not discuss specific treatments to reduce BP. Indication that a range of drugs were used.
Webb A.J. Fischer U. Mehta Z. Rothwell P.M. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. The Lancet. 375(9718)(pp 906-915), 2010.	High quality SR. Specific to stroke outcomes. Mix of primary and secondary prevention.

Wright J, Musini V. First-line drugs for hypertension. Cochrane Database of Systematic Reviews 2009, Issue 3. Art No.: CD001841.DOI: 10.1002/14651858. CD001841.pub2.	High quality SR.

Question 10. What is the evidence for one blood pressure lowering drug class or any combination of drug classes being more effective than any other blood pressure lowering drug class or combination for reducing CVD events and all cause mortality?	
References	**Comments / quality**
Blood pressure trialists Collaboration; Turnbull F et al. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet*. 2003; 362: 1527-35.	High quality SR. Individual patient data. Mix of primary and secondary prevention. Included in SIGN.
Blood pressure trialists Collaboration; Turnbull F, Neal B, Algert C, Chalmers J, Chapman N, Cutler J*, et al.* Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Arch Intern Med*. 2005; 165: 1410-9.	Good quality SR. Mix of primary and secondary prevention.
Blood pressure trialists Collaboration; Turnbull F, Neal B, Ninomiya T, Algert C, Arima H, Barzi F*, et al.* Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *BMJ*. 2008; 336: 1121-3.	Good quality SR. Mix of primary and secondary prevention.
P Bramlage, J Hasford. Blood pressure reduction, persistence and costs in the evaluation of antihypertensive drug treatment – a review, 2009, Cardiovascular Diabetology 8:18	Low quality SR with risk of bias.
J Chalmers Comparison of Various Blood Pressure Lowering Treatments on the Primary Prevention of Cardiovascular Outcomes in Recent Randomised Clinical Trials, 2004, CLINICAL AND EXPERIMENTAL HYPERTENSION Vol. 26, Nos. 7 & 8, pp. 709–719	Moderate quality SR. Poor reporting of methods.
Michel Komajda, Paula Curtis, Markolf Hanefeld, Henning Beck- Nielsen, Stuart J Pocock, Andrew Zambanini, Nigel P Jones, Ramon Gomis, Philip D Home. Effect of the addition of rosiglitazone to metformin or sulfonylureas versus metformin/sulfonylurea combination therapy on ambulatory blood pressure in people with type 2 diabetes: A randomized controlled trial (the RECORD study) Cardiovascular Diabetology 2008, 7:10	Good quality RCT. Diabetes specific.
Law, M., Morris, J., Wald, N. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ (2009); 338; 1245-1261	High quality SR. Included primary and secondary trials and cohort studies.
MUSINI, V. M., WRIGHT, J. M., BASSETT, K. & JAUCA, C. D. (2009) Blood pressure lowering efficacy of loop diuretics for primary hypertension. *Cochrane Database Syst Rev***,** CD003825.	High quality SR. Surrogate outcomes.
OSTERGREN, J., POULTER, N. R., SEVER, P. S., DAHLOF, B., WEDEL, H., BEEVERS, G., CAULFIELD, M., COLLINS, R., KJELDSEN, S. E., KRISTINSSON, A., MCINNES, G. T., MEHLSEN, J., NIEMINEN, M. & O'BRIEN, E. (2008) The Anglo-Scandinavian Cardiac Outcomes Trial: blood pressure-lowering limb: effects in patients with type II diabetes. *J Hypertens,* 26**,** 2103-11.	Subanalysis of good quality RCT. Specific to diabetes

Staessen, J., Li, Y., Thijs, L., Wang, J. Blood Pressure Reduction and Cardiovascular Prevention: An Update Including the 2003-2004 Secondary Prevention Trials. Hypertension Research 2005; 28(5); 385-407	Moderate quality SR. Mix primary and secondary prevention.
Strippoli GF, Craig M, Craig JC. Antihypertensive agents for preventing diabetic kidney disease. Cochrane Database Syst Rev. 2005: CD004136.	High quality SR.
Strippoli GF, Bonifati C, Craig M, Navaneethan SD, Craig JC. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. Cochrane Database Syst Rev. 2006: CD006257.	High quality SR.
Webb A.J. Fischer U. Mehta Z. Rothwell P.M. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. The Lancet. 375(9718)(pp 906-915), 2010.	High quality SR. Specific to stroke outcomes. Mix of primary and secondary prevention.
Weber MA, Bakris GL, Jamerson K, Weir M, Kjeldsen SE, Devereux RB*, et al.* Cardiovascular events during differing hypertension therapies in patients with diabetes. *J Am Coll Cardiol*. 2010; 56: 77-85.	Subgroup analysis (diabetes) of good quality RCT (ACCOMPLISH). 41% had preexisting CVD.
Wright J, Musini V. First-line drugs for hypertension. Cochrane Database of Systematic Reviews 2009, Issue 3. Art No.: CD001841.DOI: 10.1002/14651858. CD001841.pub2.	High quality SR.

Question 11. Should blood pressure therapy be initiated with a single drug or with a combination?	
References	**Comments / quality**
Law, M., Morris, J., Wald, N. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ (2009); 338; 1245-1261	High quality SR. Included primary and secondary trials and cohort studies.
J Chalmers Comparison of Various Blood Pressure Lowering Treatments on the Primary Prevention of Cardiovascular Outcomes in Recent Randomised Clinical Trials, 2004, CLINICAL AND EXPERIMENTAL HYPERTENSION Vol. 26, Nos. 7 & 8, pp. 709–719	Moderate quality SR. Poor reporting of methods.

Question 12. Should antihypertensive therapy employ drugs at fixed doses or should individuals always be titrated to target blood pressure levels?	
References	**Comments / quality**

Arguedas J, Perez M, Wright J. Treatment blood pressure targets for hypertension. Cochrane Database of Systematic Reviews 2009, Issue 3. Art No.: CD004349.DOI: 10.1002/14651858. CD004349.pub2.	High quality SR.
Law, M., Morris, J., Wald, N. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ (2009); 338; 1245-1261	High quality SR.
Staessen, J., Li, Y., Thijs, L., Wang, J. Blood Pressure Reduction and Cardiovascular Prevention: An Update Including the 2003-2004 Secondary Prevention Trials. Hypertension Research 2005; 28(5); 385-407	Moderate quality SR. Mix primary and secondary prevention.

Question 13. Does more intensive blood pressure lowering produce greater reductions in CVD events and all cause mortality?	
References	**Comments / quality**
Arguedas J, Perez M, Wright J. Treatment blood pressure targets for hypertension. Cochrane Database of Systematic Reviews 2009, Issue 3. Art No.: CD004349.DOI: 10.1002/14651858. CD004349.pub2.	High quality SR.
Howard et al Effect of Lower Targets for Blood Pressure and LDL Cholesterol on Atherosclerosis in Diabetes The SANDS Randomized Trial, 2008 Journal of American Medical Association, April 9, 2008—Vol 299, No. 14	Good quality RCT. Diabetic population
Law, M., Morris, J., Wald, N. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ (2009); 338; 1245-1261	High quality SR. Included primary and secondary trials and cohort studies.
Ruilope LM, Usan L, Segura J, Bakris GL. Intervention at lower blood pressure levels to achieve target goals in type 2 diabetes: PRADID (PResión Arterial en DIabéticos tipo Dos) study. J Hypertens. 2004 Jan;22(1):217-22.	Good quality RCT. Diabetic population
Zanchetti, B. Bottom blood pressure or bottom cardiovascular risk? How far can cardiovascular risk be reduced? Journal of Hypertension, 2009; 27(8);1509	Low quality SR with risk of bias.

Evidence details

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS

Guideline topic: Blood Pressure		**Question number:** 9	
Characteristics of study			
Checklist completed by: KH			
Study citation	Agarwal R, Sinha AD. Cardiovascular protection with antihypertensive drugs in dialysis patients: systematic review and meta-analysis. Hypertension. 2009; 53: 860-6.		
Study design	**Systematic review**	**N (total)**	5 trials (1202 patients)
Search strategy	Pubmed (Jan 1996 to Oct 2008) and EMBASE database and The Cochrane Central Register of Controlled Trials (3rd Quarter 2008). The terms "hypertension" and "dialysis" were searched in the title, original title, abstract, MESH headings, heading words and keyword. The result was limited to randomized controlled trials using a highly sensitive filter. Manually reviewed references cited in the retrieved articles and review articles. Also searched the proceedings of the American Society of Nephrology and European Dialysis and Transplantation Association to retrieve unpublished studies.		
Selection criteria	To be included in this review, studies had to randomize hemodialysis patients to antihypertensive drugs regardless of the presence or absence of hypertension and reported cardiovascular and/or mortality outcomes.		
Intervention	antihypertensive therapy		
Comparison	Placebo or control		
Outcomes	The overall benefit of antihypertensive therapy compared to control or placebo group had a combined hazard ratio for cardiovascular events of 0.69 (95% CI 0.56 to 0.84) using a fixed effects model and 0.62 (95% CI 0.44 to 0.88) using a random effects model. In a sensitivity analysis we found that the hypertensive group had a pooled hazard ratio of 0.49 (95% CI 0.35 to 0.67), but when normotensives were included in the trial lesser cardiovascular protection was seen (pooled hazard ratio of 0.86 (95% CI 0.67 to 1.12)). Test for herterogenity between hypertensive and "normotensive-included" groups was significant ($p<0.006$). Similar results were seen for risk ratio for death and cardiovascular events. There was evidence of publication bias based on Egger's test and funnel plot. Randomized trials suggest benefit of antihypertensive therapy among hemodialysis patients.		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		Y	Well covered
Description of the methodology used is included		Y	Well covered
The literature search was sufficiently rigorous to identify all the relevant studies		Adequate	Only included trials since 1996
Study quality was addressed and taken into account?		N	
There were enough similarities between the studies to justify combining them.		Y	
SECTION 2: Overall assessment of the study			

How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
	+	+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?	No consideration to study quality may bias results to be more positive than if quality is considered.	
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		
Moderate quality review without discussion on study quality. Relatively small number and size of trials and publication bias noted.		

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Blood Pressure		**Question number:** 12, 13	
Characteristics of study			
Checklist completed by: SH			
Study citation	Arguedas J, Perez M, Wright J. Treatment blood pressure targets for hypertension. Cochrane Database of Systematic Reviews 2009, Issue 3. Art No.: CD004349.DOI: 10.1002/14651858. CD004349.pub2.		
Study design	**Systematic review**	**N (total)**	7 trials; 22000 patients
Search strategy	Electronic search of Medline, Embase, Central (until June 2008); references from review articles, clinical guidelines and clinical trials.		
Selection criteria	RCTs comparing patients randomized to lower or to standard BP targets and providing data n any of the primary outcomes.		
Intervention	Blood pressure reduction drugs		
Comparison	Lower BP targets (≤ 135/85 mmHg) vs standard BP targets (≤140-160 / 90-100 mmHg)		
Outcomes	Total mortality, total serious adverse events, total CV events, MI, stroke, CHF, and end stage renal disease. Secondary outcomes were achieved decrease in systolic and diastolic BP, withdrawal due to adverse drug effects. Attempting to achieve “lower target” instead of “standard” did not change total mortality, MI, stroke, CHF, CV events or end-stage renal disease. Influence on total serious adverse events and withdrawal due to adverse effects due to lack of information.		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		Y	Well covered
Description of the methodology used is included		Y	Well covered

The literature search was sufficiently rigorous to identify all the relevant studies	Y	Well covered
Study quality was addressed and taken into account?	Y	Well covered
There were enough similarities between the studies to justify combining them.	Y	Well covered
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		
This is a rigorous Cochrane review that justifies conclusions regarding the lack of evidence to support reducing target BP levels from the current standard. Preliminary sensitivity analysis did not support lower levels for higher risk groups such as diabetic patients and patients with chronic renal disease either – these are the subject of current reviews.		

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic:		**Question number: Q10**	
Characteristics of study			
Checklist completed by: Janine			
Study citation	P Bramlage, J Hasford. Blood pressure reduction, persistence and costs in the evaluation of antihypertensive drug treatment – a review, 2009, Cardiovascular Diabetology 8:18		
Study design	**Systematic review**	**N (total)**	8 studies
Search strategy	Database – PubMed. Terms: hypertens* AND (complia*OR adhere* OR persiste*) AND (cost* OR econo*)" A manual search of the reference lists from retrieved publications was also performed.		
Selection criteria	Inclusion criteria: 1. English language, 2. involving humans, 3. published before 2008, 4. involved patients with hypertension. 5. examined compliance (adherence) and/or persistence to pharmaceutical interventions ((even if the primary objective was not to measure compliance/persistence),		

	6. provided an economic evaluation or cost analysis and 7. quantified the cost consequences of compliance/persistence. Exclusion criteria: 1. published before 1995 (results cannot be compared with recent studies due to changes in treatment patterns, study methodology and price of healthcare resources, including drug prices) 2. economic consequence of compliance/ persistence was not quantified
Intervention	Anti hypertensive drugs - Classes: 1. Thiazides 2. Beta blockers 3. ACE inhibitors 4. Angiotensin II receptor antagonists 5. Calcium channel blockers
Comparison	No treatment and those under monotherapy
Outcomes	Blood pressure. Reported adverse effects. Persistence with treatment. Cost and cost effectiveness (includes drug costs, direct costs and indirect costs) All were of similar effectiveness in BP reduction; ARBs were superior in persistence/compliance though marginally more expensive.

Quality of study		
Quality criteria (from SIGN)	***Met?**	**Comments**
SECTION 1: Internal validity		
Study addresses an appropriate and clearly focused question	WC	
Description of the methodology used is included	partly	
The literature search was sufficiently rigorous to identify all the relevant studies	Poorly addressed	Literature search was not rigorously done as the search was done in only one database, PubMed.
Study quality was addressed and taken into account?	Not addressed	Evaluation of the study design was not done as part of the methods.
There were enough similarities between the studies to justify combining them.	Poorly addressed	
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
	-	- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?	Real risk of bias issues in any direction.	

SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**
Angiotensin II receptor blockers on the average provided a better blood pressure reduction than ACE-inhibitors (net difference 1.8/1.0 mmHg), which could translate into a reduction in morbidity and mortality. This was not reported as significant. However the ARBs were taken more persistently/higher compliance and were also more expensive. Full consideration of effectiveness, compliance and cost came out in favour of ARBs. This review considered the classification of drugs and presented information on each of the classification allowing comparisons to be made. This information is helpful in answering the key question. However, the review was not made on a very robust methodology and as mentioned, the flaws may affect the general findings presented.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Blood Pressure		**Question number:Q10 & Q11**	
Characteristics of study			
Checklist completed by:			
Study citation	J Chalmers Comparison of Various Blood Pressure Lowering Treatments on the Primary Prevention of Cardiovascular Outcomes in Recent Randomised Clinical Trials, 2004, CLINICAL AND EXPERIMENTAL HYPERTENSION Vol. 26, Nos. 7 & 8, pp. 709–719		
Study design	Systematic review	**N (total)**	15 trials
Search strategy	The trials included in this paper were selected using the criteria used by the Blood Pressure Lowering Treatment s Trialists' Collaboration (BPLTTC) for comparative studies.		
Selection criteria	Criteria was based from the Blood Pressure Lowering Treatment Trialists' Collaboration which are: 1. Trials should have a minimum of 1000 patient-years of follow-up in each randomised group, 2. Should not have published or presented their main results before July 1995 when the collaboration was first established		
Intervention	Blood pressure lowering treatments		
Comparison	Differing classes versus each other or vs. placebo: ACE-inhibitor-based regimens, Calcium-antagonist-based, diuretic-based or Beta blocker-based regimens.		
Outcomes	Outcomes are: 1. stroke, defined as a non-fatal stroke or death from cerebrovascular disease 2. coronary heart disease defined as non-fatal myocardial infarction, death from coronary heart disease, or sudden death; 3. heart failure defined as heart failure causing death or requiring hospital admission		
Quality of study			
Quality criteria (from SIGN)	***Met?**	**Comments**	
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question	√	Adequately covered	

Description of the methodology used is included	Not reported	But based on Blood pressure trialists collaboration
The literature search was sufficiently rigorous to identify all the relevant studies	Not reported	But based on Blood pressure trialists collaboration
Study quality was addressed and taken into account?	Not mentioned	
There were enough similarities between the studies to justify combining them.	Not reported	
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
	-	- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?	This study did not give enough detail to fully assess its quality. Had to trace the source of the methods as it was mentioned that it was reported in a previous study. Some information was found but the actual protocol for the study has not been found yet.	
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		
"The available evidence suggests that the differences between the effects of the different classes in the primary prevention of cardiovascular outcomes, are slight and much less important than the differences between active treatment and no drug treatment. The clear exception is heart failure, since the comparative studies now available demonstrate convincingly, that calcium antagonists are less effective in the primary prevention of this condition in hypertensive subjects than the other major blood pressure lowering drugs". This review presents good results and findings but not very clear on how these were derived given that a full description of the methods was not provided.		

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS	
Guideline topic: Blood pressure	**Question:** Q9 and Q10 for high risk and CKD subgroups
Characteristics of study	
Checklist completed by: Valentin C. Dones III	
Study citation	*Hiddo J Lambers Heerspink*, *Toshiharu Ninomiya, Sophia Zoungas, Dick de Zeeuw, Diederick E Grobbee, Meg J Jardine, Martin Gallagher, Matthew A Roberts, Alan Cass, Bruce Neal, Vlado Perkovic (2009)* Effect of lowering blood pressure on cardiovascular events and mortality in patients on dialysis: a systematic review and meta-analysis of randomised controlled trials *Lancet*; 373: 1009–15

Study design	**Systematic review**	**N (total)**	8 relevant RCT
Search strategy	"renal dialysis", "kidney failure", and "cardiovascular disease" The complete search strategy is in Webappendix 3.		
Selection criteria	All RCTs assessing the effects of blood pressure lowering agents on key outcome measures in patients undergoing dialysis were included in this study. Patients receiving maintenance dialysis.		
Intervention	Taking medications that lower blood pressure (Carvedilol, Ramipril, Telmisartan, Candesartan, Fosinopril,, Amlodipine, Candesartan)		
Comparison	Conventional treatment, matched placebo		
Outcomes	Myocardial infarction, cardiovascular death, peripheral vascular disease, stroke, heart failure needing hospital admission, unstable angina, severe arrhythmia, sudden death, revascularisation, cardiac arrest, cardiomyopathy, CABG, percutaneous coronary intervention, all-cause mortality		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		Well covered	This SR aims to assess the effect of treatments that reduce blood pressure in patients receiving maintenance dialysis. It was noted that the previous trials on blood pressure lowering had excluded patients undergoing dialysis.
Description of the methodology used is included		Well covered	This SR searched the available literature using the QUORUM guidelines for the conduct of meta-analyses of intervention studies. Relevant studies were taken from Medline via Ovid, Embase, and the Cochrane Library database. Key search terms were shown. Pearling and manual search were done. The literature search, data extraction and quality assessment were done independently by two reviewers using a standardised approach.
The literature search was sufficiently rigorous to identify all the relevant studies		Well covered	Relevant studies were taken from Medline via Ovid, Embase, and the Cochrane Library database. Key search terms were shown. Pearling and manual search were done.
Study quality was addressed and taken into account?		Well covered	The literature search, data extraction and quality assessment were done independently by two reviewers by use of a standardised approach. The two reviewers extracted data on patients characteristics, follow-up duration, inclusion and exclusion, pressuring lowering agent among other variables. Any disagreements in abstracted data were resolved by a third reviewer.

There were enough similarities between the studies to justify combining them.	Well covered	All RCT studies involving patients undergoing dialysis and receiving medications for blood pressure were included in this systematic review. There were common outcome measures (i.e. myocardial infarction/cardiovascular deaths) used across the included studies. There was no strong evidence of heterogeneity of effect size among the studies of the outcomes of all-cause mortality or cardiovascular mortality.
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	**++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.**
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		
This systematic review has rigorous methodology and clear clinical aims. Though, it was mentioned also that there is a small number of studies included in this SR and full results were not obtained from all complete studies. Treatment using agents that lower blood pressure reduces cardiovascular morbidity and mortality in patients on maintenance dialysis. The effects are consistent with or without the presence of hypertension and other comorbidities and across a range of drug classes. The benefit of blood pressure lowering drugs was similar in trials that did and did not select participants on the basis of raised baseline blood pressure levels. Blood pressure lowering was well tolerated. The data suggest that renin-angiotensin-system blockers, beta-blockers and calcium-channel blockers are all suitable for use in patients on dialysis. Secondary choices include alpha-blocker and centrally acting agents. ACE inhibitors have effects that might have arisen by chance. If the data gathered in this SR were applied to a broad population of patients on dialysis with an annual mortality rate of about 10%, it is calculated that BP lower treatment could prevent two of the ten deaths expected to occur every 100 patients per year.		

METHODOLOGY CHECKLIST: RANDOMISED CONTROLLED TRIALS

Study citation (*Include author, title, year of publication, journal title, pages*) Howard et al **Effect of Lower Targets for Blood Pressure and LDL Cholesterol on Atherosclerosis in Diabetes** The SANDS Randomized Trial, 2008 Journal of American Medical Association, April 9, 2008—Vol 299, No. 14

Guideline topic:		Key Question No:	
Checklist completed by: Janine			
Section 1: Internal validity			
	Quality criteria (from SIGN)	***Met?**	**Comments**
1.1	The study addresses an appropriate and clearly focused question.	Well covered	
1.2	The assignment of subjects to treatment groups is randomised	Well covered	The urn method of randomization was used.
1.3	An adequate concealment method is used	Not addressed	
1.4	Subjects and investigators are kept 'blind' about treatment allocation	Adequately addressed	Investigators (research assistants, technicians, readers and laboratory personnel) were kept blinded to the study assignment
1.5	The treatment and control groups are similar at the start of the trial	Well covered	Baseline comparisons were computed and reported to have no meaningful differences in baseline characteristics except that mean clinic SBP was 5mmHg lower in the randomized to the aggressive group.
1.6	The only difference between groups is the treatment under investigation	Well covered	
1.7	All relevant outcomes are measured in a standard, valid and reliable way	Well covered	
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	**252 Randomized to receive aggressive treatment** 224 Completed 36-mo carotid ultrasound 235 Assessed for end-of-study systolic blood pressure 232 Assessed for end-of-study low-density liproprotein cholesterol 252 Assessed for end-of-study vital status 249 Alive 3 Died 252 analyzed **224/252 = 89% **247 Randomized to receive standard treatment** 229 Completed 36-mo carotid ultrasound 236 Assessed for end-of-study systolic blood pressure 233 Assessed for end-of-study low-density liproprotein cholesterol 247 Assessed for end-of-study vital status 242 Alive 5 Died 247 analyzed	

		**229/247 = 93%	
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)	Well covered	
1.10	Where the study is carried out at more than one site, results are comparable for all sites	Well covered	
Section 2: Overall assessment of the study			
2.1	How well was the study done to minimise bias? *Code ++, +, or -*	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
			+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
			- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
2.2	If coded as +, or - what is the likely direction in which bias might affect the study results?		
2.3	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	Yes as the methods of the research was good enough to generate believable results.	
2.4	Are the results of this study directly applicable to the patient group targeted by this guideline?		
Section 3: Description of the study (the following information is required to complete evidence tables facilitating cross-study comparisons. Please complete all sections for which information is available). Please print clearly			
3.1	Do we know who the study was funded by?	[ ] Academic Institution [ ] Healthcare Industry [x] Government [ ] NGO [ ] Public funds [ ] Other Funder: National Heart, Lung, and Blood Institute (NHLBI) grant 1U01 HL67031-01A1 and the National Institutes of Health.	
3.2	How many centres are patients recruited from?	Four (4) centres	
3.3	From which countries are patients selected? *(Select all those involved. Note additional countries after "Other")*	[ ] Scotland [ ] UK [x] USA [ ] Canada [ ] Australia [ ] New Zealand [ ] France [ ] Germany [ ] Italy [ ] Netherlands [ ] Scandinavia [ ] Spain [ ] Other:	

<table>
<tr><td>3.4</td><td>What is the social setting (ie type of environment in which they live) of patients in the study?</td><td>[ ] Urban [ ] Rural [ ] Mixed
Clinical centers in southwestern Oklahoma, Phoenix, Arizona and South Dakota</td></tr>
<tr><td>3.5</td><td>What criteria are used to decide who should be INCLUDED in the study?</td><td>Eligibility criteria included documented type 2 diabetes,31,32 plus LDL-C of at least 100 mg/dL and SBP greater than 130 mm Hg within the previous 12 months. Diabetes was based from Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997 and diagnosis and classification of diabetes mellitus provisional report of a WHO consultation 1998</td></tr>
<tr><td>3.6</td><td>What criteria are used to decide who should be EXCLUDED from the study?</td><td>Major exclusion criteria were characteristics that might preclude trial completion or confound the outcomes. These included New York Heart Association class III or IV heart failure, SBP greater than 180mmHg, liver transaminase levels more than twice the upper limit of normal, or diagnosis of primary hyperlipidemia or hypercholesterolemia due to hyperthyroidism or nephrotic syndrome.</td></tr>
<tr><td>3.7</td><td>What intervention or risk factor is investigated in the study? (Include dosage where appropriate)</td><td>The aggressive treatment group goal was LDL -C goal of 70mg/dL or lower and the mean SBP goal of 115mmHg or lower and non–HDL-C goals was 100 mg/dL or lower</td></tr>
<tr><td>3.8</td><td>What comparisons are made in the study? (ie what alternative treatments are used to compare the intervention with?). Include dosage where appropriate.</td><td>The standard treatment group goal was LDL -C goal of 100 mg/dL or lower and non–HDL-C) goals was 130 mg/dL or lower</td></tr>
<tr><td>3.9</td><td>What methods were used to randomise patients, blind patients or investigators, and to conceal the randomisation process from investigators?</td><td>The Urn method of randomization was used to allot patients in the intervention and standard groups. Investigators (research assistants, technicians, readers and laboratory personnel) were kept blinded to the study assignment of the patients. Upon assessment and reading of screening and laboratory tests, the readers did not know to which group the patients were allotted.</td></tr>
<tr><td>3.10</td><td>How long did the active phase of the study last?</td><td>3 years</td></tr>
<tr><td>3.11</td><td>How long were patients followed-up for, during and after the study?</td><td>Participants were observed from date of entry until death, loss to follow-up, request for no further contact, or completion of the study, regardless of adherence to the medication intervention</td></tr>
<tr><td>3.12</td><td>List the key characteristics of the patient population. Note if there are any significant differences between different arms of the trial.</td><td>
<table>
<tr><td>Characteristics</td><td>No. (Mean)
[95% Confidence Interval]</td><td>P</td></tr>
</table>
</td></tr>
</table>

			Treatment group	**Standard group**	***P value***
		Age, mean	55 (54-57)	57 (56-58)	.05
		Women, %	167 (66) [60-72]	160 (65) [59-71]	.73
		% Diabetes therapy Lifestyle	27 (11) [7-15]	34 (14) [10-18]	.33
		Oral hypoglycemics	206 (82) [77-87]	180 (73) [67-78]	.02
		Insulin	70 (29) [23-34]	53 (22) [17-27]	.10
		Insulin plus hypoglycemics	230 (91) [88-95]	196 (79) [74-84]	.002
		Estimated glomerular filtration rate, mL/min	246 (91) [88-94]	242 (88) [85-91]	.21
		Smoker, %	54 (22) [16-27]	48 (20) [15-24]	.58
		Aspirin use _80 mg/d, %	177 (70) [65-76]	168 (69) [63-75]	.74
3.13	Record the basic data for each arm of the study. If there are more than four arms, note data for subsequent arms at the bottom of the page				
	Arm 1: Treatment: **Aggressive** **Sample size: 252** **No. analysed: 252** **With outcome: 235** **Without outcome: 17**	**Arm 2: Treatment:** **Standard** **Sample size: 247** **No. analysed: 247** **With outcome:236** **Without outcome 11** **Primary outcome?** **End of study SBP**	**Arm 3:** **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome** **Primary outcome?**	**Arm 4:** **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome** **Primary outcome?**	
3.14	Record the basic data for each IMPORTANT outcome in the study. If there are more than four, not data for additional outcomes at the bottom of the page.				
	Outcome 1: **SBP of the treatment group** **Value:** **after 36 months** **Measure: mmHg**	**Outcome 2:** **Value:** **Measure:**	**Outcome 3:** **Value:** **Measure:**	**Outcome 4:** **Value:** **Measure:**	

	P value: **<.001** **Upper CI: 118** mean = 117 **Lower CI:115** **Primary outcome?**	**P value** **Upper CI** **Lower CI** **Primary outcome?**	**P value** **Upper CI** **Lower CI** **Primary outcome?**	**P value** **Upper CI** **Lower CI** **Primary outcome?**
3.15	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question. *{Much of this is likely to be contributed by GDG members).*			

In terms of BP, there was a significant decrease from baseline up to 36 months.

Outcome	**Baseline No. (Mean) [95% Confidence Interval]**		**Baseline No. (Mean) [95% Confidence Interval]**		***Mean change***		***P***
	Treatment group	**Standard group**	**Treatment group**	**Standard group**	**Treatment group**	**Standard group**	***P value***
DBP	74 (73 to 76	76 (75 to 78)	67 (66 to 68)	73 (72 to 74)	−7 (−8 to −6)	−3 (−4 to −1)	***<.001***
SBP	128 (126 to 130	133 (131 to 135	117 (115 to 118)	129 (128 to 130)	−11 (−13 to −9)	−3 (−5 to −1)	***<.001***

* Assessment of whether the criteria has been met should be made according to one of the following descriptors

Well covered
Adequately addressed
Poorly addressed
Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
Not applicable.

METHODOLOGY CHECKLIST: RANDOMISED CONTROLLED TRIALS

Study citation Michel Komajda, Paula Curtis, Markolf Hanefeld, Henning Beck- Nielsen, Stuart J Pocock, Andrew Zambanini, Nigel P Jones, Ramon Gomis, Philip D Home. Effect of the addition of rosiglitazone to metformin or sulfonylureas
versus metformin/sulfonylurea combination therapy on ambulatory blood pressure in people with type 2 diabetes: A randomized controlled trial (the RECORD study)

Cardiovascular Diabetology 2008, 7:10			
Guideline topic:		Key Question: Q10	
Checklist completed by: Valentin C. Dones III			
Section 1: Internal validity			
	Quality criteria (from SIGN)	***Met?**	**Comments**
1.1	The study addresses an appropriate and clearly focused question.	Well covered	This study aims to test the effect in blood pressure of rosiglitazone in combination with metformin or sulfonylureas compared to metformin and sulfonylureas in people with type 2 diabetes.
1.2	The assignment of subjects to treatment groups is randomised	Well covered	The allocation to groups were stratified, randomized and concealed.
1.3	An adequate concealment method is used	Well covered	The allocation was concealed.
1.4	Subjects and investigators are kept 'blind' about treatment allocation	Well covered	The validity of the ambulatory blood pressure monitoring was determined by a third investigator who was blinded to treatment allocation. There was no blind assessment done for insulin sensitivity, body weight and adverse events.
1.5	The treatment and control groups are similar at the start of the trial	Well covered	The randomized groups were well matched. However, the background metformin stratum was younger, more overweight and had shorter duration of diabetes than the sulfonylurea stratum. The distribution of class of antihypertensive treatment and number of agents was very similar in all four treatment groups.
1.6	The only difference between groups is the treatment under investigation	Well addressed	Those taking a sulfonylurea were randomized to additional rosiglitazone or metformin, and those taking metformin to additional rosiglitazone or a sulfonylurea (glibenclamide, gliclazide or glimepiride, according to local practice). Although, background antihypertensive therapies could be modified during the study, increases in dose, addition of new agents and the time course of these events were well balanced across all study treatment groups.
1.7	All relevant outcomes are measured in a standard, valid and reliable way	Well covered	The Ambulatory BP Monitoring was measured using a Spacelabs 90207 device. The validity of recordings was determined by a third party, blind to treatment allocation. Homoeostasis model assessment estimates of insulin sensitivity were calculated using the HOMA Calculator. The inputs to the HOMA model, fasting plasma glucose and serum insulin were assayed at a central laboratory. Body weight was assessed at baseline and all six follow-up visits. Assessors were blinded.
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was	Not applicable	No drop-outs were reported.

	completed?		
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)	Well addressed	The subjects were analyzed based on their original allocations.
1.10	Where the study is carried out at more than one site, results are comparable for all sites	Well addressed	The study is multi-centre based. The randomized groups were well matched.
Section 2: Overall assessment of the study			
2.1	How well was the study done to minimise bias? *Code ++, +, or -*		**++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.**
			+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
			- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
2.2	If coded as +, or - what is the likely direction in which bias might affect the study results?		
2.3	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	The over-all effect is secondary to the intervention done and not by chance. Effects of biases were negligible in this study.	
2.4	Are the results of this study directly applicable to the patient group targeted by this guideline?	The study is applicable to subjects who have type 2 diabetic patients.	
Section 3: Description of the study (the following information is required to complete evidence tables facilitating cross-study comparisons. Please complete all sections for which information is available). Please print clearly			
3.1	Do we know who the study was funded by?	[ ] Academic Institution [ ] **Healthcare Industry** [ ] Government [ ] NGO [ ] Public funds [ ] Other	
3.2	How many centres are patients recruited from?	330 study centres in 23 countries in Europe and Australasia	
3.3	From which countries are patients selected? *(Select all those involved. Note additional countries after "Other")*	[ ] Scotland [ ] UK [ ] USA [ ] Canada [ ] Australia [ ] New Zealand [ ] France [ ] Germany [ ] Italy [ ] Netherlands [ ] Scandinavia [ ] Spain [ ] **Other**: Europe and Australasia	
3.4	What is the social setting (ie type of environment in which they live) of patients in the study?	[ ] Urban [ ] Rural [ ] **Mixed** secondary care clinics and general practitioner surgeries, including site management organisations and private diabetes clinics	

3.5	What criteria are used to decide who should be INCLUDED in the study?		Eligible participants had type 2 diabetes as defined by the 1999 World Health Organization criteria [30], were aged 40–75 years, with a body mass index of > 25.0 kg/m2 and HbA1c 7.1–9.0%, on maximum permitted or tolerated doses of metformin or a sulfonylurea (glibenclamide [glyburide], glimepiride or gliclazide) at study entry.	
3.6	What criteria are used to decide who should be EXCLUDED from the study?		Individuals were not to be included if their clinic BP was > 180/105 mmHg.	
3.7	What intervention or risk factor is investigated in the study? (Include dosage where appropriate)		Throughout the study, participants were treated to a target HbA1c of ≤ 7.0%. If HbA1c rose above 7.0% at any point after 8 weeks of randomized treatment, the dose of the study medication was increased to a maximum of 4 mg rosiglitazone twice daily, 2550 mg/day metformin, 15 mg/day glibenclamide (or equivalent), 240 mg/day gliclazide or 4 mg/day glimepiride. If HbA1c was ≥ 8.5% (confirmed) on the maximum tolerated dose for at least 8 weeks, a third glucose-lowering agent was added and their data censored from that point onwards.	
3.8	What comparisons are made in the study? (ie what alternative treatments are used to compare the intervention with?). Include dosage where appropriate.		Metformin and Sulfonylurea	
3.9	What methods were used to randomise patients, blind patients or investigators, and to conceal the randomisation process from investigators?		A stratified concealed randomization was performed. ABPM was measured by third party blinded to treatment allocation. There was no blind assessment done for insulin sensitivity, body weight and adverse events.	
3.10	How long did the active phase of the study last?		The study was for 12 months.	
3.11	How long were patients followed-up for, during and after the study?		Patients were followed-up at 6 and 12 months during the study. No follow-up was done after the study.	
3.12	List the key characteristics of the patient population. Note if there are any significant differences between different arms of the trial.		Approximately half of the participants were male and all but one was Europid. Within stratum the randomized groups were well matched, but the background metformin stratum was younger, more overweight and had shorter duration of diabetes than the sulfonylurea stratum. The presence of microalbuminuria at baseline was low in all four treatment groups. The distribution of class of antihypertensive treatment and number of agents was very similar in all four treatment groups.	
3.13	Record the basic data for each arm of the study. If there are more than four arms, note data for subsequent arms at the bottom of the page			
	Arm 1: **Treatment: Metformin + Rosiglitazone** **Sample size: 176** **No. analysed**	**Arm 2:** **Treatment: Metformin + sulfonylurea**	**Arm 3:** **Treatment: Sulfonylurea + Rosiglitazone** **Sample size: 160**	**Arm 4:** **Treatment: Sulfonylurea + Metformin** **Sample size:** **No. analysed: 167**

	With outcome: **Without outcome:**	**Sample size: 165** **No. analysed** **With outcome:** **Without outcome** **Primary outcome?**	**No. analysed** **With outcome:** **Without outcome** **Primary outcome?**	**With outcome:** **Without outcome** **Primary outcome?**
3.14	Record the basic data for each IMPORTANT outcome in the study. If there are more than four, not data for additional outcomes at the bottom of the page.			
	Background Metformin		**Background sulfonylurea**	
	Outcome 1: **Value: SBP (mmHg) at 12 months** **Mean** -4.9 **Upper/Lower CI** (-6.7, -3.2) **Primary outcome?**	**Outcome 2:** **Value: SBP (mmHg) at 12 months** **Mean** -2.2 **Upper/Lower CI** (-4.2, -0.3) **Primary outcome?**	**Outcome 3:** **Value: SBP (mmHg) at 12 months** **Mean** -3.8 **Upper/Lower CI** (-5.9, -1.8) **Primary outcome?**	**Outcome 4:** **Value: SBP (mmHg) at 12 months** **Mean** -1.3 **Upper/Lower CI** (-3.3, + 0.7) **Primary outcome?**
	Difference (95%CI): -2.7 (-4.9, -0.5), **p value:** 0.016		**Difference (95%CI):** -2.5 (-4.8, -0.2), **p value:** 0.031	
	Background Metformin		**Background sulfonylurea**	
	Outcome 1: **Value: DBP (mmHg) at 12 months** **Mean** -3.8 **Upper/Lower CI** (-4.9, -2.7) **Primary outcome?**	**Outcome 2:** **Value: DBP (mmHg) at 12 months** **Mean** -1.7 **Upper/Lower CI** (-2.9, -0.5) **Primary outcome?**	**Outcome 3:** **Value: DBP (mmHg) at 12 months** **Mean** -3.7 **Upper/Lower CI** (-4.9, -2.5) **Primary outcome?**	**Outcome 4:** **Value: DBP (mmHg) at 12 months** **Mean** -0.6 **Upper/Lower CI** (-1.7, + 0.6) **Primary outcome?**
	Difference (95%CI):-2.1 (-3.4, -0.7), P value: 0.003		**Difference (95%CI):**-3.1 (-4.5, -1.8), P value: < 0.001	
	Background Metformin		**Background sulfonylurea**	

	Outcome 1: **Value: Heart rate change (beat.min) at 12 months** **Mean** -0.9 **Upper/Lower CI** (-2.2, + 0.4) **Primary outcome?**	**Outcome 1:** **Value: Heart rate change (beat.min) at 12 months** **Mean** 0.0 **Upper/Lower CI** (-1.3, + 1.3) **Primary outcome?**	**Outcome 1:** **Value: Heart rate change (beat.min) at 12 months** **Mean** -0.9 **Upper/Lower CI** (-2.3, + 0.5) **Primary outcome?**	**Outcome 1:** **Value: Heart rate change (beat.min) at 12 months** **Mean** 1.7 **Upper/Lower CI** (+ 0.3, + 3.1) **Primary outcome?**
	Difference (95%CI): -0.9 (-2.5, 0.7) **p value:** NS		**Difference (95%CI):** -2.6 (-4.2, -1.0) **p value:** 0.002	
3.15	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question. *{Much of this is likely to be contributed by GDG members).*			
	This research is robust in its methodology. It had directly answered the guided question posted above. This sub-study has demonstrated that rosiglitazone, added to either metformin or to a sulfonylurea, reduces ambulatory BP and that this effect, following 12-month treatment, is greater than that observed the standard glucose-lowering combination of metformin and a sulfonylurea. Whether the reduction in BP observed with this compound translated into improved cardiovascular outcome needs further evaluation.			

* Assessment of whether the criteria has been met should be made according to one of the following descriptors

Well covered
Adequately addressed
Poorly addressed
Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Blood Pressure		**Question number:** 9,10,11, 12 (in part), 13	
Characteristics of study			
Checklist completed by:			
Study citation	Law, M., Morris, J., Wald, N. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ (2009); 338; 1245-1261		
Study design	**Systematic review**	**N (total)**	147 studies, 958000 participants.
Search strategy	Databases: Medline, Cochrane Collaboration, and Web of Science between 1966 and December 2007. Total of 147 trial reports were included; 108 blood pressure difference trials and 46 drug comparison trials		
Selection criteria	RCTs; Trials divided into three categories: recruitment of participants with no history of cardiovascular disease, a history of CHD or history of stroke.		

Intervention	Blood pressure lowering drugs – five classes: thiazides, β-blockers, angiotensin converting enzyme inhibitors, anigotensin receptor blockers and calcium channel blockers		
Comparison	Categorized trials as: "blood pressure difference trials" (given and not given study drug) and "drug comparison trials" (compared two or more blood pressure lowering drugs)		
Outcomes (of interest)	Preventive effect of drugs in people (with and) without history of cardiovascular disease: Preventative effect similar in people with and without history. For people without a history: summary relative risk estimates (and 95%CIs) for CHD events (0.79: 0.72-0.86) and for stroke (0.54: 0.45-0.65), for a reduction in BP of 10mmHG systolic or 5mmHG diastolic. Drug comparison trials of 5 major drug classes Summary of relative risk for comparing classes of drugs with other classes were close to 1.0 – therefore no advantage of one drug over others in preventing CHD. Differences between classes of drugs in average blood pressure reductions were close to zero Increased risk of sudden cardiac death from using thiazides in very high doses Summary of relative risk estimates for stroke in drug comparison trails close to 1.0. However, greater preventive effect of calcium channel blockers than other drugs (relative risk 0.91, CI 0.84 to 0.98, p=0.01), and lesser effect of β-blockers (relative risk 1.18, CI 1.03 to 1.36, p=0.02). Effect of one or more BP lowering drugs on lowering BP and preventing CHD & stroke: One drug at standard dose reduces CHD by about 24% and stroke by 35% in 60-69 year olds with BP of 90 mmHg Three drugs at half standard doses doubles this effect, reducing CHD by 45% and stroke by 60% At higher BP (180/105 mmHg) and lower BP (120/75 mmHg), the effect of one drug at standard dose is about 7-9% greater and smaller respectively. Three drugs at half standard dose is about 12-14 percentage points greater and smaller. (see fig 3 for prediction models) Fixed doses or titrated: infers (only) that dose to reduce BP irrespective of pre-treatment BP has a preventive effect and that there is a direct relationship between dose and BP reduction - so treat all. More intense produce greater preventive effects: Proportional relationship between BP reduction and preventive effect : see fig 3 for reduction in incidence of CHD and stroke in relation to reduction in Diastolic BP according to rug dose, number of drugs, pre-treatment Diastolic BP and age. *Note- Heart failure:* *β-blockers without cardioselective or α blocking properties (e..g propranolol) lacked preventative effect on heart failure (relative risk 1.01, CI 0.76 to 1.35) but β-blockers with such properties had effect (0.77, CI 0.69 to 0.87, p=0.01)* *Calcium channel blockers reduced heart failure by 19% (p=0.007) in BP difference trials.* *Other four classes of drugs significantly reduced heart failure (p<0.001) by average of 24% with no sign. differences between each class.*		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			

Study addresses an appropriate and clearly focused question	Y	Well covered
Description of the methodology used is included	Y	Adequately covered (covered fully in online version)
The literature search was sufficiently rigorous to identify all the relevant studies	Y	Adequately covered (covered fully in online version)
Study quality was addressed and taken into account?	Y	Adequately covered (covered fully in online version)
There were enough similarities between the studies to justify combining them.	Y	Adequately covered (covered fully in online version)
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?	NR	
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		
Extremely sound SR. Study types covered were blood pressure difference trials and drug comparison trials, 5 main drug classes. Conclusion: Lowering of BP using any main drug classes reduces CHD events by about 25%. Effect of drugs can be enhanced by combining different drug classes - however, *does not specify which classes of drugs are combined*. Suggests that drug classes are all similar in their effect ie produced similar reductions in BP taken at standard dose or at the multiple of standard dose. The effect of the drugs in reducing BP increased with dose – by about 2mmHg systolic and 1mmHg diastolic for a doubling in dose.		

METHODOLOGY CHECKLIST: RANDOMISED CONTROLLED TRIALS

Study citation (*Include author, title, year of publication, journal title, pages*) OSTERGREN, J., POULTER, N. R., SEVER, P. S., DAHLOF, B., WEDEL, H., BEEVERS, G., CAULFIELD, M., COLLINS, R., KJELDSEN, S. E., KRISTINSSON, A., MCINNES, G. T., MEHLSEN, J., NIEMINEN, M. & O'BRIEN, E. (2008) The Anglo-Scandinavian Cardiac Outcomes Trial: blood pressure-lowering limb: effects in patients with type II diabetes. *J Hypertens,* 26**,** 2103-11.			
Guideline topic: Treatment of Blood pressure		Key Question No: 10	
Checklist completed by: Jonathan Ucinek			
Section 1: Internal validity			
	Quality criteria (from SIGN)	***Met?**	**Comments**

1.1	The study addresses an appropriate and clearly focused question.	WC	To compare the effects of two antihypertensive treatment strategies for the prevention of coronary heart disease and other cardiovascular events in the large subpopulation (nU5137) with diabetes mellitus in the blood pressure-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial
1.2	The assignment of subjects to treatment groups is randomised	WC	
1.3	An adequate concealment method is used	WC	
1.4	Subjects and investigators are kept 'blind' about treatment allocation	AC	
1.5	The treatment and control groups are similar at the start of the trial	WC	
1.6	The only difference between groups is the treatment under investigation	WC	Baseline blood pressures and other characteristics of the diabetic participants in the two randomized groups were well matched
1.7	All relevant outcomes are measured in a standard, valid and reliable way	WC	
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	Not Reported Complete information was obtained on 98.5% of the 5137 diabetic patients originally randomized. Thirteen patients were lost to follow-up.	
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)	WC	
1.10	Where the study is carried out at more than one site, results are comparable for all sites	Not Reported	
Section 2: Overall assessment of the study			
2.1	How well was the study done to minimise bias? *Code ++, +, or -*	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
			+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
			- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
2.2	If coded as +, or - what is the likely direction in which bias might affect the study results?		
2.3	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study	yes	

	intervention?	
2.4	Are the results of this study directly applicable to the patient group targeted by this guideline?	yes
Section 3: Description of the study (the following information is required to complete evidence tables facilitating cross-study comparisons. Please complete all sections for which information is available). Please print clearly		
3.1	Do we know who the study was funded by?	[ ] Academic Institution [ ] Healthcare Industry [ ] Government [ ] NGO [ ] Public funds [x] Other : pharma The study was supported by grants from Pfizer and Servier. All authors have served as consultants or received travel expenses, or payment for speaking at meetings, or funding for research from one or more pharmaceutical companies that market blood pressure-lowering or lipid lowering drugs, including Pfizer.
3.2	How many centres are patients recruited from? Number of	Nordic countries: • 686 family practices randomized patients UK and Ireland: 32 regional centresto which patients were referred by their family physicians, recruited patients Total number of patients randomized to one of the two antihypertensive regimens n=19 342 • n=5137 had a diagnosis of diabetes at baseline • n=2572 patients were randomized to the atenolol-based regimen • n=2565 to the amlodipine based regimen
3.3	From which countries are patients selected? *(Select all those involved. Note additional countries after "Other")*	[ ] Scotland [x] UK [ ] USA [ ] Canada [ ] Australia [ ] New Zealand [ ] France [ ] Germany [ ] Italy [ ] Netherlands [x] Scandinavia [ ] Spain [x] Other: Ireland
3.4	What is the social setting (ie type of environment in which they live) of patients in the study?	[ ] Urban [ ] Rural [ ] Mixed Not Reported
3.5	What criteria are used to decide who should be INCLUDED in the study?	men and women • aged between 40 and 79 years, • with either untreated hypertension, defined as systolic blood pressure of 160mmHg or more, and/or diastolic blood pressure of 100mmHg or more, • or treated hypertension with systolic blood pressure of 140mmHg or more, and/or diastolic

		blood pressure 90mmHg or more. • Study population was required to have at least three additional risk factors for cardiovascular disease: type II diabetes, peripheral arterial disease, previous stroke or transient ischemic attack, male sex, age 55 years or older, micro albuminuria or proteinuria, smoking, plasma total cholesterol to high-density lipoprotein (HDL) cholesterol ratio of 6 or higher, or family history of premature CHD. • For those with type II diabetes, therefore, at least two of the remaining additional risk factors were required together with hypertension
3.6	What criteria are used to decide who should be EXCLUDED from the study?	• previous myocardial infarction, currently treated angina, a cerebrovascular event within the previous 3 months, fasting triglyceride levels higher than 4.5mmol/l, heart failure, uncontrolled arrhythmias or any clinically important hematological or biochemical abnormality on routine screening
3.7	What intervention or risk factor is investigated in the study? (Include dosage where appropriate)	compared the effects of two antihypertensive treatment strategies • Calcium channel blocker-based regimen (amlodipine) • b-Blocker-based regimen (atenolol) for the prevention of coronary heart disease and other cardiovascular events in the large subpopulation (nU5137) with diabetes mellitus in the blood pressure-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial.
3.8	What comparisons are made in the study? (ie what alternative treatments are used to compare the intervention with?). Include dosage where appropriate.	Calcium channel blocker-based regimen (amlodipine) vs. b-Blocker-based regimen (atenolol) in hypertensive patients with type II diabetes
3.9	What methods were used to randomise patients, blind patients or investigators, and to conceal the randomisation process from investigators?	Methods as described in ASCOT Protocol
3.10	How long did the active phase of the study last?	5.5 years
3.11	How long were patients followed-up for, during and after the study?	
3.12	List the key characteristics of the patient population. Note if there are any significant differences between different arms of the trial.	

3.13	Record the basic data for each arm of the study. If there are more than four arms, note data for subsequent arms at the bottom of the page			
	Arm 1: Blood pressure Lowering Arm **Treatment:** Effect of Calcium channel blocker-based regimen (amlodipine) vs. b-Blocker-based regimen (atenolol) on blood pressure in hypertensive patients with type II diabetes Atenolol titrated up to 100mg Amlodipine titrated up to 10mg **Sample size:** From a total pool of n=19 342 • n=5137 had a diagnosis of diabetes at baseline and where randomly placed into either the atenolol or amlodipine based regimens: • n=2572 patients were randomized to the atenolol-based regimen • n=2565 to the amlodipine based regimen **No. analysed** • n=5137 **With outcome:** • n=5137 Reduction in blood pressure was reported, however it did not reach statistical difference **Without outcome:**	**Arm 2:** **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome** **Primary outcome?**	**Arm 3:** **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome** **Primary outcome?**	**Arm 4:** **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome** **Primary outcome?**
3.14	Record the basic data for each IMPORTANT outcome in the study. If there are more than four, note data for additional outcomes at the bottom of the page.			
	Outcome 1: **Treatment effect on adverse CVD events** Amlodipine based regimen:	**Outcome 2:** **Treatment effect on blood pressure reduction** Amlodipine based regimen:		

	• Significantly fewer CVD events in the amlodipine treated group compared with the atenolol treated group. **Value:** amlodipine-based regimen was associated with a significantly lower incidence of total cardiovascular events and procedures compared with the atenolol-based regimen (hazard ratio 0.86, CI 0.76–0.98, P=0.026) **Measure:** **In amlodipine based group (compared to atenolol based group)** • fatal and nonfatal strokes were 25% lower (P=0.017), • peripheral arterial disease was 48% lower (P=0.004) • and non coronary revascularization procedures were 57% lower (P<0.001) • but for the other endpoints included in the composite endpoint, the differences were less clear and non significant • CHD death and nonfatal myocardial infarction (the primary endpoint in ASCOT) were reduced by a non significant 8% (hazard ratio 0.92, CI 0.74–1.15) **P value** P=0.026 **Upper CI** 0.98 **Lower CI** 0.76 **Primary outcomeY**	• There was a reduction of blood pressure in patients with type II diabetes was non significant **Value:** Blood pressure was reduced more by treatment based on amlodipine, however not significantly. At 1year: • systolic blood pressure was 143mmHg in amlodipine and 148mmHg in the atenolol • diastolic pressures in the two groups were 81 amlodipine and 84 mmHg atenolol At end of Study: • differences were smaller • amlodipine therapy had a blood pressure of 136/75mmHg • atenolol therapy 137/76mmHg **Measure:** **P value** **Upper CI** **Lower CI**		
3.15	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question. *{Much of this is likely to be contributed by GDG members).*			

	In the large diabetic subgroup in the blood pressure-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial, the benefits of amlodipine-based treatment, compared with atenolol-based treatment, on the incidence of total cardiovascular events and procedures was significant (14% reduction) and similar to that observed in the total trial population (16% reduction). **Findings** A majority of patients received combination treatment with either amlodipine and perindopril or atenolol and thiazide. Blood pressure was reduced more by treatment based on amlodipine. At year 1 of the follow-up, systolic blood pressure was 143mmHg in the amlodipine group and 148mmHg in the atenolol group. The corresponding diastolic pressures in the two groups were 81 and 84 mmHg, respectively. By the end of the study, these differences were smaller. Patients on the amlodipine therapy had a blood pressure of 136/75mmHg and those on the atenolol therapy 137/76mmHg. The mean systolic and diastolic blood pressures throughout the study were 3.0 and 1.9mmHg lower among those on treatment with the amlodipine-based regimen. **EVENTS** The amlodipine-based regimen significantly lower incidence of total cardiovascular events and procedures compared with the atenolol-based regimen (hazard ratio 0.86, CI 0.76–0.98, P=0.026) (Figs 3 and 4, Table 4). The effect was similar to that in non diabetic patients in ASCOT for almost all of the secondary endpoints, with no significant heterogeneity except for strokes (P for heterogeneity¼0.046) and stable angina (P for heterogeneity ¼0.004) (Fig. 4). no difference in the effect when major subgroups of diabetic patients were compared. Thus, the reduction in events was comparable in men and women, in age groups above and below 60 years and whether or not systolic blood pressure was above or below the median at baseline (P for heterogeneity= 0.41–0.51). Among individual components of the composite endpoint, fatal and nonfatal strokes were 25% lower (P¼0.017), peripheral arterial disease was 48% lower (P¼0.004) and noncoronary revascularization procedures were 57% lower (P<0.001) in the amlodipine-based group, but for the other endpoints included in the composite endpoint, the differences were less clear and nonsignificant (Fig. 4). CHD death and nonfatal myocardial infarction (the primary endpoint in ASCOT) were reduced by a nonsignificant 8% (hazard ratio 0.92, CI 0.74–1.15).

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Blood Pressure			**Question number: 10**
Characteristics of study			
Checklist completed by: Jonathan Ucinek			
Study citation	MUSINI, V. M., WRIGHT, J. M., BASSETT, K. & JAUCA, C. D. (2009) Blood pressure lowering efficacy of loop diuretics for primary hypertension. *Cochrane Database Syst Rev*, CD003825.		
Study design	**Systematic review**	**N (total)**	9 trials; 460 participants.
Search strategy	Medline (Jan.1966-March-2009), EMBASE (Jan.1988-March-2009), CENTRAL (issue 1, 2009) and bibliographic citations were searched.		
Selection criteria	Double blind randomized placebo controlled trials of at least 3 weeks duration comparing loop diuretic with a placebo or no treatment in patients with primary hypertension defined as BP >140/90 mmHg at baseline		
Intervention	Loop diuretics on blood pressure reduction (effect of 5 different loop diuretics)		

Comparison	Placebo		
Outcomes	Blood pressure lowering effect was modest; lowering systolic pressure by 8 mmHg and diastolic pressure by 4 mmHg No loop diuretic drug appears to be any better or worse than others in terms of blood pressure lowering ability		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		WC	To determine the dose related decrease in systolic and/or diastolic blood pressure as well as adverse events leading to patient withdrawal and adverse biochemical effects (serum potassium, uric acid, creatinine, glucose and lipids profile) due to loop diuretics versus placebo control in the treatment of patients with primary hypertension
Description of the methodology used is included		WC	
The literature search was sufficiently rigorous to identify all the relevant studies		WC	
Study quality was addressed and taken into account?		WC	
There were enough similarities between the studies to justify combining them.		WC	
SECTION 2: Overall assessment of the study			
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
			+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
			- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		The effect size of this review may be an overestimate due to the high risk of bias in the included studies.	
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**			

Findings

Suggests the best estimate of the blood pressure lowering effects of loop diuretics class of drugs is modest ie 8/4mmHg (systolic/diastolic) (-10.4 to -5.4/ -5.6 to -2.8, CI 95%) as compared to placebo control. However it states this result is based on too few patients and that whether effect may be greater or lower than other classes of antihypertensive drugs is difficult to say.

Recommends:

More RCTs are needed assessing the blood pressure lowering effect of loop diuretics as compared to placebo and as compared to other classes of drugs where the blood pressure lowering effect has been established. The benefit of loop diuretics in the setting of renal insufficiency, the patient population where loop diuretics are often used for their antihypertensive effect, needs to be assessed

Note:

There are no clinically meaningful BP lowering differences between different drugs within the loop diuretic class. No conclusions could be drawn regarding the dose related decrease in systolic and diastolic blood pressure of loop diuretics in the treatment of primary hypertension. The review did not provide a good estimate of the incidence of harms associated because of the short duration of the trials and the lack of reporting of adverse effects in many of the trials.

RCT template

KEY QUESTION(S)	
Q13 BP targets	
COMPLETED BY:	
KH	
REFERENCE(S)	
Ruilope LM, Usan L, Segura J, Bakris GL. Intervention at lower blood pressure levels to achieve target goals in type 2 diabetes: PRADID (PResión Arterial en DIabéticos tipo Dos) study. J Hypertens. 2004 Jan;22(1):217-22.	
SOURCE OF FUNDING	
METHOD	
Patient Eligibility Criteria	previously untreated type 2 diabetic patients diagnosed as high normal or borderline hypertensive.
Study design	double-blind, placebo-controlled study with a 16-week follow-up in three groups
Setting	Multicentric (Europe)
Intervention(s)	antihypertensive efficacy and safety of the fixed-dose combination of the non-dihydropiridine calcium channel blocker (CCB) and ACE inhibitor verapamil SR/trandolapril 180/2 mg (V + T), versus trandolapril 2 mg (T), versus placebo (P)
Primary outcome measure	Target attained for SBP lower than 130 mmHg in all patients and a DBP lower than 85 mmHg in high normal BP group.
Additional outcome measures	BP reduction, adverse events, withdrawal rates
Sample Size	438 participants
Main results	Numbers analysed:
	Study duration:
	Patients characteristics and group comparability:
	Effect size – primary outcome: Both active groups were more effective than placebo to decrease SBP and DBP. The mean difference in SBP from placebo was 7.1 mmHg (3.3-10.9, 95% confidence interval (CI); P < 0.001) for T and 7.8 mmHg (3.9-11.6, 95% CI; P < 0.001) for V + T, with no statistical difference between both active groups. Combined treatment (V + T) decreased DBP by 4.6 mmHg (2.3-6.9, 95% CI; P < 0.001) more than placebo and 2.1 mmHg (0.3-4.0, 95% CI; P = 0.021) more than T. At the end of the study, 36.5% in the T

	group, 37.8% in the V + T group, and 14.9% (P = 0.009, P versus V + T and T) had attained the primary end-point. No significant difference was found between T and V + T with regard to the percentage of good control for SBP, but the control rate on the DBP (DBP < 85 mmHg) was significantly higher in the V + T group (88.8%), when compared with T (79.1%) or P (63.5%) (P = 0.002). Withdrawal rates due to adverse effects did not differ among trandolapril alone (9.4%), the combination (11.7%) and placebo (8.1%).
	Effect size – additional outcomes:

QUALITY CHECK [3]		
Patient selection	YES/NO	Comment
Were the eligibility criteria specified?	Y	
Was a method of randomisation performed?	Y	
Was the treatment allocation concealed?	N	
Were the groups similar at baseline regarding the most important prognostic indicators?	Y	
Interventions		
Were the index and control interventions explicitly described?	Y	
Was the care provider blinded for the intervention?	Y	
Were co-interventions avoided or comparable?	Y	
Was the compliance acceptable in all groups?	Y	
Was the patient blinded to the intervention?	Y	
Outcome measurement		
Was the outcome assessor blinded to the interventions?	Y	
Were the outcome measures relevant?	Y	But no CVD outcomes only BP targets
Were adverse effects described?	Y	
Was the withdrawal/drop-out rate described and acceptable?	Y	
Was a short-term follow-up measurement performed?	Y	
Was a long-term follow-up measurement performed?	N	
Was the timing of the outcome assessment in both groups comparable?	Y	
Statistics		
Was the sample size for each group described?	Y	
Did the analysis include an intention-to-treat analysis?	Y	
Were point estimates and measures or variability presented for the primary outcome measures?	Y	

CLINICAL IMPLICATIONS	
Benefits	ACEi+CCB or ACEi alone beter than placebo to reach BP targets
Harms	No difference between groups
Comments	Relatively small study without CVD outcomes

REASON FOR EXCLUSION

RELEVANCE TO AN AUSTRALIAN CONTEXT
yes

OVERALL CONCLUSIONS
Only just over 1/3 of patients reached BP targets of 130/85 mmHg. No CVD events were included.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS

Guideline topic:			**Question number:** Q. 10 and Q 12/13 (final points inferred)
Characteristics of study			
Checklist completed by: Carly			
Study citation	Staessen, J., Li, Y., Thijs, L., Wang, J. Blood Pressure Reduction and Cardiovascular Prevention: An Update Including the 2003-2004 Secondary Prevention Trials. Hypertension Research 2005; 28(5); 385-407		
Study design	**Systematic review**	**N (total)**	Total not given, see comparison for breakdown of no. of trials in each subset (some may overlap)
Search strategy	Not available		
Selection criteria	Not available		
Intervention	Blood pressure reducing medication		
Comparison	New vs. old antihypertensive drugs: 2003 report: reviewed 18 reports on 15 trials with 120, 574 patients Calcium-channel blockers vs. conventional therapy 2003 report: 9 trials with 67, 435 patients ACE inhibitors vs. conventional therapy: 2003 reviewed 6 trials, total of 47, 519 patients AR1 Blockers vs. Conventional therapy: Two trials; 1 compared losartan and atenolol and the second was placebo-controlled trial consisting of diuretics, beta-blockers or both. Calcium-channel blockers vs. AR1 blockers: Two secondary prevention trials; IDNT2 – 1 715 hypertensive patients; VALUE – 15, 245 patients Placebo-controlled secondary trials 18 trials		
Outcomes	New vs old antihypertensive drugs: • No significant difference in outcomes for total and CV mortality and myocardial infarction • For CV events, stroke and heart failure, significant heterogeneity ($p<0.001$) across the 15 trials • First line therapy with diuretic provided more benefit than amlodipine & doxozosin with regard to heart failure, and more benefit than lisinopril and doxazosin in prevention of stroke. Calcium-channel blockers vs. conventional therapy • Pooled odd ratio expressing possible benefit of calcium-channel blockers over old drugs were non-significant for total mortality (0.98, 95% CI 0.92 to 1.03, p=0.42) • Calcium-channel blockers provided slightly better protection against fatal and non-fatal stroke than old drugs (pooled odd ratios for stroke: 0.92, CI 0.84 to 1.01, p=0.07) • Calcium channel blockers provided less protection than conventional therapy for heart failure (1.33; CI, 1.22 to 1.44; $p<0.0001$) • Re-run of analysis in Dec 04 included two more studies, with coronary heart disease and stroke as outcome of interest found the p-values for heterogeneity remained non-significant. Pooled estimates were 1.02 (CI, 0.96 to 1.09; p=0.055) and 0.92 (CI 0.85 to 0.99) for heart disease and stroke respectively. ACE inhibitors vs. conventional therapy • Pooled odd ratio for possible benefit of ACE inhibitors over conventional therapy found no significant differences for total mortality, cardiovascular mortality, cardio events, myocardial infarction and heart failure. • Compared to old drugs, ACE inhib gave slightly less protection against stroke: 1.10 (CI, 1.01 to 1.20; p=0.03) • Review in Dec 04' did not find any new trials in addition to the 6 studies already analysed. AR1 Blockers vs conventional therapy:		

	• The level of protection against total mortality, CV death and myocardial infarction were similar between control and AR1 treated groups. Calcium-channel blockers vs. AR1 blockers • IDNT2 study found trend toward a decrease in strokes in patients who received amlodipine vs. placebo, ratio 0.62 (CI, 0.35 to 1.22, p=0.18) and decrease in myocardial infarction (0.58, CI, 0l.37 to 0.92, p=0.02). Patients receiving irbesartan had lower incident of heart failure than amlodipine (0.65; CI, 0.48 to 0.87, p=0.004) • VALUE study found that cardiac endpoints occurred at similar rates in valsartan and amlodipine treatment groups. Placebo-controlled secondary trials: • Across 8 studies, pooled odds ratio for ACE inhibition vs. placebo were highly significant (p<0.0001) 0.81 (CI, 0.77 to 0.86) for cardiovascular events, 0.77 (CI 0.69 to 0.84) for stroke and 0.80 (CI, 0.73 to 0.86) for myocardial infarction. Role of blood pressure reduction: • Meta-regression line relating odds ratios for CV mortality to within-trial differences in SBP was linear (p,0.0001). • For CV events, stroke and myocardial infarction the relations were curvilinear (p=0.0002)

Quality of study		
Quality criteria (from SIGN)	***Met?**	**Comments**
SECTION 1: Internal validity		
Study addresses an appropriate and clearly focused question	Y	Well covered
Description of the methodology used is included	N	Poorly addressed
The literature search was sufficiently rigorous to identify all the relevant studies	N	Not reported
Study quality was addressed and taken into account?	Y	Adequately addressed
There were enough similarities between the studies to justify combining them.	Y	Adequately addressed
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
	+	+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or – what is the likely direction in which bias might affect the study results?		
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		

Extremely comprehensive analysis of a number of trials. Provides evidence for the question of which class of drugs effectively lowers various cardiovascular events compared to placebo or other classes of drugs: calcium-channel blockers might offer a slight but selective benefit in the prevention of stroke and inhibitors of the renin-angiotensin system in the prevention of heart failure. For prevention of myocardial infarction, the published results were more equivocal. NOTE: mix of primary and secondary prevention trials.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Blood Pressure		**Question number:** 9, 10	
Characteristics of study			
Checklist completed by: KH			
Study citation	Strippoli GF, Bonifati C, Craig M, Navaneethan SD, Craig JC. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. Cochrane Database Syst Rev. 2006: CD006257.		
Study design	**Systematic review**	**N (total)**	Forty nine studies (12,067 patients)
Search strategy	MEDLINE (1966 to December 2005), EMBASE (1980 to December 2005), the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library issue 4 2005) and contacted known investigators.		
Selection criteria	RCTs of at least six months duration in which ACEi or ARB were compared with placebo or no treatment or in which the relative effects of the agents were compared directly, head-to-head, in patients with Diabetic kidney disease (DKD), were included		
Intervention	ACEi and or ARBs		
Comparison	Placebo or head to head		
Outcomes	There was no significant difference in the risk of all-cause mortality for ACEi versus placebo (RR 0.91, 95% CI 0.71 to 1.17) and ARB versus placebo (RR 0.99, 95% CI 0.85 to 1.17). A subgroup analysis of studies using full-dose ACEi versus studies using half or less than half the maximum tolerable dose of ACEi showed a significant reduction in the risk of all-cause mortality with the use of full-dose ACEi (RR 0.78, 95% CI 0.61 to 0.98). Baseline mortality rates were similar in the ACEi and ARB studies. The effects of ACEi and ARB on renal outcomes (ESKD, doubling of creatinine, prevention of progression of micro- to macroalbuminuria, remission of micro- to normoalbuminuria) were similarly beneficial. Reliable estimates of effect of ACEi versus ARB could not be obtained from the three studies in which they were compared directly because of their small sample size.		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		Y	Well covered
Description of the methodology used is included		Y	Well covered
The literature search was sufficiently rigorous to identify all the relevant studies		Y	Well covered
Study quality was addressed and taken into account?		Y	Well covered
There were enough similarities between the studies to justify		Y	Well covered

combining them.		
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		
This is a rigorous Cochrane review that found little difference between ACEi or ARBs for reducing renal outcomes. Both were similar (no advantage) to other agents for CVD outcomes.		

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Blood Pressure		**Question number:** 9, 10	
Characteristics of study			
Checklist completed by: KH			
Study citation	Strippoli GF, Craig M, Craig JC. Antihypertensive agents for preventing diabetic kidney disease. Cochrane Database Syst Rev. 2005: CD004136.		
Study design	**Systematic review**	**N (total)**	Sixteen trials (7603 patients)
Search strategy	MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, conference proceedings, and contact with investigators were used to identify relevant trials.		
Selection criteria	(RCTs) comparing any antihypertensive agent with placebo or another agent in hypertensive or normotensive patients with diabetes and no kidney disease (albumin excretion rate < 30 mg/d)		
Intervention	Blood pressure reduction drugs		
Comparison	six trials of angiotensin converting enzyme inhibitors (ACEi) versus placebo, six of ACEi versus calcium channel blockers (CCBs), one of ACEi versus CCBs or combined ACEi and CCBs and three of ACEi versus other agents.		
Outcomes	Compared to placebo, ACEi significantly reduced the development of microalbuminuria (six trials, 3840 patients: RR 0.60, 95% CI 0.43 to 0.84) but not doubling of creatinine (three trials, 2683 patients: RR 0.81, 95% CI 0.24 to 2.71) or all-cause mortality (four trials, 3284 patients: RR 0.81, 95% CI 0.64 to 1.03). Compared to CCBs, ACEi significantly reduced progression to microalbuminuria (four trials, 1210 patients: RR 0.58, 95% CI 0.40 to 0.84).		
Quality of study			

Quality criteria (from SIGN)	*Met?	Comments
SECTION 1: Internal validity		
Study addresses an appropriate and clearly focused question	Y	Well covered
Description of the methodology used is included	Y	Well covered
The literature search was sufficiently rigorous to identify all the relevant studies	Y	Well covered
Study quality was addressed and taken into account?	Y	Well covered
There were enough similarities between the studies to justify combining them.	Y	Well covered
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		
This is a rigorous Cochrane review that found a significant reduction in the risk of developing microalbuminuria in normoalbuminuric patients with diabetes has been demonstrated for ACEi only. It appears that the effect of ACEi is independent of baseline blood pressure, renal function and type of diabetes. No trials of ARBs were included which have been the focus of more recent trials. Although renal complications were prevented the effects on CVD are unclear and more trials/data is needed to get a more precise effect given the current wide CIs.		

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Blood pressure			**Question number:** 9, 10
Characteristics of study			
Checklist completed by: Carly			
Study citation	Turnbull F, Neal B, Algert C, Chalmers J, Chapman N, Cutler J*, et al.* Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Arch Intern Med*. 2005; 165: 1410-9. (Blood pressure trialists Collaboration)		
Study design	**Systematic review**	**N (total)**	27 RCTs (N=158 709 participants) that included 33 395 individuals with diabetes and 125 314 without diabetes
Search strategy	Databases not reported. Trial data obtained by Dec 2003.		

Selection criteria	Inclusion criteria: randomized patients between a drug to lower BP and control, or randomized patients between regimes based on different classes of drug to lower BP. Minimum of 1000 patient years of planned follow up in each randomized group		
Intervention	Blood pressure lowering drugs		
Comparison	a) ACE inhibitor vs. placebo b) Calcium antagonist vs. placebo c) More intensive vs. less intensive regimes d) Angiotensin receptor blocker vs. control e) ACE inhibitor vs. diuretics/beta blockers f) Calcium antagonist vs. diuretics/beta blockers g) ACE vs. calcium antagonists		
Outcomes	**Primary outcome was total of major CVD events, comprising stroke, coronary heart disease and heart failure.** Total major cardiovascular events were reduced to a comparable extent in individuals with and without diabetes by regimens based on angiotensin-converting enzyme inhibitors, calcium antagonists, angiotensin receptor blockers, and diuretics/beta-blockers (P > 0.19 for all by chi(2) test of homogeneity). There was limited evidence that lower BP goals produced larger reductions in total major cardiovascular events in individuals with vs without diabetes (P = .03 by chi(2) test of homogeneity).		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		Y	Well covered
Description of the methodology used is included		Y	Well covered
The literature search was sufficiently rigorous to identify all the relevant studies		NR	Search strategy no reported
Study quality was addressed and taken into account?		Y	Well covered
There were enough similarities between the studies to justify combining them.		Y	
SECTION 2: Overall assessment of the study			
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
			+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
			- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or – what is the likely direction in which bias might affect the study results?		The actual search methodology is not reported. It is reported in full as a protocol in 1998 elsewhere.	

SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**
• Provide support for use of drugs to lower BP in those with diabetes, though no strong evidence for selective use of specific classes of drugs. • Lower blood pressure targets may be useful but data not clear.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Blood pressure		**Question number:** 9, 10	
Characteristics of study			
Checklist completed by: Carly			
Study citation	Turnbull, F. Effects of different regimes to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomized trials. BMJ 2008; 336 (7653); 1121		
Study design	**Systematic review**	**N (total)**	31 trials; 190 606 participants
Search strategy	Databases not reported. Trial data obtained by Sept 2006.		
Selection criteria	Inclusion criteria: randomized patients between a drug to lower BP and control, or randomized patients between regimes based on different classes of drug to lower BP Minimum of 1000 patient years of planned follow up in each randomized group Age groups defined as <65 and >65. Mean age 57 and 72 respectively and proportion of men was 58% and 51% Excluded: Must not have presented or published main results before protocol was finalized in July 1995 (this is obtuse).		
Intervention	Blood pressure lowering drugs		
Comparison	h) ACE inhibitor vs. placebo i) Calcium antagonist vs. placebo j) More intensive vs. less intensive regimes k) Angiotensin receptor blocker vs. control l) ACE inhibitor vs. diuretics/beta blockers m) Calcium antagonist vs. diuretics/beta blockers n) ACE vs. calcium antagonists		
Outcomes	**Primary outcome was total of major CVD events, comprising stroke, coronary heart disease and heart failure.** • In trials examining BP lowering compared to placebo or less active control, there was no evidence of any difference in reduction in relative risk in different age groups (all P>0.2 for heterogeneity) • Trials compared BP lowering based on different drug classes, there was no difference in proportional reductions in total major CV events observed between age groups for any comparison (all p>0.3 for heterogeneity) • In 8 trials that examined beta blockers and diuretics compared with other drug classes (ACE inhibitor and calcium antagonist combined) according to patients' age – no evidence of a difference in proportional risk reduction between younger and older adults for either comparison (all P>0.3) • Found no evidence of interaction between age and effect of treatment on primary outcome of major CV events for any BP lowering		

	treatment compared to control (all P>0.09) • Meta-regression effects of BP lowering in different age groups: no difference in risk reduction achieved per unit reduction in BP for individual aged <65 compared with >65 (P=0.38) o ACE inhibitor vs placebo: risk ratio 0.76 (95% CI 0.66 to 0.88) for <65; 0.83 (CI 0.74 to 0.94) for >65 o Calcium antagonist vs placebo: 0.84 (CI 0.54 to 1.31) for <65; 0.74 (CI 0.59 to 0.92) for 65 o More vs less intensive lowering regimes: 0.88 (CI 0.75 to 1.04) for <65; 1.03 (CI 0.85 to 1.24) for >65 o Favours angiotensin receptor blocker vs. favours other: 0.89 (CI 0.75 to 1.05) for <65; 0.91 (CI 0.81 to 1.02) for >65 o ACE inhibitor vs. diuretic or beta blocker: 1.05 (CI 0.96 to 1.14) for <65; 1.01 (0.95 to 1.06) for >65 o Calcium antagonist vs. diuretic or beta blocker: 1.06 (CI 0.98 to 1.14) for <65; 1.02 (CI 0.97 to 1.06) for > 65 o ACE inhibitor vs. calcium antagonist: 0.91 (CI 0.78 to 1.06) for < 65; 0.98 (0.92 to 1.05) for > 65

Quality of study		
Quality criteria (from SIGN)	***Met?**	**Comments**
SECTION 1: Internal validity		
Study addresses an appropriate and clearly focused question	Y	Well covered
Description of the methodology used is included	Y	Well covered
The literature search was sufficiently rigorous to identify all the relevant studies	NR	Search strategy no reported
Study quality was addressed and taken into account?	Y	Well covered
There were enough similarities between the studies to justify combining them.	Y	
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or – what is the likely direction in which bias might affect the study results?	The actual search methodology is not reported. It is reported in full as a protocol in 1998 elsewhere.	
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		

- Provide support for use of drugs to lower BP in older and younger adults, though no strong evidence for selective use of specific classes of drugs according to age.
- Article largely based on comparison of effects between young (<65) and older (>65) patients

* Assessment of whether the criteria has been met should be made according to one of the following descriptors
Well covered
Adequately addressed
Poorly addressed
Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
Not applicable.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Blood Pressure		**Question number:** Q 9	
Characteristics of study			
Checklist completed by: Carly			
Study citation	Wang, J., Staessen, S., Franklin, S., Fagard, R., Gueyffier, F. Systolic and Diastolic Blood Pressure Lowering as Determinants of Cardiovascular Outcome. Hypertension, 2005; 45(5); 907-913		
Study design	**Systematic review**	**N (total)**	10 trials; 51 293 patients in total
Search strategy	Required access to individual patient data, therefore used trials available in the Individual Data Analysis of Antihypertensive Intervention trials (INDANA) data set and the Study Coordinating Centre in Leuven (Belgium)		
Selection criteria	Excluded 1 intervention trial of multiple risk factors and 1 small pilot trial		
Intervention	Blood pressure reduction medication		
Comparison	Medication vs. other		
Outcomes	**Outcomes measured as total and cardiovascular mortality, all CV events, fatal & non fatal stroke and fatal & non fatal coronary heart disease. Patients categorised as young (30 to 49 years) with baseline BP as 154/100; old (60 to 79 years) baseline BP 174/83mmHg; and very old (>80) baseline 176/78mmHg** • Young patients: active treatment reduced SBP by 8.3 mmHg (95% CI, 5.7 to 11.0), DBP 4.6 (CI 2.6 to 6.6) • Old: reduced SBP by 10.7 (CI 8.3 to 13.0), DBP 4.2 (CI 2.4 to 6.0) • Very old: reduced SBP by 9.4 (CI 4.4 to 14.3), DBP 3.2 (CI -1.0 to 7.3) • With increasing age, ratio of DBP to SBP decreases significantly (p=0.004) • In old patients with intermediate ratio of DBP to SBP, active treatment reduced total mortality by 17% (CI 6% to 26%; P=0.003) and cardiovascular mortality by 21% (CI 7% to 33%, p=0.004) – this was not apparent in other two age groups • In matched actively treated vs control patients, the achieved BP in actively treated averaged 123.6/62.1, while control was 153.5/83.8mmHg. Relative hazard ratios were 0.46 (CI 0.27 to 0.80 p=0.006) for total mortality; 0.34 (CI 0.16 to 0.74, p=0.007) for cardiovascular mortality; 0.59 (CI 0.37 to 0.94, p=0.02) for all CV events; 0.35 (CI 0.14 to 0.85, p=0.02) for stroke and 0.86 (CI 0.47 to		

	1.56 p=0.61) for myocardial infarction.		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		Y	Adequately covered.
Description of the methodology used is included		Y	Well covered
The literature search was sufficiently rigorous to identify all the relevant studies		Y	Well covered
Study quality was addressed and taken into account?		Y	Adequately addressed
There were enough similarities between the studies to justify combining them.		Y	Well covered
SECTION 2: Overall assessment of the study			
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
			+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
			- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or – what is the likely direction in which bias might affect the study results			
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**			
Adequately discusses the benefits of lowering the DBP and SBP ratio, but does not specifically address which active treatments were utilised in lowering blood pressure. Table indicates a range of BP lowering medications were used – thiazides, B blockers, calcium channel etc.			

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Blood Pressure		**Question number:** 10 (indirectly)	
Characteristics of study			
Checklist completed by:			
Study citation	Webb AJ, Fischer U, Mehta Z, Rothwell PR. Effects of anti-hypertensive drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. Lancet 2010, 375:906-15		
Study design	**Systematic review**	**N (total)**	398 trials

Hypothesis	Calcium channel blockers reduced risk of stroke and coronary events more than expected from drop in SBP alone, and beta blockers were less effective than expected in reducing risk. Previous work has demonstrated that • within-individual visit-to-visit variability in SBP is a powerful predictor of stroke independently of mean SBP in several cohorts, and • effects on within-individual variability in SBP account for the previously unexplained effects of treatment on risk of stroke in two RCTs of antihypertensive drugs		
Search strategy	Searched Medline and Cochrane (1950 to 1st week July 2009) keywords "meta analysis, antihypertensive agaents OR blood pressure lowering". Searched reference lists of all reviews. Thorough and CONSORT style explanation provided.		
Selection criteria	Identified RCTs from published systematic reviews		
Intervention	Amount of decrease of CVD risk due to interindividual variation in SBP in different drug classes, over and above difference in risk accounted for by reduced mean SBP.		
Comparison			
Outcomes	Risk of stroke: **Unexplained differences between classes of antihypertensive drugs in their effectiveness in preventing stroke are most likely due to class effects on intra-individual variability in blood pressure.**		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		y	Well covered
Description of the methodology used is included		y	Well covered
The literature search was sufficiently rigorous to identify all the relevant studies		y	Adequately-well covered
Study quality was addressed and taken into account?		y	Adequately addressed through selection criteria
There were enough similarities between the studies to justify combining them.		Y	
SECTION 2: Overall assessment of the study			
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
			+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
			- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?			

SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**	
Highly consistent effects of drug-class on SBP VR and CV—ie, calcium-channel blockers, non-dihydropyridine calcium-channel blockers, and diuretic drugs reduced group variation in SBP, whereas angiotensin-receptor blockers, ACE inhibitors,and beta blockers increased it. Across all trials in which data were reported, effects of treatment on interindividual variation in SBP were correlated with effects on risk of stroke independently of differences in mean SBP. **Higher or lower dose more effective?** ***Depends on drug class*****.** In trials in which groups of patients allocated to different doses of the same drug were compared, group variation was lower in patients allocated a higher dose of calcium-channel blocker (0·86, 0·74–0·99, p=0·038, 20 trials) but greater in patients allocated the higher dose of a β blocker (1·31, 1·01–1·69, p=0·040, six trials).	

Template for Intervention Study – Randomised Controlled Trial

KEY QUESTION(S)	
BP –class of drug (Q10)	
COMPLETED BY:	
Kelvin Hill	
REFERENCE(S)	
Weber MA, Bakris GL, Jamerson K, Weir M, Kjeldsen SE, Devereux RB, et al. Cardiovascular events during differing hypertension therapies in patients with diabetes. J Am Coll Cardiol. 2010; 56: 77-85.	
SOURCE OF FUNDING	
Novartis	
METHOD	
Patient Eligibility Criteria	Hypertensive with increased risk of CVD. (11 506 in initial total trial with 6946 with diabetes of whom 2842 had preexisting CVD).
Study design	Double blind, RCT
Setting	Multicentre, five countries (USA, Sweden, Norway, Denmark, and Finland)
Intervention(s)	**An ACEi, benazepril, combined with a calcium chanel blocker, amlodipine (B+ A) or a diuretic, hydrochlorothiazide (B+ H). A separate analysis in diabetic patients was pre-specified.**
Primary outcome measure	time to the first recorded event. This was defined as the composite of the first occurrence of a cardiovascular event or death from cardiovascular causes.
Additional outcome measures	The secondary end point of the trial was a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Other pre-specified end points included coronary revascularization procedures, unstable angina, hospitalization for heart failure, progression of renal disease, and all-cause mortality. In
Sample Size	The power and sample size of the study were originally calculated based on the entire study cohort, with the intent that the ACCOMPLISH trial would have 90% power to detect a 15% reduction in risk for the

	B A group, based on the assumption of a 3.5% annual event rate for the B H group. However, no such calculations were made purely for the patients with diabetes cohort in this trial.
Main results	In the combined diabetes group, the mean achieved BP were 131.5/72.6 and 132.7/73.7 mm Hg; during 30 months, there were 307 (8.8%) and 383 (11.0%) primary events (hazard ratio [HR]: 0.79, 95% confidence interval [CI]: 0.68 to 0.92, p 0.003). For the diabetic patients at very high risk, there were 195 (13.6%) and 244 (17.3%) primary events (HR: 0.77, 95% CI: 0.64 to 0.93, p 0.007). In the nondiabetic patients, there were 245 (10.8%) and 296 (12.9%) primary events (HR: 0.82, 95% CI: 0.69 to 0.97, p 0.020). In the diabetic patients, there were clear coronary benefits with B A, including both acute clinical events (p 0.013) and revascularizations (p 0.024). There were no unexpected adverse events. Significantly fewer renal complicatins with B+A (6.6 v 12.2% p<0.001) –but this was post hoc analysis.

QUALITY CHECK [3]		
Patient selection	YES/NO	Comment
Were the eligibility criteria specified?	Y	
Was a method of randomisation performed?	Y	randomly assigned via a central, telephone-based interactive voice response system
Was the treatment allocation concealed?		
Were the groups similar at baseline regarding the most important prognostic indicators?	NA	Subgroup analysis
Interventions		
Were the index and control interventions explicitly described?	Y	
Was the care provider blinded for the intervention?	y	
Were co-interventions avoided or comparable?	y	
Was the compliance acceptable in all groups?	y	
Was the patient blinded to the intervention?	y	
Outcome measurement		
Was the outcome assessor blinded to the interventions?	y	
Were the outcome measures relevant?	y	
Were adverse effects described?	y	
Was the withdrawal/drop-out rate described and acceptable?	y	
Was a short-term follow-up measurement performed?	y	
Was a long-term follow-up measurement performed?	y	But terminated early <3years
Was the timing of the outcome assessment in both groups comparable?	y	
Statistics		
Was the sample size for each group described?	NA	Subgroup analysis
Did the analysis include an intention-to-treat analysis?	y	
Were point estimates and measures or variability presented for the primary outcome measures?	y	

CLINICAL IMPLICATIONS	
Benefits	Reduced CVD events
Harms	Similar adverse events
Comments	The trial was terminated early (mean follow-up 2.9 years).

REASON FOR EXCLUSION
Include

RELEVANCE TO AN AUSTRALIAN CONTEXT
Yes

OVERALL CONCLUSIONS
ACEi + CCB found to be more effective at reducing CVD events than ACEi + diuretic. Large subgroup of those with diabetes. Similar results to those without diabetes.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Blood Pressure		**Question number:** 9, 10	
Characteristics of study			
Checklist completed by: SH			
Study citation	Wright J, Musini V. First-line drugs for hypertension. Cochrane Database of Systematic Reviews 2009, Issue 3. Art No.: CD001841.DOI: 10.1002/14651858. CD001841.pub2.		
Study design	**Systematic review**	**N (total)**	24 trials; 58040 patients
Search strategy	Electronic search of Medline, Embase, Cinahl, Cochrane clinical trial register (until June 2008); using standard Cochrane search strategy for hypertension.		
Selection criteria	RCTs of at least one year duration comparing one of 6 major drug classes. More than 70% of people must have BP >140/90 mmHg at baseline.		
Intervention	Blood pressure reduction drugs		
Comparison	Meds vs placebo or no treatment		
Outcomes	Mortality, stroke, CHD, CV events, decrease in systolic and diastolic BP, withdrawal due to adverse drug effects. • Thiazides reduced mortality (RR 0.89, 95% 0.83 to 0.96), stroke (RR 0.63, 95% CI 0.57 to 0.71), CHD (RR 0.84, 95% CI 0.75 to 0.95) and CV events (RR 0.70, 95% 0.66 to 0.76). Low dose thiazides reduced CHD but high dose did not. • Beta-blockers reduced stroke (RR 0.83 95% CI 0.72 to 0.97) and CV events (RR 0.89 95% CI 0.81 to 0.98) but not CHD or mortality • ACE inhibitors reduced mortality (RR 0.83 95%CI 0.72 to 0.95) , stroke (RR 0.65, 95%CI 0.52 to 0.82), CHD (RR 0.81, 95% CI 0.70 to 0.94) and CV events (RR 0.76, 95% 0.67 to 0.85). • Calcium channel blocker reduced stroke (RR 0.58, 95% CI 0.41 to 0.84) and CV events (RR 0.71, 95% CI 0.57 to 0.87) but not CHD or mortality. • No RCTs were found for ARBs or alpha blockers. First-line low-dose thiazides reduce all morbidity and mortality outcomes. First line ACE inhibitors and Calcium channel blockers may be similarly effective but the evidence is less robust. First-line high dose thiazides and first-line beta-blockers are inferior to first line low dose thiazides.		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		Y	Well covered

Description of the methodology used is included	Y	Well covered
The literature search was sufficiently rigorous to identify all the relevant studies	Y	Well covered
Study quality was addressed and taken into account?	Y	Well covered
There were enough similarities between the studies to justify combining them.	Y	Well covered
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		
This is a rigorous Cochrane review that justifies clear conclusions regarding drug class type for the treatment of high BP in reducing CVD morbidity and mortality: "First-line low-dose thiazides reduce all morbidity and mortality outcomes. First line ACE inhibitors and Calcium channel blockers may be similarly effective but the evidence is less robust. First-line high dose thiazides and first-line beta-blockers are inferior to first line low dose thiazides."		

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Blood Pressure		**Question number:** 13 (in part) and possibly 7-8?	
Characteristics of study			
Checklist completed by: Carly			
Study citation	Zanchetti, B. Bottom blood pressure or bottom cardiovascular risk? How far can cardiovascular risk be reduced? Journal of Hypertension, 2009; 27(8);1509		
Study design	**Systematic review**	**N (total)**	53 trials;
Search strategy	Not stated		
Selection	Only included trials directly providing data on incidence of major cardiovascular events (cardiovascular death, nonfatal		

criteria	myocardial infarction, and nonfatal stroke.
Intervention	Blood pressure reduction
Comparison	Meds vs other
Outcomes	Low risk patients (13 studies): • Achieved level of risk doesn't correlate with SBP values achieved • Incidence of revascularization reported in three most recent trials only Elderly hypertensive patients (11 studies) • Treatment seldom reduced 5-year incident of major CV events below high-risk cut off of 10% • Achieved incident was higher when mean age was higher or when baseline cardiovascular disease was more prominent. • Most trials were placebo-controlled and CV incidents in placebo groups indicate that baseline risk was variable between trials. • Only the Systolic Hypertension in Elderly Program (SHEP) provides info on incidence of revascularization (only 2-3% in 5 years) • Not many studies provided information on concomitant therapies. Diabetic patients (11 studies): • Untreated, less treated or less successfully treated had different incidents of CV events (from 10-38% in 5 years) • In trials in which cardiovascular disease was highly prevalent at baseline, incidence of major CV events was high despite several trials liberally using concomitant therapies. • In very-high-risk diabetic patients, even more intense treatment and BP reduction below 140mmHg did not succeed in reducing CV events below 15% in 5 years. • Only 4 trials reported revascularization: 5-year incident was 5.9/6.7% in ADVANCE; 15.5/18.2% in MicroHOPE; 4.6/4.7/4.4% in IDNT; 1.5/3.0% in SHEP High cardiovascular risk (18 studies): • Most trials reported an endpoint incidence of revascularization. • Incidence of revascularization was extremely high in ACCOMPLISH (twice as large), CAMELOT (three times as large), EUROPA (at least as large as incidence of major events) • In all other trials, incident of major CV event remained within high-risk range: it was never lower than 11% in 5 years and often between 12 and 14% even in more successful of randomised treatment groups. • Low SBP values were achieved by treatment (between 130 and 139mmHg) both in trials in which event incident was close to 10% in 5 years and in those in which it remained very high (between 15-40% in 5 years) suggested by the authors that once a high level of risk has been attained, the residual risk during therapy depends more on baseline risk than on achieved BP.

Quality of study		
Quality criteria (from SIGN)	***Met?**	**Comments**
SECTION 1: Internal validity		
Study addresses an appropriate and clearly focused question	N	Not addressed
Description of the methodology used is included	N	Not addressed
The literature search was sufficiently rigorous to identify all the relevant studies		Not addressed
Study quality was addressed and taken into account?	N	Not addressed
There were enough similarities between the studies to justify combining them.	N	Not addressed
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
	-	- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?	This review did not detail any systematic search methodology nor evaluation of risk of bias. It makes strong claims and appears to have a wide reference source but this is not confirmed.	
SECTION 3: Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.		
The studies reviewed are RCTs – major drug trials – however the systematic approach is not documented therefore selection bias is a real issue. The conclusions confirm that "earlier (BP) management is better than late" because there appears to be a ceiling effect for high risk patients. Ie the evidence suggests that once a person reaches high risk status whatever is done can not bring them back to low risk. There are also comments on combination management that may be useful for earlier questions. There does not seem to be a clear answer to the title question as to whether to aim for BP levels or risk levels?		

FORM framework Question 9

Key question(s): Q9 Does pharmacological blood pressure lowering reduce CVD events and all cause mortality compared to control?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Multiple high quality SR in general and specific populations (diabetes and CKD)	A	**One or more level I studies with a low risk of bias or several level II studies with a low risk of bias**
	B	**One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias**
	C	**One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias**
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
All papers confirm that lowering BP using pharmacology reduces CVD events and mortality compared to control groups. The papers make the point that the effect appears to be wholly related to blood pressure reduction and not other mechanisms because the effect is consistent across drug classes.	A	**All studies consistent**
	B	**Most studies consistent and inconsistency can be explained**
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
	NA	**Not applicable (one study only)**
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention*		
Evidence applies to a large patient population, is associated with substantial potential benefits, but no harms reported and has significant resource and organisational implications.	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Large amount of data related to diverse populations, international trials	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Highly applicable.	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

There is a substantial and consistent body of literature that confirms that pharmacological lowering of BP reduces cardiovascular disease across all subgroups. BP lowering and lipid lowering therapy are both recommended for those assessed as high absolute risk. Therefore for ease of use the EWG agreed to combine this recommendation.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1.Evidence base	A	High quality, low risk reviews
2.Consistency	A	with consistent findings at 2005 and 2009
3.Clinical impact	A	Remains high
4. Generalisability	A	High
5. Applicability	A	High

Evidence statement

Pharmacological blood pressure lowering reduces CVD events and all cause mortality compared to controls. This effect appears consistent irrespective of groups. While trials have not recruited patients specifically on the basis of their absolute risk it is reasonable to suggest this evidence applies to different risk classes although the greatest absolute benefit would relate to those at highest risk or in whom isolated high blood pressure is present. Although relative risk reduction for CVD events is fairly consisitent even at 'normal' or low baseline BP, it is less clear from the evidence from relative risk approach to those at low and moderate absolute risk levels.

Indicate any dissenting opinions

Level of individual blood pressure irrespective of absolute risk levels had significant discussion. Focusing on BP alone does not fit within absolute risk approach. Large volume of evidence for relative risk approach. Main issue was cut off decided by assessment guidelines as 180/110. Most of the EWG felt uncomfortable leaving BP untreated with medication over 160/100 mmHg. Agreement that benefits of lowering blood pressure on other related CVD outcomes and notion that this is embedded clinical culture and would be hard to change suggested 160/100 mmHg irrespective of absolute risk level.

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE OF RECOMMENDATION**	

a) Adults at high absolute risk of CVD should be simultaneously treated with lipid and blood pressure lowering pharmacotherapy in addition to lifestyle intervention unless contraindicated or clinically inappropriate. (Grade B –downgraded due to no direct evidence for trials using absolute risk as selection)
b) Adults at moderate absolute risk of CVD should have their risk factors initially managed by lifestyle interventions. Pharmacotherapy for blood pressure and lipid lowering is not routinely recommended but may be considered if 3–6 months of lifestyle intervention does not reduce the individual's risk factors. (consensus based recommendation)
c) Adults at moderate absolute risk of CVD may treated with pharmacotherapy for blood pressure and/or lipid lowering in addition to lifestyle intervention if one or more of the following applies:

- Persistent blood pressure ≥ 160/100 mmHg;
- Family history of premature CVD;
- Aboriginal and Torres Strait Islander peoples;
- Other populations where FRE is known to underestimate risk (South Asians, Maori and Pacific Islanders, people from the Middle East). (Consensus based recommendation)

d) Adults at low risk of CVD who have persistent blood pressure ≥ 160/100 mmHg may be treated with blood pressure lowering pharmacotherapy in addition to lifestyle intervention. (Consensus based recommendation)

UNRESOLVED ISSUES	
NA	
IMPLEMENTATION OF RECOMMENDATION	
Will this recommendation result in changes in usual care? Yes for high risk –irrespective of BP levels. Also some people may start BP for moderate and low risk under the 160mmHg threshold.	**YES**
Are there any resource implications associated with implementing this recommendation? This will be determined by the separate economic analyses.	
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation? Change in usual care as noted above.	**YES**

FORM framework Question 10

Key question(s): Q10 What is the evidence for one BP lowering drug class or any combination of drug classes being more effective than any other for reducing CVD events and all cause mortality. Secondary outcomes– reduction of BP.		**Evidence table ref:**
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Multiple high quality systematic reviews		**One or more level I studies with a low risk of bias or several level II studies with a low risk of bias**
	B	**One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias**
	C	**One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias**
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
General agreement that of the 5-6 major drug classes investigated that no one class has a major advantage over another except in certain situations: ARBs may have greater persistence (compliance): Bramlage 2009 Thiazides (low dose) recommended as first-line because evidence is stronger (effects equivalent to ACE inhibitors and calcium channel blockers - latter have less robust evidence): Wright 2009. High doses of thiazides have an increased risk of sudden cardiac death: Law 2009 Beta blockers have lesser effect in stroke prevention: Law 2009, whilst calcium channel blockers may have slightly superior effect for stroke prevention: Staessen 2004 Heart failure has strong preventive effect from all classes except calcium channel blockers: Law 2009 Loop diuretics are no better or worse than other classes: Musini 2009 Unexplained differences between classes most likely due to class effects on intra-individual variability in	A	**All studies consistent**
	B	**Most studies consistent and inconsistency can be explained**
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could*		
	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Turnbull (2008) found no evidence of interaction between age and effect of treatment on CV events for any BP lowering treatment compared to control. Therefore generalisable across ages.	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to**
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Consideration of drug class availability is required for Australian healthcare sector.	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**

	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

See factors for differential effects and compliance. Also need to consider other outcomes especially for those with diabetes and CKD and benefits of specific classes to reduce microvascular outcomes.
For consistency with the secondary prevention in those with type 2 diabetes, recommendations for combination therapy have been considered.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
6. Evidence base	A	High quality, low risk reviews over last 5 years
7. Consistency	B	Strongest consistency is for classes to have no clear advantage except for specific prevention effects (eg stroke or heart failure)
8. Clinical impact	A	Remains high
9. Generalisability	A	Diverse, large international populations
10. Applicabilit	A	

Evidence statement

There is no evidence for one BP lowering drug class or any combination of drug classes being more effective than any other for reducing CVD events and all cause mortality generally, nor for the secondary outcome of reduction of BP.

However there may be differential benefits for different classes for example for stroke prevention, calcium channel blockers may be superior to beta blockers; however calcium blockers may be inferior for heart failure prevention compared to the other classes; ARBs may have greater persistence (although effects are equivalent); low-dose thiazides have the strongest evidence across all outcomes however high dose thiazides increase the risk of sudden cardiac death. ACEi and ARBs found to be beneficial for preventing or managing renal complications in those with diabetes or CKD. Beta blockers not recommended as first line agents.

For those with diabetes requiring more than one agent to sufficiently reduce BP, the strongest evidence (based on two two large trials) is for and ACE inhibitor plus a calcium channel blocker. There is weaker evidence for the use of an ACE inhibitor plus a diuretic.

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE OF RECOMMENDATION**	A

a) Treatment should begin with any one of these agents: (Grade A)
   - ACE inhibitor
   - Angiotensin receptor blocker
   - Calcium channel blocker
   - Low dose thiazide or thiazide-like diuretic

b) Blood pressure lowering therapy in people with diabetes should preferentially include an ACE inhibitor or angiotensin receptor blocker. (Grade A)

c) If a second agent is required, the preferred combinations are:
   - ACE inhibitor plus calcium channel blocker (Grade B [Evidence base B –two prespecified subgroup analysis specific to diabetes; Consistency B; Clinical impact A –while risk reductions relatively small large impact for individual; Generalisability A; Applicability A])
   - ACE inhibitor plus low dose thiazide or thiazide-like diuretic (Grade C [Evidence base B –one large study; Consistency C; Clinical impact C; Generalisability A; Applicability A])

d) Blood pressure lowering therapy in people with CKD should begin with an ACE inhibitor or angiotensin receptor blocker. (Grade A)

e) Treatable secondary causes for raised blood pressure should be considered before commencing blood pressure drug therapy. (Practice Point)

UNRESOLVED ISSUES

If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up

For this question we have not reviewed individual studies ie looking at individual drug classes published after the SRs as this would lead to potentially giving greater strength to the individual drug class than the collective.

IMPLEMENTATION OF RECOMMENDATION

Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.

Will this recommendation result in changes in usual care?	**NO**
Are there any resource implications associated with implementing this recommendation?	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**NO**

FORM framework Question 11

Key question(s): Q11 Should blood pressure therapy be initiated with a single drug or with a combination?		**Evidence table ref:**
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
3 Systematic reviews (variable quality): - Chalmers 2004; Law 2009; Staessen 2004 - Refer to prediction model (Figure 3) in Law 2009		**One or more level I studies with a low risk of bias or several level II studies with a low risk of bias**
	B	**One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias**
	C	**One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias**
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
All reviews agree that the most important clinical implication is to get the correct total dosage and therefore appropriate BP control.	A	**All studies consistent**
	B	**Most studies consistent and inconsistency can be explained**
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could*		
	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to**
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Consideration of drug class availability is required for Australian healthcare sector.	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The authors are clear that appropriate dosage and control is the issue – if this is most easily achieved with single or with combination then that is the clinical driver, not that single or combination in and of themselves are more effective. Compliance however should be considered as increasing number of pills decreases compliance.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
11. Evidence base	A	High quality, low risk reviews over last 6 years for at least one recent SR (Law 2009)
12. Consistency	A	
13. Clinical impact	A	Remains high
14. Generalisability	A	Diverse, large international populations
15. Applicability	A	

Evidence statement

Blood pressure therapy can be initiated with a single drug or with a combination. The main indicator is blood pressure control.

"One drug at standard dose reduces CHD by about 24% and stroke by 35% in 60-69 year olds with BP of 90 mmHg. Three drugs at half standard doses doubles this effect, reducing CHD by 45% and stroke by 60%.At higher BP (180/105 mmHg) and lower BP (120/75 mmHg), the effect of one drug at standard dose is about 7-9% greater and smaller respectively. Three drugs at half standard dose is about 12-14 percentage points greater and smaller" (Law et al 2009; see fig 3 for prediction models)

Indicate any dissenting opinions

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE OF RECOMMENDATION**	

a) If monotherapy does not sufficiently reduce blood pressure add a second agent from a different pharmacological class. (Grade A)

b) The following combinations should generally be avoided: (practice point)

- potassium-sparing diuretic plus either ACE inhibitor or angiotensin II receptor antagonist
- beta-blocker plus verapamil

c) If blood pressure is not responding to pharmacotherapy, reassess for: (practice points)

- non-adherence
- undiagnosed secondary causes for raised blood pressure

- hypertensive effects of other drugs
- treatment resistance due to sleep apnoea
- undisclosed use of alcohol or recreational drugs
- unrecognised high salt intake (particularly in patients taking angiotensin- converting enzyme inhibitors or angiotensin II receptor antagonists)
- 'white coat' raised blood pressure
- technical factors affecting measurement
- volume overload, especially with CKD

d) If dual therapy at higher doses does not sufficiently reduce blood pressure, add an additional agent. (Practice point)

e) If combination therapy does not sufficiently reduce blood pressure, consider specialist advice. (Practice point)

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up*	
IMPLEMENTATION OF RECOMMENDATION	
Will this recommendation result in changes in usual care?	**NO**
Are there any resource implications associated with implementing this recommendation? This will be determined by the separate economic analyses.	
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**NO**

FORM framework Question 12

Key question(s): Q12 Should antihypertensive therapy employ drugs at fixed doses or should individuals always be titrated to target blood pressure levels?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There are no specific studies or reviews that answer this question directly. An answer can be inferred by two systematic reviews – Law 2009 and Staessen 2004. One review examined lower versus standard target levels and found there was no benefit for total mortality or CVD events when targeting the lower level – Arguedas 2009		**One or more level I studies with a low risk of bias or several level II studies with a low risk of bias**
	B	**One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias**
	C	**One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias**
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
All reviews agree that the most important clinical implication is to get the correct total dosage and therefore appropriate BP control – this is easier by an individualised approach.	A	**All studies consistent**
	B	**Most studies consistent and inconsistency can be explained**
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could*		
	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to**
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Consideration of drug class availability is required for Australian healthcare sector.	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The authors are clear that appropriate dosage and control is the issue. By inference this requires individualised dosage.

EVIDENCE STATEMENT MATRIX

Component	Rating	Description
1. Evidence base	A	High quality, low risk reviews over last 6 years
2. Consistency	A	
3. Clinical impact	A	Remains high
4. Generalisability	A	Diverse, large international populations
5. Applicability	A	

Evidence statement

Antihypertensive therapy should employ drugs for individuals, titrated to target blood pressure levels (≤ 140-160 /90-100 mmHg). However, there is little direct evidence for specific blood pressure targets.

RECOMMENDATION	**GRADE OF RECOMMENDATION**	
Nil made		

UNRESOLVED ISSUES

If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up

IMPLEMENTATION OF RECOMMENDATION N/A

FORM framework Question 13

Key question(s): Q13 Does more intensive blood pressure lowering produce greater reduction in CVD events and all cause mortality.		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One high quality review examined lower versus standard target levels and found there was no benefit for total mortality or CVD events when targeting the lower level – Arguedas 2009 Other systematic reviews have confirmed a proportional relationship between BP levels and CVD events (Law 2009); and Staessen 2004 confirmed a curvilinear relationship between BP and CVD events. Zanchetti 2009 report a ceiling effect for high risk patients where further reductions in BP do not lead to further reductions in CVD events. (low quality SR)		**One or more level I studies with a low risk of bias or several level II studies with a low risk of bias**
	B	**One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias**
	C	**One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias**
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
All reviews agree that the most important clinical implication is to get the correct total dosage and therefore appropriate BP control to the target level	A	**All studies consistent**
	B	**Most studies consistent and inconsistency can be explained**
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could*		
	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to**
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Consideration of drug class availability is required for Australian healthcare sector.	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The authors are clear that appropriate dosage and control is the issue. Target levels are confirmed as the standard level of ≤ 140-160 /90-100 mmHg. There is a question around specific at risk groups (diabetes and CKD – these are the subject of current reviews, however sensitivity analyses conducted by Aguedas 2009 do not support a lower target level at this point).

NOTE: During finalization of the guidelines several updated MA for diabetes and CKD were identified and reviewed. CKD targets have been under review separately from a CARI guideline working group and hence has undergone more consensus development which was also agreed to be included by this guidelines EWG. The diabetes meta-analysis are more recent and the diabetes clinical community have not had sufficient time to discuss and reach consensus so the EWG agreed to leave current targets but flag new mata-analysis and possibility of change in the future. The guidelines text for both CKD and diabetes targets have been modified but only the CKD recommendation has changed since the systematic literature review. Given the limited direct evidence from trials all recommendations are consensus based.

EVIDENCE STATEMENT MATRIX

Component	Rating	Description
1. Evidence base	B	High quality, low risk reviews over last 6 years; one low quality SR
2. Consistency	A	
3. Clinical impact	A	Remains high
4. Generalisability	A	Diverse, large international populations
5. Applicability	A	

Evidence statement

More intensive blood pressure lowering produces greater reduction in CVD events and all cause mortality but only up to a point. (≤ 140/90 mmHg). There is little direct evidence for targets and this is derived secondarily to previous trials.

Indicate any dissenting opinions

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE OF RECOMMENDATION**	

Pharmacotherapy for blood pressure lowering should aim towards the following targets while balancing the risks/benefits: (consensus based recommendations) • ≤140/90 mmHg for adults without CVD (including those with CKD) • ≤130/80 mmHg for adults with micro or macro albuminuria (UACR >3.5 mg/mmol in women and >2.5 mg/mmol in men) • ≤130/80 mmHg for all adults with diabetes

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up*	
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	**NO**
Are there any resource implications associated with implementing this recommendation?	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**NO**

Subgroup evidence for BP questions:

a. Those deemed clinically high risk as outlined in the assessment guidelines (those with SBP >180 or DBP>110mmHg, diabetes >60yrs, diabetes with microalbuminuria, CKD [see levels below], familial hypercholesterolaemia, cholesterol >7.5mmol/L)

9. Does pharmacological blood pressure lowering reduce CVD events and all cause mortality compared to 'control'?
General evidence statement: Pharmacological blood pressure lowering reduces CVD events and all cause mortality compared to controls.
There is no evidence to suggest that those at high risk as defined do not receive the same or similar benefits of prevention as those who are not deemed at high risk.
Level I evidence (high quality systematic review) confirms that treatment using agents that lower blood pressure reduces cardiovascular morbidity and mortality in patients on maintenance dialysis (Heerspink 2009).

10. What is the evidence for one blood pressure lowering drug class or any combination of drug classes being more effective than any other blood pressure lowering drug class or combination for reducing CVD events and all cause mortality? Report evidence for secondary outcome defined as: Reduction of BP
General: There is no evidence for one BP lowering drug class or any combination of drug classes being more effective than any other for reducing CVD events and all cause mortality, nor for the secondary outcome of reduction of BP.
However there may be differential benefits for different classes for example for stroke prevention, calcium channel blockers may be superior to beta blockers; however calcium blockers may be inferior for heart failure prevention compared to the other classes; ARBs may have greater persistence (although effects are equivalent); low-dose thiazides have the strongest evidence across all outcomes however high dose thiazides increase the risk of sudden cardiac death.
Level I high quality systematic review confirms that the effects of blood pressure lowering are consistent across the range of drug classes for people on maintenance dialysis. The data suggest that renin-angiotensin system blockers, beta blockers and calcium channel blockers are all suitable for use in patients on dialysis. Secondary choices include alpha- blockers and centrally acting agents. Other drug classes such as ACE inhibitors are likely to also be effective (given data from general population studies) but in this review had negative effects that probably arose by chance (Heerspink 2009). The choice of BP lowering drug for people on dialysis should be made on the basis of "general tolerability, side effects profile and other patient variables" (Heerspink 2009, page 1014).
Level II (high quality RCT) investigating a population with Type II diabetes and at least one other high risk factor, an amlodipine-based regimen was associated with a significantly lower incidence of total cardiovascular events and procedures compared with the atenolol-based regimen (hazard ratio 0.86, CI 0.76–0.98, P=0.026) however other endpoints (BP lowering, specific stroke, MI etc events) were non significant (Ostergrem, 2008).

11. Should blood pressure therapy be initiated with a single drug or with a combination?
General: Blood pressure therapy can be initiated with a single drug or with a combination. The main indicator is blood pressure control.
"One drug at standard dose reduces CHD by about 24% and stroke by 35% in 60-69 year olds with BP of 90 mmHg. Three drugs at half standard doses doubles this effect, reducing CHD by 45% and stroke by 60%.At higher BP (180/105 mmHg) and lower BP (120/75 mmHg), the effect of one drug at standard dose is about 7-9% greater and smaller respectively. Three drugs at half standard dose is about 12-14 percentage points greater and smaller" (Law et al 2009; see fig 3 for prediction models)
No reported evidence to suggest high risk people differ from this other than they are more likely to have higher BP and therefore require combination to get necessary high dosage/increased control.

Exceptions to this for people with T2D were reported in:
1. Level II (RCT, Ruilope 2004) where antihypertensive treatment was firstly shown to be more effective than placebo for controlling SBP and DBP in previously untreated participants with type 2 diabetes, exhibiting low threshold BP values. Combination therapy with verapramil SR/trandolapril was more effective than trandolapril alone for controlling DBP.
2. Level II trial (Komajda 2008) reported that for people with type 2 diabetes "when added to metformin or a sulfonylurea, 12 month treatment with rosiglitazone reduces ambulatory BP to a greater extent than when metformin and a sulfonylurea are combined" (page 2).

12. Should antihypertensive therapy employ drugs at fixed doses or should individuals always be titrated to target blood pressure levels?
General: Antihypertensive therapy should employ drugs for individuals, titrated to target blood pressure levels (≤ 140-160 /90-100 mmHg).
No reported evidence to suggest people at high risk differ from this.
Heerspink confirms there are no clear target levels for people on dialysis and that the above level is generally accepted (Heerspink, 2009).

13. Does more intensive blood pressure lowering produce greater reductions in CVD events and all cause mortality?
General: More intensive blood pressure lowering produces greater reduction in CVD events and all cause mortality but only up to a point (≤ 140-160 /90-100 mmHg).
The evidence from one low quality systematic review (Zanchetti 2009) suggests a ceiling effect for high risk patients where further reductions in BP do not lead to further reductions in CVD events.

Howard 2008 conducted an RCT (high quality) to investigate if more aggressive BP targets (SBP<115 mmHg) were beneficial for people with type 2 diabetes. They reported physiological benefits but not for CV events which remained non-significant between the lower target versus standard target groups.

b. Those with atrial fibrillation

No studies found to differentiate those with AF from the general population in BP management

c. High, medium and low absolute risk of CVD

No studies found reporting absolute risk in regard to BP management.

d. Abnormal BP and normal BP

No studies found which differentiated between abnormal and normal BP for BP management

e. Hypercholesterol and normal cholesterol

Those studies which reported cholesterol did not differentiate BP management between hyper and normal.

f. Diabetes and no diabetes

No studies directly compared effects of BP management for people with and without diabetes however studies did look exclusively at response to BP management of people with type II diabetes in relation to Qs as reported above and repeated below:

Q10
Level II (high quality RCT) investigating a population with Type II diabetes and at least one other high risk factor, an amlodipine-based regimen was associated with a significantly lower incidence of total cardiovascular events and procedures compared with the atenolol-based regimen (hazard ratio 0.86, CI 0.76–0.98, P=0.026) however other endpoints (BP lowering, specific stroke, MI etc events) were non significant (Ostergrem, 2008).

Q11
Level II (RCT, Ruilope 2004) where antihypertensive treatment was firstly shown to be more effective than placebo for controlling SBP and DBP in previously untreated participants with type 2 diabetes, exhibiting low threshold BP values. Combination therapy with verapramil SR/trandolarpil was more effective than trandolapril alone for controlling DBP.

Level II trial (Komajda 2008) reported that for people with type 2 diabetes "when added to metformin or a slfonylurea, 12 month treatment with rosiglitazone reduces ambulatory BP to a greater extent than when metformin and a sulfonylurea are combined" (page 2).

Q 13
Howard 2008 conducted an RCT (high quality) to investigate if more aggressive BP targets (SBP<115 mmHg) were beneficial for people with type 2 diabetes. They reported physiological benefits but not for CV events which remained non-significant between the lower target versus standard target groups.

g. Chronic kidney disease and no chronic kidney disease (break down into GFR <45 ml/min, GFR 45-60 ml/min and GFR >60 ml/min)

No studies directly compared effects of BP management for people with and without CKD however one SR did look exclusively at response to BP management of people on maintenance dialysis in relation to Qs as reported above and repeated below:

Q9
Level I evidence (high quality systematic review) confirms that treatment using agents that lower blood pressure reduces cardiovascular morbidity and mortality in patients on maintenance dialysis (Heerspink 2009).

Q10
Level I high quality systematic review confirms that the effects of blood pressure lowering are consistent across the range of drug classes for people on maintenance dialysis. The data suggest that renin-angiotensin system blockers, beta blockers and calcium channel blockers are all suitable for use in patients on dialysis. Secondary choices include alpha- blockers and centrally acting agents. Other drug classes such as ACE inhibitors are likely to also be effective (given data from general population studies) but in this review had negative effects that probably arose by chance (Heerspink 2009). The choice of BP lowering drug for people on dialysis should be made on the basis of “general tolerability, side effects profile and other patient variables” (Heerspink 2009, page 1014).

Q12
Heerspink confirms there are no clear target levels for people on dialysis and that the standard target level is generally accepted (Heerspink, 2009).

6. Lipid lowering therapy (Q14-17)

Search results

Sources	Dates	Total hits	Retrieval list	Final inclusions
Databases Medline; Embase ; Cinahl; PsychINFO Cochrane Library, including CENTRAL Cochrane Controlled Trial Register (CCTR) **Other sources:** pearling; expert working group.	**2002-2010**	**413 + 64**	**49**	**26** Alleman 2006 Amarenco 2009 Ara 2008 Brugt 2009 Chen 2005 Corvol 2003 Delahoy 2009 Edwards 2003 Ginsberg 2010 Hartweg 2008 Henyan 2007 Jun 2010 Keech 2005 Marik 2009 Mikhailidis 2009 Navaneethan 2009 O'Regan 2008 Ray 2010 Ridker 2010 Robinson 2009 Saha 2007 Studer 2005 Thavendiranathan 2006 Vijan 2004 Ward 2007 Zhou 2006
Search terms:	antilipemic agent; hypocholesterolemic agent$. lipid$ adj2 (low$ or depress$) lipid modifying drugs; Dislipidaemia; Statins; HMGCoA inhibitors; familial hypercholesterolemia			

	Added: HMGCoA REductase; Inhibitors, Simvastatin, Clofibrate, Procetafen, Bezafibrate, Niacin, Azetidienes, Colesevelam, Fibrate, Fenofibrate, Nicotinic Acid, Ezetimibe, Anticholesteremic agent, Omega-3 fatty acids, Bioacids

Included literature

Question 14: Does pharmacological lipid modification reduce CVD events and all cause mortality compared to control?	
References	**Comments / Quality**
AMARENCO P, LABREUCHE, J. Stroke (2009) Lipid management in the prevention of stroke: a review and updated meta-analysis of statins for stroke prevention. Lancet 8: 453-63	Good quality SR. Most trials mix primary and secondary prevention. Specific to stroke only.
BRUGTS, J. J., YETGIN, T., HOEKS, S. E., GOTTO, A. M., SHEPHERD, J., WESTENDORP, R. G., DE CRAEN, A. J., KNOPP, R. H., NAKAMURA, H., RIDKER, P., VAN DOMBURG, R. & DECKERS, J. W. (2009) The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. *BMJ,* 338**,** b2376.	High quality. Inclusion criteria of no more than 20% with pre-existing CVD.
DELAHOY, P. J., MAGLIANO, D. J., WEBB, K., GROBLER, M. & LIEW, D. (2009) The relationship between reduction in low-density lipoprotein cholesterol by statins and reduction in risk of cardiovascular outcomes: an updated meta-analysis. Clin Ther, 31, 236-44.	Good quality SR. More trials of secondary than primary prevention
EDWARDS, J., MOORE, A. Statins in hypercholesterolaemia: A dose-specific meta-analysis of lipid changes in randomized, double blind trials. BMC Family Practice, 2003; 4	Good quality SR. Doesn't specifically address CVD events, focuses on cholesterol . Mix primary and secondary prevention
HENYAN, N. N., RICHE, D. M., EAST, H. E. & GANN, P. N. (2007) Impact of statins on risk of stroke: a meta-analysis. Ann Pharmacother, 41, 1937-45.	Good quality SR. Most trials mix primary and secondary prevention
O'REGAN, C., WU, P., ARORA, P., PERRI, D. & MILLS, E. J. (2008) Statin therapy in stroke prevention: a meta-analysis involving 121,000 patients. Am J Med, 121, 24-33	Good quality SR. Most trials mix primary and secondary prevention. Specific to stroke only.
RAY, KK., SESHASAI, SR., ERGOU, S., SEVER, P., JUKEMA, JW., FORD, I., SATTAR, N. (2010) Statins and all-	High quality SR. Only considered mortality (no specific

cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 69,229 participants. Arch Int Med, 170(12), 1024	CVD outcomes included)
ROBINSON, J. G., WANG, S., SMITH, B. J. & JACOBSON, T. A. (2009) Meta-analysis of the relationship between non-high-density lipoprotein cholesterol reduction and coronary heart disease risk. J Am Coll Cardiol, 53, 316-22.	Moderate quality SR. Moderate quality SR. The analysis was confined to CHD events because earlier trials did not report stroke outcomes
THAVENDIRANATHAN, P., BAGAI, A., BROOKHART, M. A. & CHOUDHRY, N. K. (2006) Primary prevention of cardiovascular diseases with statin therapy: a meta-analysis of randomized controlled trials. Arch Intern Med, 166, 2307-13.	Good quality SR.
WARD, S., LLOYD JONES, M., PANDOR, A., HOLMES, M., ARA, R., RYAN, A., YEO, W. & PAYNE, N. (2007) A systematic review and economic evaluation of statins for the prevention of coronary events. *Health Technol Assess,* 11**,** 1-160, iii-iv.	High quality SR. Only 2 trials specifically in those without existing CVD and some others mixed.

LIPIDS: 15. What is the evidence for one lipid modifying drug class or any combination of drug classes being more effective than any other for reducing CVD events and all cause mortality?	
References	**Comments / quality**
Ara R, Tumur I, Pandor A, Duenas A, Williams R, Wilkinson A*, et al.* Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation. *Health Technol Assess* 2008; 12: 1–212.	High quality SR. Not specific to primary prevention.
CHEN, J. T., WESLEY, R., SHAMBUREK, R. D., PUCINO, F. & CSAKO, G. (2005) Meta-analysis of natural therapies for hyperlipidemia: plant sterols and stanols versus policosanol. Pharmacotherapy, 25, 171-83.	Good quality SR.
CORVOL et al 2003, Differential Effects of Lipid-Lowering Therapies on Stroke Prevention, Archives of Internal Medicine;163:669-676	Moderate quality SR. Most trials mix primary and secondary prevention
EDWARDS, J., MOORE, A. Statins in hypercholesterolaemia: A dose-specific meta-analysis of lipid changes in randomized, double blind trials. BMC Family Practice, 2003; 4	Good quality SR. Doesn't specifically address CVD events, focuses on cholesterol . Mix primary and

	secondary prevention
GINSBERG, H. N., ELAM, M. B., LOVATO, L. C., CROUSE, J. R., 3RD, LEITER, L. A., LINZ, P., FRIEDEWALD, W. T., BUSE, J. B., GERSTEIN, H. C., PROBSTFIELD, J., GRIMM, R. H., ISMAIL-BEIGI, F., BIGGER, J. T., GOFF, D. C., JR., CUSHMAN, W. C., SIMONS-MORTON, D. G. & BYINGTON, R. P. 2010. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med, 2010, 362, 1563-74. (ACCORD study)	Good quality RCT. Majority of participants without CVD.
Hartweg J, Perera R, Montori V, Dinneen S, Neil HA, Farmer A. Omega-3 polyunsaturated fatty acids (PUFA) for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2008: CD003205.	High quality SR. Diabetic population (mixed primary/secondary prevention). No CVD endpoints
Hooper L, Thompson RL, Harrison RA, Summerbell CD, Moore H, Worthington HV*, et al.* Omega 3 fatty acids for prevention and treatment of cardiovascular disease. *Cochrane Database Syst Rev*. 2004: CD003177.	High quality. From SIGN guidelines
JUN, M., FOOTE, C., LV, J., NEAL, B., PATEL, A., NICHOLLS, S. J., GROBBEE, D. E., CASS, A., CHALMERS, J. & PERKOVIC, V. (2010) Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. Lancet, 375, 1875-84.	High quality. 4/18 trials specific to primary prevention and a further 4 with mixed populations.
Marik PE, Varon J. Omega-3 dietary supplements and the risk of cardiovascular events: a systematic review. Clin Cardiol. 2009 Jul;32(7):365-72.	Hgh quality SR. Categorises into high and moderate risk (but still mixes primary and secondary prevention)
MIKHAILIDIS, D. P., SIBBRING, G. C., BALLANTYNE, C. M., DAVIES, G. M. & CATAPANO, A. L. (2007) Meta-analysis of the cholesterol-lowering effect of ezetimibe added to ongoing statin therapy. Curr Med Res Opin, 23, 2009-26.	Good quality SR. This paper only presents the results of the analyses including trials of ezetimibe/statin combination therapy, in patients who were not at lipid goal as a result of previous treatment with statin monotherapy
SAHA, S. A., KIZHAKEPUNNUR, L. G., BAHEKAR, A. & ARORA, R. R. (2007) The role of fibrates in the prevention of cardiovascular disease--a pooled meta-analysis of long-term randomized placebo-controlled clinical trials. Am Heart J, 154, 943-53.	Good quality SR. Only 2 trials were completely primary prevention and 2 others partly. Not all trials had appropriate endpoints for this question
STUDER, M., BRIEL, M., LEIMENSTOLL, B., GLASS, T. R. & BUCHER, H. C. (2005) Effect of different anti	Good quality SR.

lipidemic agents and diets on mortality: a systematic review. Arch Intern Med, 165, 725-30.	
WARD, S., LLOYD JONES, M., PANDOR, A., HOLMES, M., ARA, R., RYAN, A., YEO, W. & PAYNE, N. (2007) A systematic review and economic evaluation of statins for the prevention of coronary events. *Health Technol Assess,* 11**,** 1-160, iii-iv.	High quality. Only 2 trials specifically in those without existing CVD
ZHOU, Z., RAHME, E. & PILOTE, L. (2006) Are statins created equal? Evidence from randomized trials of pravastatin, simvastatin, and atorvastatin for cardiovascular disease prevention. Am Heart J, 151, 273-81.	Good quality SR. Mixed primary/secondary prevention

Question 16: Should lipid lowering therapy employ drugs at fixed doses or should individuals always be titrated to target lipid levels?	
References	**Comments / quality**
EDWARDS, J., MOORE, A. Statins in hypercholesterolaemia: A dose-specific meta-analysis of lipid changes in randomized, double blind trials. BMC Family Practice, 2003; 4	Good quality SR. Doesn't specifically address CVD events, focuses on cholesterol. Mix primary and secondary prevention

LIPIDS: 17 Does more intensive lipid modification produce greater reductions in CVD events and all cause mortality?	
References	**Comments / quality**
AMARENCO P, LABREUCHE, J. Stroke (2009) Lipid management in the prevention of stroke: a review and updated meta-analysis of statins for stroke prevention. Lancet 8: 453-63	Good quality SR. Most trials mix primary and secondary prevention. Specific to stroke only.
EDWARDS, J., MOORE, A. Statins in hypercholesterolaemia: A dose-specific meta-analysis of lipid changes in randomized, double blind trials. BMC Family Practice, 2003; 4	Good quality SR. Doesn't specifically address CVD events, focuses on cholesterol. Mix primary and secondary prevention
CORVOL et al 2003, Differential Effects of Lipid-Lowering Therapies on Stroke Prevention, Archives of Internal Medicine;163:669-676	Moderate quality SR. Most trials mix primary and secondary prevention

Evidence details

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: lipids		**Question number: 14**	
Characteristics of study			
Checklist completed by: Jonathan Ucinek			
Study citation	ALLEMANN, S., DIEM, P., EGGER, M., CHRIST, E. R. & STETTLER, C. (2006) Fibrates in the prevention of cardiovascular disease in patients with type 2 diabetes mellitus: meta-analysis of randomised controlled trials. Curr Med Res Opin, 22, 617-23.		
Study design	**Systematic review**	**N (total)**	Eight trials and 12 249 patients with type 2 diabetes were included in the analyses
Search strategy	We aimed to identify all randomised controlled trials of lipid lowering treatment by fibrates that prospectively assessed cardiovascular outcomes in patients with type 2 diabetes mellitus. Using Cochrane methodology13 we searched MEDLINE (from inception to November 2005) and the Cochrane Controlled Trials Register (issue 3, 2005) for relevant studies in any language. Electronic searches were supplemented by manual searching of reference lists, reviews, conference abstracts and specialist journals.		
Selection criteria	We evaluated each study for inclusion in the meta-analysis on the basis of five criteria: (1) study design (randomised controlled trial); (2) comparison of lipid lowering therapy with a fibrate to placebo; (3) inclusion of patients with type 2 diabetes mellitus; (4) follow-up of at least 2 years; and (5) prospective recording of cardiovascular events		
Intervention	fibrates with placebo		
Comparison	placebo		
Outcomes	Cardiovascular outcomes in patients with type 2 diabetes mellitus; Coronary heart disease; Death due to coronary heart disease; Myocardial infarction and stroke		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		WC	To assess the impact of lipid lowering treatment with fibrates on cardiovascular endpoints in patients with type 2 diabetes mellitus. We performed a systematic review and meta-analysis of randomised controlled trials in order to assess the effectiveness of fibrates in the prevention of CHD in this patient group
Description of the methodology used is included		WC	

The literature search was sufficiently rigorous to identify all the relevant studies	WC	
Study quality was addressed and taken into account?	WC	
There were enough similarities between the studies to justify combining them.	WC	
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		
Fibrates are associated with a substantial reduction of CHD events, but their exact role in lipid lowering treatment of patients with type 2 diabetes mellitus remains to be defined.		

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS

Guideline topic: Lipid modification		**Question number: Q. 14 and 17**	
Characteristics of study			
Checklist completed by: Carly			
Study citation	Amarenco P, Labreuche, J. Stroke (2009) Lipid management in the prevention of stroke: a review and updated meta-analysis of statins for stroke prevention. Lancet 8: 453-63		
Study design	**Systematic review**	**N (total)**	26 trials; 165792 patients
Search strategy	Computerized search of PubMed for RTCs testing statin drugs and previous meta-analyses published sept 2003 to Dec 2008 Manual search also performed using reference list from trials identified.		
Selection criteria	Inclusion trials: patients randomly assigned to statin or control Trials relating to primary or secondary prevention of CHD were considered eligible Trials with no data available on stroke end point or in which no stroke event occurred, and trials evaluating dose-response ratio were excluded.		
Intervention	statins		
Comparison	Placebo, control		
Outcomes	All strokes, stroke death, hemorrhagic stroke, LDL-C reduction , carotid atherosclerosis		

Quality of study		
Quality criteria (from SIGN)	***Met?**	**Comments**
SECTION 1: Internal validity		
Study addresses an appropriate and clearly focused question	Y	Well covered
Description of the methodology used is included	Y	Well covered
The literature search was sufficiently rigorous to identify all the relevant studies	Y	Well covered
Study quality was addressed and taken into account?	Y	Well covered – assessed presence of biases, results suggested the presence of some biases in the meta-analysis.
There were enough similarities between the studies to justify combining them.	Y	Adequately addressed.
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or – what is the likely direction in which bias might affect the study results?		
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		
Statins in combination with other preventive strategies shows that each 1mmol/L (39mg/dL) decrease in LDL cholesterol equates to a reduction in relative risk for stroke of 21.1% (95%CI 6.3-33.5, p=0.009).		

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS	
Guideline topic: Lipid modification	**Question number: Q. 14 and 17**
Characteristics of study	
Checklist completed by: Carly	
Study citation	Amarenco, P., Labreuche, J., Lavallee, P., Touboul, P. Statins in Stroke Prevention and Cartoid Atherosclerosis. Systematic Review and Up-to-Date Meta-Analysis. Stroke (2004); 35(12); 2902-2909

Study design	**Systematic review**	**N (total)**	26 trials; >90 000 patients
Search strategy	Computerized search of PubMed for RTCs testing statin drugs and previous meta-analyses published before August 2003 Manual search also performed using reference list from trials identified.		
Selection criteria	Inclusion trials: patients randomly assigned to statin or control Trials relating to primary or secondary prevention of CHD were considered eligible Trials with no data available on stroke end point or in which no stroke event occurred, and trials evaluating dose-response ratio were excluded.		
Intervention	statins		
Comparison	Placebo, control		
Outcomes	All strokes, stroke death, hemorrhagic stroke, LDL-C reduction , carotid atherosclerosis		

Quality of study		
Quality criteria (from SIGN)	***Met?**	**Comments**
SECTION 1: Internal validity		
Study addresses an appropriate and clearly focused question	Y	Well covered
Description of the methodology used is included	Y	Well covered
The literature search was sufficiently rigorous to identify all the relevant studies	Y	Well covered
Study quality was addressed and taken into account?	Y	Well covered – assessed presence of biases, results suggested the presence of some biases in the meta-analysis.
There were enough similarities between the studies to justify combining them.	Y	Adequately addressed.
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or – what is the likely direction in which bias might affect the study results?		
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		

Directly answers Q14: Statins, compared to control trials, significantly reduced all strokes without increasing brain haemorrhage, though stroke death was not significantly reduced.
Statins appear to decrease risk of stroke by lowering LDL-C.
All strokes:

- Main analysis of all trials, summary effect of statins was significant (P<0.0001) with no evidence of heterogeneity between trials (P=0.35). Relative odd reduction was -21% (95% CI, -27% to -15%)

Stroke death:

- 11 trials not included in this analysis
- Remaining 15 trials showed no significant reduction in fatal strokes with statins (P=0.37) with no heterogeneity between trials (P=0.71). Sensitivity analysis: pooled OR of 0.94 (95% CI, 0.78 to 1.13; P=0.52)

Hemorrhagic Stroke:

- 12 trials included in analysis; 49 843 patients, however 4 trials with zero hemorrhagic strokes were not included.
- Findings: hemorrhagic stroke occurred in 78 patients in statin group (0.32%) and 84 patients in control group (0.36%)
- Specific effect of statins on incidence of hemorrhagic stroke was not significant, with a pooled OR of 0.90 (95% CI, 0.65 to 1.22)

Between-group difference in LDL-C Reduction:
Stroke:

- Relationship between size effect of statin treatment on stroke incidence and LDL-C reduction was significant (r=0.58, P=0.002)
- Each 10% LDL-C reduction was estimated to reduce risk of all strokes by 15.6% (95% CI, 6.7 to 23.6)

Carotid IMT:

- 9 trials included
- Analysis found strong correlation between LDL reduction and carotid IMT reduction (r=0.65; P=0.004)
- Each 10% reduction in LDL-C was estimated to reduce carotid IMT by 0.73% per year (95% CI, 0.27 to 1.19)

Template for Intervention Study – Systematic Review		
Topic/question: Lipids Q 14		
Completed by: Kelvin Hill		
REFERENCE: Ara R, Tumur I, Pandor A, Duenas A, Williams R, Wilkinson A*, et al.* Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation. *Health Technol Assess* 2008; 12: 1–212.		
SOURCE OF FUNDING		
SUMMARY		
Inclusion criteria	Types of studies	No RCTs (>12weeks) with clinical endpoints. 13 Phase III RCTs with surrogate end-points used.
	Participants	Inclusion:18 years of age, with diagnosis of primary hypercholesterolaemia and an LDL-c concentration of 3.38–6.50 mmol/l and a TG level of 3.85 mmol/l.
	Interventions	Ezetimibe

	Primary outcome	survival, fatal and non-fatal CV events, adverse effects of treatment and HRQoL.
	Additional outcomes	Where information on clinical end-points is unavailable, consideration was given to surrogate end-points, such as LDL-c, Total-c and HDL-c.
Search		7 databases searched, plus internet plus handsearching. Methodological filter aimed at restricting search results to RCTs was used in the searches of MEDLINE and EMBASE. April –June 2006.
Methods of review	Method of applying inclusion criteria	Two reviewers independently screened all titles and abstracts. Data relating to study design, quality and results were extracted by one reviewer into a standardised data extraction form and independently checked for accuracy by a second reviewer. Any discrepancies were resolved by consensus. Where multiple publications of the same study were identified, data were extracted and reported as a single study. The quality of the included studies was assessed (unblinded) by one reviewer and independently checked for agreement by a second.
	Assessment of methodological quality	Yes The quality of the clinical effectiveness studies was assessed according to criteria based on those proposed by the NHS Centre for Reviews and Dissemination.
Comparisons		Placebo or other lipid lowering (for monotherapy) or statin alone for dual therapy
Main results		For patients not adequately controlled with a statin alone, a meta-analysis of six studies showed that a fixed-dose combination of ezetimibe and statin treatment was associated with a statistically significant reduction in low-density lipoprotein cholesterol (LDL-c) and total cholesterol (Total-c) compared with statin alone ($p < 0.00001$). Four studies (not eligible for metaanalysis) that titrated (either forced or stepwise) the statin doses to LDL-c targets generally showed that the co-administration of ezetimibe and statin was significantly more effective in reducing plasma LDL-c concentrations than statin monotherapy ($p < 0.05$ for all studies). For patients where a statin is not considered appropriate, a meta-analysis of seven studies demonstrated that ezetimibe monotherapy significantly reduced LDL-c levels compared with placebo ($p < 0.00001$). There were no statistically significant differences in LDL-c-lowering effects across different subgroups.
CLINICAL IMPLICATIONS		

QUALITY CHECK

Process	**Questions**	**Answer**	**Comment**
Search:	**Are**:		
	two or more databases named and used	Y	
	reference lists of selected articles searched	Y	
	experts and trialists contacted	N	
	any journals searched by hand	Y	
	databases searched from their inception	Y	
	all languages accepted	Y	
Selection:	**Is there a clear definition of**:		
	the population being studied	Y	
	the interventions being investigated	Y	
	the principal outcomes being studied	Y	
	the study designs included (and excluded)	Y	
Validity:	**Does the review process**:		
	assess (measure, quantify) the quality of studies identified	Y	
	blind reviewers to study origin (authors, journal etc)	N	
	abstract data into a structured database	Y	
	use two independent people to abstract data and assess study quality	Y	

	measure heterogeneity and bias of studies included	Y	
Data:	**For each study are the details (or their absence) noted of**:		
	participants included in study (number and type)	Y	
	interventions studied	Y	
	outcome	Y	
Analysis:	**Does the review process**:		
	undertake meta-analysis or state why not done	Y	
	investigate agreement between independent assessors	Y	
	give confidence intervals for outcomes reported	Y	

Benefits	Ezetimibe with or without statin improves control of LDL-C and TC.
Harms	No significantly increase adverse events
Comments / quality	High quality systematic review.

REASON FOR EXCLUSION (Poor quality +not clinically relevant / interesting or if relevant for preamble)
None

RELEVANCE TO AN AUSTRALIAN CONTEXT
Directly relevant

OVERALL CONCLUSION
Robust HTA with 13 RCTs using surrogate outcomes finding ezetimibe is useful to supplimant or treat cholesterol. Studies were from mixed populations.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic:		**Question number: 14**	
Characteristics of study			
Checklist completed by: Jonathan Ucinek			
Study citation	BRUGTS, J. J., YETGIN, T., HOEKS, S. E., GOTTO, A. M., SHEPHERD, J., WESTENDORP, R. G., DE CRAEN, A. J., KNOPP, R. H., NAKAMURA, H., RIDKER, P., VAN DOMBURG, R. & DECKERS, J. W. (2009) The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. *BMJ,* 338**,** b2376.		
Study design	**Meta-Analysis**	**N (total)**	10 trials enrolled a total of 70 388 people,
Search strategy	Searched the Cochrane Central Register of Controlled Trials, Medline (1990-November 2008), Embase (1980-November 2008), DARE, and the ACP Journal Club for randomised clinical trials that compared statins with a control group in people without established cardiovascular disease but with cardiovascular risk factors. MeSH terms “HMG-CoA reductase inhibitor”, “atorvastatin”, “simvastatin”, “pravastatin”, “fluvastatin”, “rosuvastatin”, or “lovastatin”, and “cardiovascular disease”, “coronary heart disease”, “cerebrovascular disease”, or “myocardial infarction”, “cholesterol”, “LDL” [low density lipoprotein], “HDL” [high density lipoprotein], or “triglycerides”, and primary prevention restricted to randomised controlled trials or meta-analyses.Eexamined the reference lists and related links of retrieved articles in PubMed to detect studies potentially eligible for inclusion.		

Selection criteria	Randomised trials of statins compared with controls (placebo, active control, or usual care) Mean follow-up of at least one year, Reported on mortality or cardiovascular disease events as primary outcomes, and included at least 80% of people without established cardiovascular disease or reported data separately on a sole primary prevention group		
Intervention	Statins –pravastatin, lovastatin, atorvastatin, simvastatin, rosuvastatin		
Comparison	Placebo control or usual care		
Outcomes	Primary end point - all cause mortality. Secondary end points were the composite of major coronary events defined as death from coronary heart disease and non-fatal myocardial infarction, and the composite of major cerebrovascular events defined as fatal and non-fatal stroke; death from coronary heart disease, non-fatal myocardial infarction, revascularisations (percutaneous coronary intervention or coronary artery bypass graft), and cancer (fatal and non-fatal). Clinical outcomes all cause mortality, major coronary events, major cerebrovascular events, and cancer.		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		WC	To investigate whether statins reduce all cause mortality and major coronary and cerebrovascular events in people without established cardiovascular disease but with cardiovascular risk factors, and whether these effects are similar in men and women, in young and older (>65 years) people, and in people with diabetes mellitus.
Description of the methodology used is included		WC	
The literature search was sufficiently rigorous to identify all the relevant studies		WC	
Study quality was addressed and taken into account?		WC	
There were enough similarities between the studies to justify combining them.		WC	We pooled studies using both fixed effect and random effects models.
SECTION 2: Overall assessment of the study			
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
			+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the

		conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		

SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**

The current meta analysis investigates the events in people without established cardiovascular disease but with cardiovascular risk factors, and whether these effects are similar in men and women, in young and older (>65 years) people, and in people with diabetes mellitus, in 10 systematic reviews.

What is already known -Statins are effective in patients with established cardiovascular disease (secondary prevention) but whether the benefits apply to primary prevention is unknown Research has provided ambiguous answers on statin use in people at relatively lower risk Furthermore, the efficacy of statins in subgroups of people aged more than 65, women, and those with diabetes mellitus is debated

What this study adds-Statins improve survival and reduce the risk of major cardiovascular and cerebrovascular events in people without established cardiovascular disease. No significant differences in treatment effect of statins were observed in clinically defined groups for age, sex, and diabetes status People at increased risk for cardiovascular disease should not be denied the relative benefits of long term statin use.

All cause Mortality- During a mean follow-up of 4.1 years 5.7% (1925/ 33 793) of participants died in the control group compared with 5.1% (1725/33 683) in the statin group. Statin therapy was therefore associated with a 12% risk reduction in all cause mortality compared with the control (odds ratio 0.88, 95% confidence interval 0.81 to 0.96; fig 2 and table 2)

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS

Guideline topic: lipids			**Question number: 14**
Characteristics of study			
Checklist completed by: Jonathan Ucinek			
Study citation	CHEN, J. T., WESLEY, R., SHAMBUREK, R. D., PUCINO, F. & CSAKO, G. (2005) Meta-analysis of natural therapies for hyperlipidemia: plant sterols and stanols versus policosanol. Pharmacotherapy, 25, 171-83.		
Study design	**Systematic review**	**N (total)**	52 eligible studies, n=4596
Search strategy	MEDLINE, EMBASE, the WEB of Science, the Cochrane Library from January 1967- June 2003.		
Selection criteria	Only randomized ,double blind, placebo controlled trials were retrieved, and only if they met the following criteria: • LDL levels were reported • Treatment duration was 4 weeks or longer		

	• Study patients were aged 18 years or older • And dosages used were plant sterol and stanols ester equivalents of 2g/day or greater or policosanol 5mg/day or greater.		
Intervention	Stanols, sterols and policosanol		
Comparison	placebo		
Outcomes	LDL levels		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		WC	To compare the efficacy and safety of plant sterols and stanols as well as policosanol in the treatment of coronary heart disease, as measured by a reduction in low-density lipoprotein cholesterol (LDL) levels.
Description of the methodology used is included		WC	
The literature search was sufficiently rigorous to identify all the relevant studies		WC	
Study quality was addressed and taken into account?		WC	
There were enough similarities between the studies to justify combining them.		WC	
SECTION 2: Overall assessment of the study			
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
			+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
			- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?			
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**			
Plant sterols and stanols and policosanol are well tolerated and safe; however, policosanol is more effective than plant sterols and stanols for LDL level reduction and more favorably alters the lipid profile, approaching antilipemic drug efficacy. Note: More power could have been added to sterol, stanols and policosanol treatment effects if studies comparing these treatments vs other antilipid drugs were included. Also trials had heterogenous populations – some normocholesterol, some hyper, some T2D, some women post MI etc.			

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Lipid therapy in the prevention of stroke		**Question number: Q14, Q15 (and subgroup for at risk)**	
Characteristics of study			
Checklist completed by: Janine Dizon			
Study citation	Corvol et al 2003, Differential Effects of Lipid-Lowering Therapies on Stroke Prevention, Archives of Internal Medicine;163:669-676		
Study design	**Systematic review**	**N (total) 38 trials**	10 on primary, 28 on secondary prevention (83161 subjects)
Search strategy	Computerized PubMed search of the literature to identify all trials testing Lipid-Lowering Therapies (LLTs), English language articles published between 1966 and 2001. Reference lists of published trials		
Selection criteria	Inclusion: 1. Randomized trials which examined the effects of any lipid lowering treatment vs placebo 2. Trials providing data on stoke incidence (fatal and/or non fatal stroke) 3. English articles published between 1996-2001 **Trials enrolling participants free of heart disease at baseline (primary prevention) and trials selecting participants with heart disease history (secondary prevention) were also included		
Intervention	Lipid-Lowering Therapies (LLTs): statins, other cholesterol-lowering drugs, diets, and "other" interventions		
Comparison	vs placebo		
Outcomes	baseline cholesterol and final cholesterol levels, percent of cholesterol reduction, stroke incidence		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		Well covered	
Description of the methodology used is included		Adequately addressed	The review had a very good way of reporting how analysis was done. However, search terms used were not identified.
The literature search was sufficiently rigorous to identify all the relevant studies		Adequately addressed	Electronic database search was conducted in PubMEd only. However, reference lists were also searched and other ways to identify trials were also done
Study quality was addressed and taken into account?		Not addressed	
There were enough similarities between the studies to justify combining them.		Well covered	

SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
	+	+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?	Only one database searched. This review did not assess the quality of the trials.	
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		
This review covered randomized trials which is the study design of choice to answer the research question. One major strength of the review is that it was able to statistically pool the results from the trials identified. The results of this meta-analysis provide strong evidence in favor of the potential of LLTs to prevent stroke and the most convincing effects are with statins. • Optimal prevention appears to be obtained when total cholesterol level is lowered to less than 232 mg/dL(6.0 mmol/L). • Effect models suggest RRR for stroke occur irrespective of level or risk (subgroup q) • Statins most effective with RRR of 24% cf overall RRR of 17% for all interventions, for stroke incidence. • No risk reduction benefits for fatal stroke though		

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Lipids		**Question number: 14**	
Characteristics of study			
Checklist completed by: Jonathan Ucinek			
Study citation	DELAHOY, P. J., MAGLIANO, D. J., WEBB, K., GROBLER, M. & LIEW, D. (2009) The relationship between reduction in low-density lipoprotein cholesterol by statins and reduction in risk of cardiovascular outcomes: an updated meta-analysis. Clin Ther, 31, 236-44.		
Study design	**Systematic review**	**N (total)**	25trials involving 155,613 subjects
Search strategy	English only, (1966-December 2008) MEDLINE, EMBASE, Derwent drug file databases, and the Cochrane library using standard MESH terms *(cardiovascular disease, death, fatal outcome, pravastatin, simvastatin, atorvastatin, rosuvastatin, fluvastatin, lovastatin,* and *hydroxymethylglutaryl coenzyme A reductase inhibitors,* combined with Boolean operators)		
Selection criteria	randomized trials of statins (placebo controlled, active controlled, or usual care) that reported clinical outcomes, enrolled >1000 subjects, and followed them up for ~1 year.		
Intervention	statins		
Comparison	Placebo, active controlled, usual care.		
Outcomes	• LDL-C at 1 year and • RR of cardiovascular end points (vascular mortality, major coronary events [defined as nonfatal myocardial infarction or		

	coronary heart disease death], • major vascular events [defined as major coronary event, fatal or nonfatal stroke, or coronary revascularization], • fatal and nonfatal stroke)

Quality of study		
Quality criteria (from SIGN)	***Met?**	**Comments**
SECTION 1: Internal validity		
Study addresses an appropriate and clearly focused question	WC	The objective of our analyses was to extend the CITC results by including active controlled trials and other trials published since 2005.
Description of the methodology used is included	WC	
The literature search was sufficiently rigorous to identify all the relevant studies	WC	
Study quality was addressed and taken into account?	AC	
There were enough similarities between the studies to justify combining them.	AC	
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		

SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**

Based on meta-regression analysis of these trials, there was a significant positive relationship between reduction in LDL-C by use of statins and reduction in the risk for major cardiovascular events. These results support and extend the findings of the CTTC (Cholesterol Treatment Trialists' Collaboration).

Separate analysis between primary and secondary studies showed no difference in above findings.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS

Guideline topic:	**Question number: Q. 14, 15, 16, 17**

Characteristics of study			
Checklist completed by: Carly			
Study citation	Edwards, J., Moore, A. Statins in hypercholesterolaema: A dose-specific meta-analysis of lipid changes in randomized, double blind trials. BMC Family Practice, 2003; 4		
Study design	**Systematic review**	**N (total)**	91 trials; 43, 404 patients on statins and 25, 081 were on placebo
Search strategy	PubMed, Cochrane Library and in-house files were searched September 2001.Followed QOROM guidelines.		
Selection criteria	Included: • Randomised, double blind controlled trials • Had a mean total cholesterol of at least 5.0mmol/L at baseline • Provided baseline and outcome data for total cholesterol, LDL, HDL and triglycerides. • Studies at of least 3 months. Excluded: • Studies without baselines • Studies with fewer than 20 participants • Studies than combined statin plus another drug • Trials examining patients with familial hyperchoelsterolaemia, diabetes mellitus, renal or hepatic pathology		
Intervention	Atorvastatin, Cerivastatin, Fluvastatin, Lovastatin, Provastatin, Rosuvastatin, Simvastatin		
Comparison	Placebo, control		
Outcomes	Total cholesterol, LDL-C, HDL-C, trigylcerides.		

Quality of study		
Quality criteria (from SIGN)	***Met?**	**Comments**
SECTION 1: Internal validity		
Study addresses an appropriate and clearly focused question	Y	Well covered
Description of the methodology used is included	Y	Well covered
The literature search was sufficiently rigorous to identify all the relevant studies	Y	Well covered
Study quality was addressed and taken into account?	Y	Well covered
There were enough similarities between the studies to justify combining them.	Y	Well covered

SECTION 2: Overall assessment of the study

How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or – what is the likely direction in which bias might affect the study results?		

SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**

- Q14. Compared to placebos, different statin at range of doses reduced total cholesterol by 17-35%, and LDL by 24-49%
- Addresses question of intensive lipid lowering: Lower doses of statin produced less cholesterol lowering
- Doesn't specifically address CVD events, focuses on cholesterol
- Reductions in total cholesterol of 25% or more and LDL cholesterol of more than 30% or more were recorded for fixed doses of simvastatin 40 mg, atorvastatin 10 mg, and rosuvastatin 5 mg and 10mg.
- Simvastatin and atorvastatin are the most commonly prescribed statins in the UK.
- Of the other statins, cerivastatin has been withdrawn, and rosuvastatin has only recently become available. Rosuvastatin produced the largest reductions in total and LDL cholesterol at 5 mg or 10 mg, though involving relatively few patients (Figure 6).
- Overall, there appeared to be no major difference between… two dose titration regimens or use of a fixed dose in the longer duration studies (p17).

Atorvastatin:

- 5 trials, 1 334 patients
- **Total cholesterol**: for all doses combined, mean initial concentration of total cholesterol was 7.2mmol/L and mean reduction was 2.0mmol/L, 27%
- **LDL cholesterol**: Dose combined, initial concentration of LDL was 5.0mmol/L; mean reduction 1.8mmol/L (36%)
- **HDL cholesterol**: initial concentration 1.30mmol/L, mean increase was 0.1mmol/L (7%)
- **Triglycerides**: initial was 2.0mmol/L, mean reduction was 0.34mmol/L (17%)

Cerivastatin:

- 5 trials, 2 316 patients given various doses (fixed or titrated)
- **Total cholesterol:** Doses combined, mean initial concentration was 7.4mmol/L, weighted mean reduction from baseline was 1.6mmol/L (21%)
- **LDl cholesterol:** Mean initial concentration 5.2mmol/L, mean reduction was 1.4 mmol/L (26%)
- **HDL cholesterol:** Initial concentration 1.3mmol/L and mean increase was 0.1mmol/L (7%)
- **Triglycerides:** Initial concentration was 2.1mmol/L, mean reduction was 0.3mmol/L (13%)

Fluvastatin:

- Nine trials, 1 209 patients given various doses
- **Total cholesterol:** Initial concentration 7.5mmol/L, mean reduction was 1.6 mmol/L (21%)
- **LDL cholesterol:** Initial: 5.3mmol/L, mean reduction was 1.6mmol/L (30%)

- **HDL cholesterol:** initial 1.3mmol/L, mean increase 0.1mmol/L (7%)
- **Triglycerides:** Initial concentration 1.9mmol/L, mean reduction 0.2mmol/L (10%)

Lovastatin:

- 13 trials, 8 561 patients
- No evidence of dose response in titration studies using 10-60mg, 20-40mg, 20-80mg, or 40-80mg
- A fixed dose o f20mg per day produced smaller changes than higher doses
- **Total cholesterol:** Doses combined: initial concentration 6.9mmol/L, mean reduction of 1.2mmol/L (17%). With fixed doses of 20mg, 40 or 80mg daily over 12 weeks to 2 years, initial concentrations were 6.7 or 6.8mmol/L and mean reductions were 1.2, 1.5 and 2.0mmol/L (17%, 23%, 29%) respectively
- **LDL cholesterol:** Initial concentration 4.8mmol/L, mean reduction of 1.5mmol/L (30%). With fixed doses of 20mg, 40 or 80mg daily over 12 weeks to 2 years, initial concentrations were 4.7 or 4.8mmol/L and mean reductions were 1.1, 1.4 and 1.6mmol/L (24%, 30%, 34%) respectively
- **HDL cholesterol:** Combined initial con. 1.3mmol/L and mean increase was 0.1mmol/L (7%)
- **Triglycerides:** Initial 1.8mmol/L, mean reduction 0.3mmol/L (15%)

Provastatin:

- 44 trials, 11 811 patients given various fixed or titrated doses
- No evidence of does response with fixed doses of 10, 15, 20 or 40mg or with titrated doses of 10-20mg, 10-40mg, 20-40mg or 40-80mg daily
- **Total cholesterol:** Doses combined, initial con. 6.6mmol/L, mean reduction 1.3mmol/L (20%). With 40mg, initial concentration was 6.5mmol/L and mean reduction was 1.3mmol/L (21%)
- **LDL:** For all doses, mean initial concentration was 4.5mmol/L and mean reduction was 1.2mmol/L (27%). With pravastatin 40mg initial concentration was 4.4mmol/L and reduction was 1.2mmol/L (28%)
- **HDL:** All doses, initial con. 1.1mmol/L and mean increase 0.1mmol/L (12%). Pravastatin 40mg, initial concentration was 1.1mmol/L and mean reduction was 0.2mmol/L (14%)
- **Triglycerides:** Doses combined, initial concentration 1.8mmol/L, reduction 0.2mmol/L (12%). Results same for 40mg

Rosuvastatin:

- Four trials, 1005 patients given 5mg or 10mg daily
- **Total cholesterol:** Pooled data for 5 and 10mg: initial concentration was 7.2mmol/L, reduction 2.2mmol/L (31%). For 5mg and 10gm, mean initial concentrations were 7.3 and 7.2mmol/L respectively and reductions were 2.2 and 2.3 mmol/L (30% and 33%)
- **LDL:** Pooled data was 4.8mmol/L and mean reduction was 2.2mmol/L (46%). Pooled data for 5-80mg or 10-80mg daily with mean initial concentration of 4.8mmol/L showed mean reduction of 2.3mmol/L (48%)
- **HDL:** Pooled data for 5mg or 10mg, initial concentration was 1.0mmol/L, mean increase was 0.1mmol/L (9%). Pooled data was rosuvastatin 5-80mg or 10-80mg daily with mean initial concentration of 1.4mmol/L showed increase of 0.06mmol/L (4.2%)
- **Triglycerides:** Pooled data for 5mg or 10mg, initial concentration was 2.0mmol/L, mean reduction was 0.4mmol/L (18%). Pooled data was rosuvastatin 5-80mg or 10-80mg daily with mean initial concentration of 2.0mmol/L showed reduction of 0.4mmol/L (19%)

Simvastatin:

- 30 trials, 17 143 patients given various doses
- **Total cholesterol:** All doses, mean initial conc. 6.2mmol/L, mean reduction was 1.6mmol/L (25%) Fixed doses of 20, 40 or 80mg daily, mean initial concentrations were 6.5, 5.7 and 7.9mmol/L and mean reductions were 1.4, 1.5, and 2.8mmol/L (21%, 26%, 35%) respectively. With 20-40mg, initial conc. 6.5mmol/L and reduction was 1.6mmol/L (25%)

- **LDL:** All doses, mean initial conc. 4.0mmol/L, mean reduction was 1.4mmol/L (34%) . Fixed doses of 20 or 40 daily, mean initial concentrations were 4.8, and 3.4mmol/L and mean reductions were 1.8, and 1.2mmol/L (37%, 34%) respectively. With 20-40mg, initial conc. 4.9mmol/L and reduction was 1.7mmol/L (36%)
- **HDL**: All doses, mean initial conc. 1.1mmol/L, mean increase was 0.1mmol/L (6%). Fixed doses of 20 or 40 daily, mean initial concentrations were 1.2, and 1.1mmol/L and mean increases were 0.1, and 0.04mmol/L (8%, 4%) respectively. With 20-40mg, initial conc. 1.2mmol/L and reduction was 0.1mmol/L (8%)
- **Triglycerides**: All doses, mean initial conc. 2.0mmol/L, mean reduction was 0.4mmol/L (17%). Fixed doses of 20 or 40 daily, mean initial concentrations were 1.9, and 2.2mmol/L and mean reductions were 0.3, and 0.4mmol/L (17%, 18%) respectively. With 20-40mg, initial conc. 1.5mmol/L and reduction was 0.2mmol/L (10%)

Placebo:

- 47 compared statin with placebo (25 081 patients)
- Mean initial concentration for total cholesterol: 6.2mmol/L, reduction 0.00f4mmol/L (0.07%)
- LDL: 4.1mmol/L and reduction was 0.2mmol/L (6%)
- HDL: 1.1mmol/L, increase was 0.04mmol/L (3%)
- Triglycerides: 2.0mmol/L and reduction 0.1 mmol/L (7%)

METHODOLOGY CHECKLIST: RANDOMISED CONTROLLED TRIALS

Study citation (*Include author, title, year of publication, journal title, pages*) GINSBERG, H. N., ELAM, M. B., LOVATO, L. C., CROUSE, J. R., 3RD, LEITER, L. A., LINZ, P., FRIEDEWALD, W. T., BUSE, J. B., GERSTEIN, H. C., PROBSTFIELD, J., GRIMM, R. H., ISMAIL-BEIGI, F., BIGGER, J. T., GOFF, D. C., JR., CUSHMAN, W. C., SIMONS-MORTON, D. G. & BYINGTON, R. P. 2010. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med, 2010, 362, 1563-74. ACCORD study			
Guideline topic: Lipids	Key Question No: 14 and 15		
Checklist completed by: Jonathan Ucinek			
Section 1: Internal validity			
	Quality criteria (from SIGN)	***Met?**	**Comments**
1.1	The study addresses an appropriate and clearly focused question.	WC	We investigated whether combination therapy with a statin plus a fibrate, as compared with statin monotherapy, would reduce the risk of cardiovascular disease in patients with type 2 diabetes mellitus who were at high risk for cardiovascular disease. The hypothesis that we tested in ACCORD Lipid was that in high-risk patients

			with type 2 diabetes, combination treatment with a fibrate (both to raise HDL cholesterol levels and to lower triglyceride levels) and a statin (to reduce LDL cholesterol levels) would reduce the rate of cardiovascular events, as compared with treatment with a statin alone
1.2	The assignment of subjects to treatment groups is randomised	WC	We randomly assigned 5518 patients with type 2 diabetes who were being treated with open-label simvastatin to receive either masked fenofibrate or placebo. The primary outcome was the first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The mean follow-up was 4.7 years. The ACCORD study was a randomized trial conducted at 77 clinical sites organized into seven networks in the United States and Canada
1.3	An adequate concealment method is used	WC	
1.4	Subjects and investigators are kept 'blind' about treatment allocation	WC	Open Label treatment
1.5	The treatment and control groups are similar at the start of the trial	WC	
1.6	The only difference between groups is the treatment under investigation	WC	
1.7	All relevant outcomes are measured in a standard, valid and reliable way	WC	
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	Not Reported	

1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)	WC	Intent to treat
1.10	Where the study is carried out at more than one site, results are comparable for all sites	Not addressed	
Section 2: Overall assessment of the study			
2.1	How well was the study done to minimise bias? *Code ++, +, or -*	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
			+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
			- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
2.2	If coded as +, or - what is the likely direction in which bias might affect the study results?		
2.3	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?		
2.4	Are the results of this study directly applicable to the patient group targeted by this guideline?		
Section 3: Description of the study (the following information is required to complete evidence tables facilitating cross-study comparisons. Please complete all sections for which information is available).			

Please print clearly		
3.1	Do we know who the study was funded by?	[ ] Academic Institution [ ] Healthcare Industry [ ] Government [ ] NGO [ ] Public funds [ ] Other Fenofibrate and matching placebo were donated by Abbott Laboratories; simvastatin was donatedby Merck. The drug manufacturers had no role in the design of the study, in the accrual or analysis of the data, or in the preparation of the manuscript. All authors vouch for the accuracy and completeness of the reported data.
3.2	How many centres are patients recruited from?	The ACCORD study was a randomized trial conducted at 77 clinical sites organized into seven networks in the United States and Canada N=5518 patients
3.3	From which countries are patients selected? *(Select all those involved. Note additional countries after "Other")*	[ ] Scotland [ ] UK [x] USA [x] Canada [ ] Australia [ ] New Zealand [ ] France [ ] Germany [ ] Italy [ ] Netherlands [ ] Scandinavia [ ] Spain [ ] Other:
3.4	What is the social setting (ie type of environment in which they live) of patients in the study?	[ ] Urban [ ] Rural [x] Mixed
3.5	What criteria are used to decide who should be INCLUDED in the study?	All patients in the ACCORD study had type 2 diabetes and a glycated hemoglobin level of 7.5% or more. If patients had evidence of clinical cardiovascular disease, the age range was limited to 40 to 79 years; if they had evidence of subclinical cardiovascular disease or at least two additional cardiovascular risk factors, the age range was compressed to 55 to 79 years. Patients were specifically eligible to participate in the lipid trial if they also had the following: an LDL cholesterol level of 60 to 180 mg per deciliter (1.55 to 4.65 mmol per liter), an HDL cholesterol level below 55 mg per deciliter (1.42 mmol per liter) for women and blacks or below 50 mg per deciliter (1.29 mmol per liter) for all other groups, and a triglyceride level below 750 mg per deciliter (8.5 mmol per liter) if they were not receiving lipid therapy or below 400 mg per deciliter (4.5 mmol per liter) if they were receiving lipid therapy. All patients provided written informed consent. Additional details regarding eligibility and the protocol for the enrollment of patients are available in

		Section 3 in Supplementary Appendix 1
3.6	What criteria are used to decide who should be EXCLUDED from the study?	**Not addressed**
3.7	What intervention or risk factor is investigated in the study? (Include dosage where appropriate)	The effect of combination therapy of statin and fibrate on the rate of CVD events in high risk patients with type 2 diabetes.
3.8	What comparisons are made in the study? (ie what alternative treatments are used to compare the intervention with?). Include dosage where appropriate.	Fibrate therapy with Statin therapy versus statin therapy on its own Average daily dose of simvastatin during the follow-up period was 22.3 mg in the fenofibrate group and 22.4 mg in the placebo group
3.9	What methods were used to randomise patients, blind patients or investigators, and to conceal the randomisation process from investigators?	Randomization was performed centrally on the trial’ s Web site with the use of permuted blocks to maintain concealment of study-group assignments.
3.10	How long did the active phase of the study last?	4.7years of treatment and follow up

3.11	How long were patients followed-up for, during and after the study?	4.7years of treatment and follow up		
3.12	List the key characteristics of the patient population. Note if there are any significant differences between different arms of the trial.	type 2 diabetes mellitus who were at high risk for cardiovascular disease		
3.13	Record the basic data for each arm of the study. If there are more than four arms, note data for subsequent arms at the bottom of the page			
	Arm 1: **Treatment:** Fenofibrate with Simvastatin **Sample size:** Fenofibrate (N = 2765) **No. analysed** **With outcome: yes** **Without outcome:**	**Arm 2:** **Treatment:** placebo with Simvastatin **Sample size:** Placebo(N = 2753) **No. analysed** **With outcome:** **Without outcome** **Primary outcome?**		
3.14	Record the basic data for each IMPORTANT outcome in the study. If there are more than four, not data for additional outcomes at the bottom of the page.			
	Outcome 1: The primary outcome was the first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes	**Outcome 2:** **Lipids** • mean LDL cholesterol level fell from 100.0 to 81.1 mg per deciliter (2.59 to 2.10 mmol per liter) in the fenofibrate group and from 101.1 to 80.0 mg per deciliter(2.61 to 2.07 mmol per liter) in the placebo group (Fig. 1, and Section 16 in Supplementary Appendix 1).	**Outcome 3:** **Value:** **Measure:**	**Outcome 4:** **Value:** **Measure:**

	Value: **Measure:** Primary outcome (major fatal or nonfatal cardiovascular event) in fenofibrate group 291,rate 2.24 per year and in placebo group 310, rate 2.41 per year; hazard ratio 0.92 (0.79–1.08) p=0.32 **P value** **Upper CI** **Lower CI** **Primary outcome? Yes**	• Mean HDL cholesterol levels increased from 38.0 to 41.2 mg per deciliter (0.98 to 1.07 mmol per liter) in the fenofibrate group and from 38.2 to 40.5 mg per deciliter (0.99 to 1.05 mmol per liter) in the placebo group. • Median plasma triglyceride levels decreased from 164 to 122 mg per deciliter (1.85 to 1.38 mmol per liter) in the fenofibrate group and from 160 to 144 mg per deciliter (1.81 to 1.63 mmol per liter) in the placebo group. **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**	**P value** **Upper CI** **Lower CI** **Primary outcome?**	**P value** **Upper CI** **Lower CI** **Primary outcome?**
3.15	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question. *{Much of this is likely to be contributed by GDG members).*			
	The combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke, as compared with simvastatin alone. These results do not support the routine use of combination therapy with fenofibrate and simvastatin to reduce cardiovascular risk in the majority of high-risk patients with type 2 diabetes.			

* Assessment of whether the criteria has been met should be made according to one of the following descriptors

Well covered
Adequately addressed
Poorly addressed

Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
Not applicable.

Template for Intervention Study – Systematic Review		
Topic/question: Lipids		
Completed by: Kelvin Hill		
REFERENCE: Hartweg J, Perera R, Montori V, Dinneen S, Neil HA, Farmer A. Omega-3 polyunsaturated fatty acids (PUFA) for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2008: CD003205.		
SOURCE OF FUNDING not stated		
SUMMARY		
Inclusion criteria	Types of studies	Twenty three randomised controlled trials (1075 participants) were included with a mean treatment duration of 8.9 weeks. Papers of any language were considered. Trials were eligible if they were randomized placebo or vegetable oil controlled trials of omega-3 polyunsaturated fatty acids (PUFA) (including cross-over trials) as the only intervention in participants with type 2 diabetes. As no phase-specific information was available for cross-over trials, data were used only from the first intervention period to prevent measurements from the second period being affected by effects carried over from the first intervention period. Where serial measurement of an outcome was given during the intervention phase, data were obtained from the final measurement since that measurement was considered the conclusion of the study. The effect of trial design was explored in a sensitivity analysis.
	Participants	Adults with type 2 diabetes mellitus
	Interventions	dietary supplementation with omega-3 PUFA were included. No restrictions were imposed on dose or formulation, although trials where the effect of omega-3 PUFA could not be separated from the effect of simultaneously applied interventions, such as exercise or monounsaturated fatty acids, were not included.
	Primary outcome	fatal myocardial infarction or sudden cardiac death; •proven non-fatal myocardial infarction; •coronary or peripheral revascularization procedures.
	Additional outcomes	•triglycerides; total cholesterol; HDL cholesterol; LDL cholesterol; VLDL cholesterol; HbA1c; fasting glucose; fasting insulin; body weight; adverse effects
Search		We carried out a comprehensive search of The **Cochrane** Library, MEDLINE, EMBASE, bibliographies of relevant papers and contacted experts for identifying additional trials. Our original search was conducted for publications from 1966 to 2000, and the second search was conducted up to 2006. Dr CR Sirtori (Milan) and Dr E Ryan (Edmonton, Alberta), two trialists, were consulted in an attempt to identify any other overlooked, unpublished or ongoing studies. We did not attempt to contact other authors where the size of the trials was small.

Methods of review	Method of applying inclusion criteria	The titles, abstracts and keywords of every record were retrieved to determine the relevant trials. Full articles were retrieved for further assessment if the information given suggested that the trial (1) included patients with type 2 diabetes mellitus, (2) compared fish oil with placebo or vegetable oil, (3) assessed one or more clinically relevant outcome measures, (4) used random allocation for the comparison groups. When there was any doubt regarding these criteria from the information given in the title and abstract, the full article was retrieved for clarification. When differences in opinion existed, these were resolved by consensus referring back to the original article.The full articles retrieved were examined independently by the two investigators to identify relevant trials. Discrepancies were resolved by consensus.
	Assessment of methodological quality	Two investigators independently assigned quality scores to studies with discrepancies resolved by consensus. A score developed from the criteria of Jadad and Schulz (Jadad 1996; Schulz 1995) was used to assess study quality, which had a possible range from zero to five with a cutoff of two used to designate studies of high versus low quality. The criteria used were: •Was the study randomised? Was the method of randomisation appropriate? •Was the study double-blinded? Were the methods of blinding appropriate? •Was compliance assessed? •Were there dropouts and withdrawals and were the numbers and reasons for withdrawal stated? Did more than 80 percent of those randomized complete the study? Kappa values were calculated for inter-rater agreement on quality.
Comparisons		No restrictions were placed on the range of compounds used as controls in the study. Some vegetable oils contain omega-3 PUFA, or complex fatty acids that might be metabolised to form omega-3 PUFA.
Main results		The mean dose of omega-3 PUFA used in the trials was 3.5 g/d. No trials with vascular events or mortality endpoints were identified. Among those taking omega-3 PUFA triglyceride levels were significantly lowered by 0.45 mmol/L (95% confidence interval (CI) -0.58 to -0.32, P < 0.00001) and VLDL cholesterol lowered by -0.07 mmol/L (95% CI -0.13 to 0.00, P = 0.04). LDL cholesterol levels were raised by 0.11 mmol/L (95% CI 0.00 to 0.22, P = 0.05). No significant change in or total or HDL cholesterol, HbA1c, fasting glucose, fasting insulin or body weight was observed. The increase in VLDL remained significant only in trials of longer duration and in hypertriglyceridemic patients. The elevation in LDL cholesterol was non-significant in subgroup analyses. No adverse effects of the intervention were reported.
CLINICAL IMPLICATIONS		

QUALITY CHECK

Process	**Questions**	**Answer**	**Comment**
Search:	**Are**:		
	two or more databases named and used	y	
	reference lists of selected articles searched	y	
	experts and trialists contacted	y	
	any journals searched by hand	n	
	databases searched from their inception	y	Update of previous search
	all languages accepted	y	
Selection:	**Is there a clear definition of**:		
	the population being studied	Y	
	the interventions being investigated	Y	

	the principal outcomes being studied	Y	
	the study designs included (and excluded)	Y	
Validity:	**Does the review process**:		
	assess (measure, quantify) the quality of studies identified	Y	
	blind reviewers to study origin (authors, journal etc)	N	
	abstract data into a structured database	Y	
	use two independent people to abstract data and assess study quality	Y	
	measure heterogeneity and bias of studies included	Y	
Data:	**For each study are the details (or their absence) noted of**:		
	participants included in study (number and type)	Y	
	interventions studied	Y	
	outcome	Y	
Analysis:	**Does the review process**:		
	undertake meta-analysis or state why not done	Y	
	investigate agreement between independent assessors	Y	
	give confidence intervals for outcomes reported	Y	

Benefits	Decrease triglyceride levels. No CVD endpoints
Harms	No adverse events noted.
Comments / quality	High quality systematic review specifically looking at those with diabetes

REASON FOR EXCLUSION (Poor quality +not clinically relevant / interesting or if relevant for preamble)
Include

RELEVANCE TO AN AUSTRALIAN CONTEXT
relevant

OVERALL CONCLUSION
Omega 3 supplements appear to reduce cholesterol (triglyc). It is unclear what effect this has on CVD endpoints.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS

Guideline topic: lipids			**Question number:**
Characteristics of study			
Checklist completed by: Jonathan Ucinek			
Study citation	HENYAN, N. N., RICHE, D. M., EAST, H. E. & GANN, P. N. (2007) Impact of statins on risk of stroke: a meta-analysis. Ann Pharmacother, 41, 1937-45.		
Study design	**Systematic review**	**N (total)**	26 trials, n=100,560: Ischemic stroke 6 trials, n= 37, 292. 9 trials, hemorrhagic stroke n= 57,895
Search strategy	Search of MEDLINE, EMBASE, Cumulative index to nursing and Allied Health literature, and web of science from June 1975 through September 2006. Manual review of abstracts presented at meetings of the American college of cardiology, the American college of clinical pharmacy, and the American stroke association from 2001 to 2006. References from articles were also reviewed to identify additional		

	relevant studies.		
Selection criteria	Included if they met the following • Controlled clinical trials versus placebo • Well-described protocol • Data reported on incidence of all CVEs, ischemic stroke, or hemorrhagic stroke Excluded if • Cerivastatin was the active treatment • If there were no events in either group • Control group included an active therapy or standard of care • Abstracts not reporting on stroke		
Intervention	Statin		
Comparison	Placebo		
Outcomes	CVEs, Ischemic stroke, Hemorrhagic stroke		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		WC	To perform a meta analysis of randomized controlled trials to assess the effect of statin therapy on all cerebrovascular events (CVEs), ischemic stroke and hemorrhagic stroke.
Description of the methodology used is included		AC	
The literature search was sufficiently rigorous to identify all the relevant studies		WC	
Study quality was addressed and taken into account?		AC	
There were enough similarities between the studies to justify combining them.		AC	
SECTION 2: Overall assessment of the study			
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
			+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
			- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?			
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your**			

own view of its strengths and weaknesses, and how it will help to answer the key question.
Note – most studies were a mixture of primary and secondary CVD prevention. Conclusions: Statin therapy significantly reduces risk of developing all CVEs and ischemic stroke; however, it is associated with a non significant increase in risk of hemorrhagic stroke. • Statin therapy significantly reduced the risk of all CVEs (RR 0.83; 95% CI 0.76 to 0.91) • Statin therapy significantly reduced the risk of ischemic stroke (RR 0.79; 95% CI 0.63 to 0.99) • Statin therapy non-significantly increased the risk of hemorrhagic stroke (RR 1.11;95% CI 0.77 to 1.60)

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS

Guideline topic: Lipids			Question number: 14
Characteristics of study			
Checklist completed by: Jonathan ucinek			
Study citation	JUN, M., FOOTE, C., LV, J., NEAL, B., PATEL, A., NICHOLLS, S. J., GROBBEE, D. E., CASS, A., CHALMERS, J. & PERKOVIC, V. (2010) Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. Lancet, 375, 1875-84.		
Study design	**Systematic review**	**N (total)**	identified 18 trials providing data for 45 058 participants
Search strategy	Used PRISMA statement for the conduct of meta-analyses of intervention studies. Data sources: Medline via Ovid (from 1950 to March, 2010), Embase (from 1966 to March, 2010), and the Cochrane Library database (Cochrane Central Register of Controlled Trials; no date restriction), with relevant text words and medical subject headings that included all spellings of fibrate, clofibrate, clofibric acid, bezafibrate, gemfibrozil, fenofibrate, procetofen, mortality, cardiovascular disease, myocardial infarction, revascularisation, stroke, retinopathy, and kidney disease (webappendix pp 6−7). Reference lists from identified trials and review articles were manually scanned to identify any other relevant studies. The ClinicalTrials.gov website was also searched for randomised trials that were registered as completed but not yet published.		
Selection criteria	Randomised controlled trials with at least 100 patient-years of follow-up in each group, but without language restriction. All completed assessing the effects of a fibrate compared with placebo, and that reported one or more of the primary or secondary outcomes, were eligible for inclusion.		
Intervention	Fibrate therapy		
Comparison	Placebo		
Outcomes	Major cardiovascular events, coronary events, stroke, heart failure, coronary revascularisation, all-cause mortality, cardiovascular death, non-vascular death, sudden death, new onset albuminuria, and drug-related adverse events.		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			

Study addresses an appropriate and clearly focused question	WC	We aimed to synthesise the available clinical trial evidence and to improve definition of the likely effects of fibrate therapy on major clinical outcomes. We undertook a systematic review and meta-analysis to investigate the effects of fibrates on major clinical outcomes
Description of the methodology used is included	WC	
The literature search was sufficiently rigorous to identify all the relevant studies	WC	
Study quality was addressed and taken into account?	WC	Study quality was quantified with the Jadad score. Any disagreement in abstracted data was adjudicated by a third reviewer (VP)
There were enough similarities between the studies to justify combining them.	AC	All studies included were multicentre and were undertaken in some or all of the USA, Canada, Europe, Oceania, and Central America. Seems to be evidence of heterogeneity between groups, however despite differences in sex and age, participants seemed to satisfy the general requirements for the included RCTs.
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		
Provides evidence for argument of use of fibrates to reduce risk of CVD in high risk individuals. Fibrates provide moderate effect, suggests clinically meaningful results are achievable. Ten trials including 42 131 participants reported 2485 non-fatal coronary outcomes with fibrate therapy, reducing risk by 19% (without evidence of heterogeneity). In conclusion, fibrate therapy reduces the risk of cardiovascular disease by preventing coronary events. The magnitude of effect is moderate, but in high-risk individuals and in those with combined dyslipidaemia, clinically meaningful reductions in risk could be achieved. With modern		

fibrates being safe and well tolerated, these agents seem to have a role in cardiac protection.
NOTE: Of the 10 included trials, four primary prevention trials, three mixed primary and secondary trials, and 11 secondary prevention trials. 8 studies enrolled only men; 6 enrolled only diabetics.
Funding Source
National Health and Medical Research Council of Australia
The funding source had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication

* Assessment of whether the criteria has been met should be made according to one of the following descriptors

Well covered
Adequately addressed
Poorly addressed
Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
Not applicable.

METHODOLOGY CHECKLIST: RANDOMISED CONTROLLED TRIALS

Study citation (Include author, title, year of publication, journal title, pages) KEECH, A., SIMES, R. J., BARTER, P., BEST, J., SCOTT, R., TASKINEN, M. R., FORDER, P., PILLAI, A., DAVIS, T., GLASZIOU, P., DRURY, P., KESANIEMI, Y. A., SULLIVAN, D., HUNT, D., COLMAN, P., D'EMDEN, M., WHITING, M., EHNHOLM, C. & LAAKSO, M. (2005) Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet, 366, 1849-61.			
Guideline topic: lipids		Key Question No: 14, 15	
Checklist completed by: Jonathan Ucinek			
Section 1: Internal validity			
	Quality criteria (from SIGN)	***Met?**	**Comments**
1.1	The study addresses an appropriate and clearly focused question.	WC	We therefore designed the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study to assess the effects on coronary morbidity and mortality of long-term treatment with fenofibrate to raise HDL-cholesterol concentrations and lower triglyceride levels in patients with type 2 diabetes and total blood cholesterol concentrations of less than 6·5 mmol/L.
1.2	The assignment of subjects to treatment groups is randomised	WC	Randomisation was done by central computer, using adynamic allocation method19 with stratification for important

			prognostic factors, including age, sex, previous myocardial infarction, lipid levels, and urinary albumin concentration. Allocated treatment was taken as a single daily dose with breakfast
1.3	An adequate concealment method is used	WC	Patients were recruited from hospital clinics and community-based sources.
1.4	Subjects and investigators are kept 'blind' about treatment allocation	WC	A double-blind, placebo-controlled trial done in 63 centres in Australia, New Zealand, and Finland—has been published.
1.5	The treatment and control groups are similar at the start of the trial	WC	All patients had to complete a 16-week run-in period, comprising 4 weeks of dietary modification, 6 weeks of single-blind placebo, and 6 weeks of single-blind fenofibrate therapy, during which time we confirmed eligibility for randomisation and documented baseline biochemical variables on several occasions
1.6	The only difference between groups is the treatment under investigation	WC	
1.7	All relevant outcomes are measured in a standard, valid and reliable way	WC	
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	4900 assigned placebo; • 5 withdrew consent • 10 lost to follow-up 4895 assigned fenofibrate; • 4 withdrew consent • 12 lost to follow-up By the end of the trial (close-out visits from January to May, 2005, median 5 years after randomisation), 950 of the patients allocated placebo (19%) and 954 of those allocated fenofibrate (20%) had discontinued study medication, corresponding to drop-out rates of 10% and 11% averaged over the 5-year study period. Most drop-outs related to deteriorating health, laboratory abnormalities, withdrawal of patient's consent, and minor possible	
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat	WC	

	analysis)		
1.10	Where the study is carried out at more than one site, results are comparable for all sites	Not Addressed	
Section 2: Overall assessment of the study			
2.1	How well was the study done to minimise bias? *Code ++, +, or -*		++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
			+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
			- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
2.2	If coded as +, or - what is the likely direction in which bias might affect the study results?		
2.3	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?		
2.4	Are the results of this study directly applicable to the patient group targeted by this guideline?		
Section 3: Description of the study (the following information is required to complete evidence tables facilitating cross-study comparisons. Please complete all sections for which information is available). Please print clearly			
3.1	Do we know who the study was funded by?	[ ] Academic Institution [ ] Healthcare Industry [ ] Government [ ] NGO [ ] Public funds [ ] Other The study was designed by an independent study management committee and coordinated by the National Health and Medical Research Council Clinical Trials Centre (CTC), University of Sydney, Australia. Two nonvoting representatives of the main sponsor attended meetings of the management committee. Members of the committee were responsible for preparation of the manuscript after all study-related data had been reviewed. The sponsor of the study had no role in data collection or data analysis. The writing committee had full access to all the data in the study and had final responsibility for the decision to submit for publication.	

3.2	How many centres are patients recruited from?	A detailed description of the design of the FIELD study—a double-blind, placebo-controlled trial done in 63 centres in Australia, New Zealand, and Finland—has been published
3.3	From which countries are patients selected? *(Select all those involved. Note additional countries after "Other")*	[ ] Scotland [ ] UK [ ] USA [ ] Canada [x] Australia [x] New Zealand [ ] France [ ] Germany [ ] Italy [ ] Netherlands [ ] Scandinavia [ ] Spain [x] Other:Finland
3.4	What is the social setting (ie type of environment in which they live) of patients in the study?	[ ] Urban [ ] Rural [ ] Mixed
3.5	What criteria are used to decide who should be INCLUDED in the study?	In brief, patients with type 2 diabetes diagnosed according to WHO criteria1 and aged 50–75 years were randomly allocated between February, 1998, and November, 2000, to once-daily micronized fenofibrate 200 mg (Laboratoires Fournier, Dijon, France) or matching placebo capsules. Patients were recruited from hospital clinics and community-based sources
3.6	What criteria are used to decide who should be EXCLUDED from the study?	Exclusion criteria included renal impairment (blood creatinine _130 _mol/L), known chronic liver disease or symptomatic gallbladder disease, and a cardiovascular event within the 3 months before recruitment
3.7	What intervention or risk factor is investigated in the study? (Include dosage where appropriate)	study to assess the effects on coronary morbidity and mortality of long-term treatment with fenofibrate to raise HDL-cholesterol concentrations and lower triglyceride levels in patients with type 2 diabetes and total blood cholesterol concentrations of less than 6·5 mmol/L.
3.8	What comparisons are made in the study? (ie what alternative treatments are used to compare the intervention with?). Include dosage where appropriate.	After a placebo and a fenofibrate run-in phase, we **randomly assigned patients** (2131 with previous cardiovascular disease and 7664 without) with a total-cholesterol concentration of 3·0–6·5 mmol/L and a total-cholesterol/HDL-cholesterol ratio of 4·0 or more or plasma triglyceride of 1·0–5·0 mmol/L **to micronised fenofibrate 200 mg daily (n=4895)** or **matching placebo (n=4900).** **assess the effects on coronary morbidity and mortality of long-term treatment with fenofibrate to raise HDL-cholesterol concentrations and lower triglyceride levels in patients with type 2 diabetes and total blood cholesterol concentrations of less than 6·5 mmol/L**

3.9	What methods were used to randomise patients, blind patients or investigators, and to conceal the randomisation process from investigators?	Randomisation was done by central computer, using a dynamic allocation method19 with stratification for important prognostic factors, including age, sex, previous myocardial infarction, lipid levels, and urinary albumin concentration. Allocated treatment was taken as a single daily dose with breakfast.
3.10	How long did the active phase of the study last?	Patients were seen for scheduled study visits at 4–6-monthly intervals over a planned period of 5 years on average against a background of usual care from their health-care professionals.
3.11	How long were patients followed-up for, during and after the study?	Patients were seen for scheduled study visits at 4–6-monthly intervals over a planned period of 5 years on average against a background of usual care from their health-care professionals.
3.12	List the key characteristics of the patient population. Note if there are any significant differences between different arms of the trial.	patients with type 2 diabetes diagnosed according to WHO criteria1 and aged 50–75 years were randomly allocated between February, 1998, and November, 2000, to once-daily micronized fenofibrate 200 mg (Laboratoires Fournier, Dijon, France) or matching placebo capsules. individuals had an initial plasma total-cholesterol concentration of between 3·0 mmol/L and 6·5 mmol/L, plus either a total-cholesterol/HDL-cholesterol ratio of 4·0 or more or a plasma triglyceride concentration of between 1·0 mmol/L and 5·0 mmol/L, with no clear indication for, or treatment with, lipid-modifying therapy at study entry. Exclusion criteria included renal impairment (blood creatinine _130 _mol/L), known chronic liver disease or symptomatic gallbladder disease, and a cardiovascular event within the 3 months before recruitment

3.13	Record the basic data for each arm of the study. If there are more than four arms, note data for subsequent arms at the bottom of the page			
	Arm 1: **Treatment:** **Sample size:** 4895 assigned fenofibrate	**Arm 2:** **Treatment:** **Sample size:** 4900 assigned placebo	**Arm 3:** **Treatment:** **Sample size:**	**Arm 4:** **Treatment:** **Sample size:**

	No. analysed **With outcome:** **Without outcome:**	**No. analysed** **With outcome:** **Without outcome** **Primary outcome?**	**No. analysed** **With outcome:** **Without outcome** **Primary outcome?**	**No. analysed** **With outcome:** **Without outcome** **Primary outcome?**
3.14	Record the basic data for each IMPORTANT outcome in the study. If there are more than four, not data for additional outcomes at the bottom of the page.			
	Outcome 1: The primary endpoint was the first occurrence of either non-fatal myocardial infarction or death from coronary heart disease. **Value:** There were 544 primary outcome events. • Fenofibrate was associated with a non-significant 11% relative reduction in the primary outcome of first myocardial infarction or coronary heart disease death (table 3 and figure 3). • This finding corresponds to a significant 24% relative reduction in non-fatal myocardial infarction, with a non-significant increase in fatal coronary heart disease. • We noted no significant excess of any particular cause of coronary heart disease death, with slightly fewer other cardiovascular disease deaths seen in the fenofibrate group than in the placebo group.	**Outcome 2:** Secondary outcomes included major cardiovascular disease events (coronary heart disease events, total stroke, and other cardiovascular death combined), total cardiovascular disease events (major cardiovascular disease events plus coronary and carotid revascularisation), coronary heart disease death, total cardiovascular disease deaths, haemorrhagic and nonhaemorrhagic stroke, coronary and peripheral revascularisation procedures, cause-specific non-coronary heart disease mortality, and total mortality. **Value:** For the secondary outcome of total cardiovascular disease events (the composite of cardiovascular disease death, myocardial infarction, stroke, and coronary and carotid revascularisation), • there was a significant 11% reduction with fenofibrate (table 3 and figure 3). This benefit was due mainly to the reduction in non-fatal myocardial infarction together with a significant 21% relative reduction in coronary revascularisation. • Differences in total cardiovascular disease events emerged mainly after 2 years, and with 5-year rates of total cardiovascular disease events of 13·9% and 12·5%. • Other secondary outcomes (including stroke, fatal	**Outcome 3:** **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**	**Outcome 4:** **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**

	Measure: **P value** **Upper CI** **Lower CI** **Primary outcome?**	cardiovascular disease events, coronary heart disease mortality, and all cause mortality) did not differ significantly between groups (table 3). **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**		
3.15	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question. *{Much of this is likely to be contributed by GDG members).*			
	Fenofibrate did not significantly reduce the risk of the primary outcome of coronary events. It did reduce total cardiovascular events, mainly due to fewer non-fatal myocardial infarctions and revascularisations. The higher rate of starting statin therapy in patients allocated placebo might have masked a moderately larger treatment benefit.			

* Assessment of whether the criteria has been met should be made according to one of the following descriptors

Well covered
Adequately addressed
Poorly addressed
Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
Not applicable.

Template for Intervention Study – Systematic Review
Topic/question: Lipids
Completed by: Kelvin Hill

REFERENCE: Marik PE, Varon J. Omega-3 dietary supplements and the risk of cardiovascular events: a systematic review. Clin Cardiol. 2009 Jul;32(7):365-72.		
SOURCE OF FUNDING not stated		
SUMMARY		
Inclusion criteria	Types of studies	11 prospective, randomized, placebo-controlled clinical trials that evaluated clinical cardiovascular end points (cardiovascular death, sudden death, and nonfatal cardiovascular events) and all-cause mortality in patients randomized to EPA/DHA or placebo. Only included studies that used dietary supplements of EPA/DHA which were administered for at least 1 year.
	Participants	39 044 patients with mixed backgrounds (MI, implanted cardioverter defibrillator, heart failure, PVD or hypercholesterolemia). Studies were grouped into high or mod risk (moderate included stable CVD and primary prevention).
	Interventions	Dieatary supplements with omega-3 fatty acids. Average dose 1.8+/-1.2g/day for 2.2+/-1.2 years
	Primary outcome	CVD mortality
	Additional outcomes	sudden death, and nonfatal cardiovascular events and all-cause mortality
Search		MEDLINE, Embase, the Cochrane Database of Systematic Reviews, and citation review of relevant primary and review articles. published from 1966 to December 2008
Methods of review	Method of applying inclusion criteria	Two authors indepentely reviewed potential trials and applied criteria.
	Assessment of methodological quality	Both authors independently abstracted data from all eligible studies using a standardized form. Disagreements were resolved by discussion between the reviewers. Data were abstracted on study design, study size, study setting, type and dosage of omega-3 fatty acid used, and duration of follow-up. We recorded the method of randomization, blinding, and concealment.
Comparisons		Placebo –either oil based (eg. olive, sunflower or corn oil) or non oil based
Main results		Decreased risk of cardiovascular deaths (OR: 0.87, 95% CI: 0.79–0.95, p = 0.002), sudden cardiac death (OR: 0.87, 95% CI: 0.76–0.99, p = 0.04), all-cause mortality (OR: 0.92, 95% CI: 0.85–0.99, p = 0.02), and nonfatal cardiovascular events (OR: 0.92, 95% CI: 0.85–0.99, p = 0.02). The mortality benefit was largely due to the studies which enrolled high risk patients, while the reduction in nonfatal cardiovascular events was noted in the moderate risk patients (secondary prevention only). Meta-regression failed to demonstrate a relationship between the daily dose of omega-3 fatty acid and clinical outcome.
CLINICAL IMPLICATIONS Omega-3 supplements may reduce CVD events but the effect is strongest for a secondary prevention cohort than primary prevention.		

QUALITY CHECK			
Process	**Questions**	**Answer**	**Comment**
Search:	**Are**:		
	two or more databases named and used	y	
	reference lists of selected articles searched	y	
	experts and trialists contacted	n	
	any journals searched by hand	n	
	databases searched from their inception	y	
	all languages accepted	y	
Selection:	**Is there a clear definition of**:		
	the population being studied	Y	
	the interventions being investigated	Y	

	the principal outcomes being studied	Y	
	the study designs included (and excluded)	Y	
Validity:	**Does the review process**:		
	assess (measure, quantify) the quality of studies identified	Y	
	blind reviewers to study origin (authors, journal etc)	N	
	abstract data into a structured database	Y	
	use two independent people to abstract data and assess study quality	Y	
	measure heterogeneity and bias of studies included	Y	
Data:	**For each study are the details (or their absence) noted of**:		
	participants included in study (number and type)	Y	
	interventions studied	Y	
	outcome	Y	
Analysis:	**Does the review process**:		
	undertake meta-analysis or state why not done	Y	
	investigate agreement between independent assessors	Y	
	give confidence intervals for outcomes reported	Y	

Benefits	Decreased CVD mortality and events (mainly due to secondary prevention data)
Harms	Not repoted
Comments / quality	High quality systematic review specifically looking at high and moderate risk groups (although moderate group still contained mix of primary and secondary groups)

REASON FOR EXCLUSION **(Poor quality +not clinically relevant / interesting or if relevant for preamble)**
Include

RELEVANCE TO AN AUSTRALIAN CONTEXT
relevant

OVERALL CONCLUSION
Omega 3 supplements may reduce CVD in a primary prevention cohort but futher studies are needed. Authors discuss one large Japanese trial in those with high cholesterol (mostly primary prevention) and note: “Furthermore, it should be noted that while there was a significant reduction is major coronary events in the JELIS study (OR: 0.81, 95% CI: 0.69–0.95), this benefit did not reach statistical significance in the primary prevention subgroup (OR: 0.82, 95% CI: 0.63–1.06). This data suggests the benefits of omega-3 fatty acid supplementation may be confined to patients with preexistent cardiovascular disease.”

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS

Guideline topic: Lipids	**Question number: 15**
Characteristics of study	
Checklist completed by: Jonathan Ucinek	
Study citation	MIKHAILIDIS, D. P., SIBBRING, G. C., BALLANTYNE, C. M., DAVIES, G. M. & CATAPANO, A. L. (2007) Meta-analysis of the cholesterol-lowering effect of ezetimibe added to ongoing statin therapy. Curr Med Res Opin, 23, 2009-26.

Study design	**Systematic review**	**N (total)**	Five RCTs total of 5039 patients
Search strategy	Trials published between January 1993 and December 2005, MEDLINE and EMBASE on 15th December 2005, using DataStar on the web24. The Cochrane Database of Systematic Reviews was also searched using the Cochrane Library on the web25. The searches were restricted to the 10 years prior to regulatory approval of ezetimibe, as it was assumed that all phase III trial data and key phase II trials would have been published during this period.		
Selection criteria	RCTs, systematic reviews and meta-analyses of ezetimibe, • Parallel-group or crossover, double-blind, single blind or open-label RCTs, with a minimum duration of 6 weeks of ezetimibe treatment and a minimum diet/placebo run-in period of 4 weeks (reported separately, or as part of a meta-analysis or systematic review) • Including patients of ≥ 18 years of age, diagnosed with non-familial or familial hypercholesterolaemia, homozygous familial sitosterolaemia or hyperlipidaemia, whose LDL‑C levels were above those recommended by NCEP Adult Treatment Panel (ATP) II/III guideline criteria4, 5 • Including a group of patients treated with oral ezetimibe 10 mg, in combination with a statin, adjunctive to a cholesterol-lowering diet, in comparison with a group of patients receiving diet alone, placebo, a statin or a fibrate		
Intervention	ezetimibe 10 mg/day added to current statin therapy		
Comparison	Placebo added to current statin therapy		
Outcomes	four co-primary outcomes: mean percentage change from baseline in total cholesterol (TC), LDL‑C, and high density lipoprotein cholesterol (HDL‑C), and number of patients achieving LDL‑C treatment goal.		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		WC	To review and analyse the evidence for the cholesterol-lowering effect of ezetimibe in adult patients with hypercholesterolaemia who are not at low-density lipoprotein cholesterol (LDL‑C) goal on statin monotherapy. We conducted a systematic review of the literature to identify trials of ezetimibe in all its indications. However, this paper only presents the results of the analyses including trials of ezetimibe/statin combination therapy, in patients who were not at lipid goal as a result of previous treatment with statin monotherapy
Description of the methodology used is included		WC	
The literature search was sufficiently rigorous to identify all the relevant studies		WC	
Study quality was addressed and taken into account?		WC	

There were enough similarities between the studies to justify combining them.	WC	
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		
The meta-analysis performed included only five studies and was restricted to analysis of the changes in cholesterol levels relative to baseline. However, the results suggest that ezetimibe co-administered with ongoing statin therapy provides significant additional lipid-lowering in patients not at LDL‑C goal on statin therapy alone, allowing more patients to reach their LDL‑C goal. The results of our meta-analyses support a greater LDL‑C- and TC-lowering effect with the ezetimibe/statin combination compared with the placebo/statin combination. A greater reduction in TG levels was also observed in patients treated with the ezetimibe/statin combination. In the two studies in which achievement of LDL‑C treatment goal was measured, more patients receiving the ezetimibe combination achieved this goal compared with patients treated with the placebo/statin combination. The effect of 6–8 weeks ezetimibe/statin combination therapy on primary outcome measures, in patients not at lipid goal on statin therapy alone, was reasonably consistent among RCTs conducted in the USA and Europe and with a 6-week cohort study conducted in Canada **Note**: 3/5 included trials were of those with CHD. It is unclear from the two non CHD trials if other CVD were included. Although results were consistent for those with CHD and those without.		

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Lipid Modification		**Question number: 14 – CKD subgroup**	
Characteristics of study			
Checklist completed by: Valetnin C. Dones III			
Study citation	Navaneethan SA, Pansini F, Perkovic V, Manno C, Pellegrini F, Johnson DW, Craig JC, Strippoli GFM. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. Cochrane Database of Systematic Reviews:2009 Issue 2 DOI:10.1002/14651858.CD007784		
Study design	**Systematic review**	**N (total)**	26 trials, 25017 patients
Search	MEDLINE, EMBASE, CENTRAL (in The Cochrane Library), and hand searched reference lists of textbooks, articles and scientific		

strategy	proceedings.		
Selection criteria	RCTs and quasi-RCTs comparing statins with placebo, no treatment or other statins in adult pre-dialysis CKD patients		
Intervention	HMG CoA reductase inhibitors (Statins)		
Comparison	Placebo or no therapy		
Outcomes	all-cause mortality, cardiovascular mortality, fatal and non-fatal cardiovascular events, elevated liver enzymes, rhabdomyolysis and withdrawal rates.		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		WC	
Description of the methodology used is included		Well covered	Cochrane strategy
The literature search was sufficiently rigorous to identify all the relevant studies		Well covered	
Study quality was addressed and taken into account?		Well covered	
There were enough similarities between the studies to justify combining them.		Well covered	Subgroup analysis was done to explore the role of potential sources of heterogeneity in modifying estimates of the effects of statins in the studies.
SECTION 2: Overall assessment of the study			
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++	**++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.**
			+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
			- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?			
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**			

In summary, this review results support the widespread use of statins in hyperlipidaemic pre-dialysis patients to reduce their mortality rates along with appropriate monitoring of adverse events even though their renoprotective role needs to be well studied.

RCTs and quasi-RCTs were included in this study. The search methodology and data extraction procedure were rigorous. Both published and unpublished studies were included leading to minimisation of publication bias. The number of RCTs included was more than that generally found in clinical nephrology research and the estimates of effects were more substantial than usual. There was failure to specify concealment, blinding or intention to treat in vast majority of studies evaluated.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS

Guideline topic: lipids		**Question number: 14**	
Characteristics of study			
Checklist completed by: Jonathan Ucinek			
Study citation	O'REGAN, C., WU, P., ARORA, P., PERRI, D. & MILLS, E. J. (2008) Statin therapy in stroke prevention: a meta-analysis involving 121,000 patients. Am J Med, 121, 24-33.		
Study design	**Systematic review**	**N (total)**	42 studies enrolling 121,285 patients
Search strategy	10 electronic databases (from inception to December 2006), contacted study authors and authors of previous reviews		
Selection criteria	Randomized trial of atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin, of any duration. Studies had to compare a statin to placebo or no treatment, and report on any of the following clinically important cardiovascular outcomes: all-cause mortality, all-stroke incidence, fatal strokes, hemorrhagic, or ischemic strokes. Excluded studies reporting only on surrogate outcomes (eg, LDL and high-density lipoprotein [HDL] levels).		
Intervention	statin therapy on both primary (and secondary stroke prevention – only one trial), and any associated mortality benefit.		
Comparison	placebo or no treatment		
Outcomes	all-cause mortality, all-stroke incidence, specific type of strokes, and cholesterol changes.		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		WC	Aimed to quantify the effects of statin therapy on both primary and secondary stroke prevention, and any associated mortality benefit. We further sought to determine differences in stroke risk reduction among a variety of statins, dosing strategies, and types of stroke.
Description of the methodology used is included		WC	

The literature search was sufficiently rigorous to identify all the relevant studies	WC	
Study quality was addressed and taken into account?	AC	
There were enough similarities between the studies to justify combining them.	Not reported	
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		
42 trials assessing statin therapy for all-stroke prevention (n=121,285), resulting in a pooled relative risk (RR) of 0.84 (95% confidence interval [CI], 0.79-0.91). The pooled RR of statin therapy for all-cause mortality (n=116,080) was 0.88 (95% CI, 0.83-0.93). Each unit increase in low-density lipoprotein (LDL) resulted in a 0.3% increased RR of death (P=0.02). Seventeen trials evaluated statins on cardiovascular death (n=57,599, RR 0.81, 95% CI, 0.74-0.90), and 11 evaluated non hemorrhagic cerebrovascular events (n=58,604, RR 0.81, 95% CI, 0.69-0.94). Eleven trials reported hemorrhagic stroke incidence (total n=54,334, RR 0.94, 95% CI, 0.68-1.30) and 21 trials reported on fatal strokes (total n=82,278, RR 0.99, 95% CI, 0.80-1.21). Only one trial reported on statin therapy for secondary prevention. Statin therapy provides high levels of protection for all-cause mortality and non hemorrhagic strokes. This overview reinforces the need to consider prolonged statin treatment in patients at high risk of major vascular events, but caution remains for patients at risk of bleeds. NOTE: This study was supported by Pfizer UK Ltd. The main author was a salaried employee of Pfizer UK Ltd.		

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS	
Guideline topic: lipids	**Question number:** 14-17
Characteristics of study	
Checklist completed by: Luke Perraton	
Study citation	RAY, KK., SESHASAI, SR., ERGOU, S., SEVER, P., JUKEMA, JW., FORD, I., SATTAR, N. (2010) Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 69,229 participants. Arch Int Med, 170(12),

	1024.		
Study design	**Systematic review**	**N (total)**	11 trials involving 65,229 participants
Search strategy	2 electronic databases (Cochrane and Medline) from January 1970 to May 2009. Searched reference lists of previous SRs and contacted authors of previous reviews as required.		
Selection criteria	Satisfied all three criteria: 1) randomized trials of statins versus placebo control, 2) trials collecting information on all-cause mortality, 3) trials conducted on individuals without CVD at baseline. Exclusion criteria: conducted on diseased populations, or assessed intermediate end points only		
Intervention	Statin therapy. Drugs included rosuvastatin, pravastatin, atorvastatin, lovastatin and fluvastatin.		
Comparison	Placebo control		
Outcomes	All-cause mortality		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		WC	Aimed to determine whether statin therapy reduced all-cause mortality in individuals (intermediate to high risk) without a history of CVD
Description of the methodology used is included		WC	Clearly outlined study selection, data extraction and statistical analysis
The literature search was sufficiently rigorous to identify all the relevant studies		AA	Only 2 electronic databases searched
Study quality was addressed and taken into account?		PA	Study quality was not formally addressed and reported
There were enough similarities between the studies to justify combining them.		WC	Baseline information was provided on participants and compared across studies. Tests of heterogeneity were performed –not significant
SECTION 2: Overall assessment of the study			
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
			+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
			- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?			
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**			
11 trials of statin therapy looking at the prevention of mortality in populations with a medium to high risk of CV related death, as compared to placebo. No statistically significant reduction was found (risk ratio 0.91, 95% CI 0.83-1.01)			

No significant relationship was seen between baseline lipid levels (P=0.97), or reduction in lipid levels and reduction in mortality (P=0.62)
Based on this meta analysis, statin therapy is not beneficial in reducing mortality in medium to high risk populations without CVD.

METHODOLOGY CHECKLIST: RANDOMISED CONTROLLED TRIALS

Study citation (*Include author, title, year of publication, journal title, pages*) RIDKER, P. M., MACFADYEN, J., CRESSMAN, M. & GLYNN, R. J. (2010) Efficacy of rosuvastatin among men and women with moderate chronic kidney disease and elevated high-sensitivity C-reactive protein: a secondary analysis from the JUPITER (Justification for the Use of Statins in Prevention-an Intervention Trial Evaluating Rosuvastatin) trial. J Am Coll Cardiol, 55, 1266-73.			
Guideline topic: lipids		Key Question No: 14	
Checklist completed by: Jonathan Ucinek			
Section 1: Internal validity			
	Quality criteria (from SIGN)	***Met?**	**Comments**
1.1	The study addresses an appropriate and clearly focused question.	AC	We evaluated the efficacy of statin therapy in primary prevention among individuals with moderate chronic kidney disease (CKD). randomized, double-blind, placebo-controlled trial designed to investigate whether rosuvastatin 20 mg daily compared with placebo decreases the rate of first-ever cardiovascular events among apparently healthy men over age 50 years and women over age 60 years with LDL-C _130 mg/dl at increased vascular risk due to hsCRP _2 mg/l
1.2	The assignment of subjects to treatment groups is randomised	Not reported	Full details of the trial protocol, procedures, and methods of confirming clinical end points and ascertaining adverse events have been previously presented.
1.3	An adequate concealment method is used	Not reported	Full details of the trial protocol, procedures, and methods of confirming clinical end points and ascertaining adverse events have been previously presented.
1.4	Subjects and investigators are kept ‘blind’ about treatment allocation	NA	Secondary analysis
1.5	The treatment and control groups are similar at the start of the trial	NA	

1.6	The only difference between groups is the treatment under investigation	AC	
1.7	All relevant outcomes are measured in a standard, valid and reliable way		
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	All analyses were performed on an intention-to-treat basis.	
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)	AC	All analyses were performed on an intention-to-treat basis.
1.10	Where the study is carried out at more than one site, results are comparable for all sites	Not addressed	
Section 2: Overall assessment of the study			
2.1	How well was the study done to minimise bias? *Code ++, +, or -*	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
			+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
			- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
2.2	If coded as +, or - what is the likely direction in which bias might affect the study results?		
2.3	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?		
2.4	Are the results of this study directly applicable to the patient group targeted by this guideline?	yes	
Section 3: Description of the study (the following information is required to complete evidence tables facilitating cross-study comparisons. Please complete all sections for which information is available). Please print clearly			
3.1	Do we know who the study was funded by?	[ ] Academic Institution [ ] Healthcare Industry	

		[ ] Government [ ] NGO [ ] Public funds [ ] Other The JUPITER trial was supported by Astra-Zeneca. The JUPITER trial was investigator-initiated; the study sponsor collected trial data and monitored sites but had no access to unblinded data until after drafting of the trial primary report.
3.2	How many centres are patients recruited from?	Not reported
3.3	From which countries are patients selected? *(Select all those involved. Note additional countries after "Other")*	[ ] Scotland [ ] UK [ ] USA [ ] Canada [ ] Australia [ ] New Zealand [ ] France [ ] Germany [ ] Italy [ ] Netherlands [ ] Scandinavia [ ] Spain [ ] Other:
3.4	What is the social setting (ie type of environment in which they live) of patients in the study?	[ ] Urban [ ] Rural [ ] Mixed
3.5	What criteria are used to decide who should be INCLUDED in the study?	Not addressed – that of JUPITER study as this is a secondary analysis
3.6	What criteria are used to decide who should be EXCLUDED from the study?	exclusion criteria included treatment within 6 weeks of screening with any lipid lowering therapies, current use of hormone replacement therapy, evidence of hepatic dysfunction, creatinine _2.0 mg/dl, diabetes, uncontrolled hypertension, prior malignancy, uncontrolled hypothyroidism, or a recent history of alcohol, drug abuse, or other medical condition that might compromise safety
3.7	What intervention or risk factor is investigated in the study? (Include dosage where appropriate)	randomized, double-blind, placebo-controlled trial designed to investigate whether rosuvastatin 20 mg daily compared with placebo decreases the rate of first-ever cardiovascular events among apparently healthy men over age 50 years and women over age 60 years with LDL-C _130 mg/dl at increased vascular risk due to hsCRP _2 mg/l
3.8	What comparisons are made in the study? (ie what alternative treatments are used to compare the intervention with?). Include dosage where appropriate.	randomized, double-blind, placebo-controlled trial designed to investigate whether rosuvastatin 20 mg daily compared with placebo decreases the rate of first-ever cardiovascular events among apparently healthy men over age 50 years and women over age 60 years with LDL-C _130 mg/dl at increased vascular risk due to hsCRP _2 mg/l

3.9	What methods were used to randomise patients, blind patients or investigators, and to conceal the randomisation process from investigators?		WC	
3.10	How long did the active phase of the study last?		Median 1.9- 5 years maximum	
3.11	How long were patients followed-up for, during and after the study?		Median 1.9- 5 years maximum	
3.12	List the key characteristics of the patient population. Note if there are any significant differences between different arms of the trial.		Baseline characteristics. Of participants in the JUPITER trial, 3,267 (18%) had baseline eGFR _60 ml/min/1.73 m2), whereas 14,528 (82%) had higher levels. Seven participants did not have eGFR values available. Among those with reduced eGFR, 3,253 had stage 3 impairment (eGFR between 30 and 59 ml/min/1.73 m2) and 14 had stage 4 impairment (eGFR between 15 and 29 ml/min/1.73 m2). Study participants with moderate CKD were older, more likely to be female, more likely to have a family history of premature atherothrombosis, and less likely to smoke (Table 1). Median baseline levels of LDL-C, high-density lipoprotein cholesterol, triglycerides, apolipoprotein A, apolipoprotein B, and hsCRP were somewhat higher among those with moderate CKD, whereas blood pressure, glucose, and hemoglobin A1c were similar. Within each eGFR category, there was no imbalance between study characteristics among those allocated to rosuvastatin or placebo.	
3.13	Record the basic data for each arm of the study. If there are more than four arms, note data for subsequent arms at the bottom of the page			
Secondary analysis of	**Arm 1:**	**Arm 2:** **Treatment:** Randomized	**Arm 3:**	**Arm 4:**

data **Arms Not reported**	**Treatment:** Randomized Rosuvastatin **Sample size:** **No. analysed** **With outcome:** **Without outcome:**	Placebo **Sample size:** **No. analysed** **With outcome:** **Without outcome** **Primary outcome?**	**Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome** **Primary outcome?**	**Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome** **Primary outcome?**
3.14	Record the basic data for each IMPORTANT outcome in the study. If there are more than four, not data for additional outcomes at the bottom of the page.			
	Outcome 1: **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**	**Outcome 2:** **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**	**Outcome 3:** **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**	**Outcome 4:** **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**
3.15	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question. *{Much of this is likely to be contributed by GDG members).*			

	Rosuvastatin reduces first cardiovascular events and all-cause mortality among men and women with LDL-C _130 mg/dl, elevated hsCRP, and concomitant evidence of moderate CKD. (JUPITER—Crestor 20 mg VersusPlacebo in Prevention of Cardiovascular [CV] Events; NCT00239681) (J Am Coll Cardiol 2010;55:1266–73) © 2010 by the American College of Cardiology Foundation • Compared with those with eGFR ≥60 ml/min/1.73 m2, JUPITER participants with moderate CKD had higher vascular event rates (hazard ratio [HR]: 1.54, 95% confidence interval [CI]: 1.23 to 1.92, p = 0.0002). • Among those with moderate CKD, rosuvastatin was associated with a 45% reduction in risk of myocardial infarction, stroke, hospital stay for unstable angina, arterial revascularization, or confirmed cardiovascular death (HR: 0.55, 95% CI: 0.38 to 0.82, p = 0.002) and a 44% reduction in all-cause mortality (HR: 0.56, 95% CI: 0.37 to 0.85, p = 0.005). • Median LDL-C and hsCRP reductions as well as side effect profiles associated with rosuvastatin were similar among those with and without CKD. Median eGFR at 12 months was marginally improved among those allocated to rosuvastatin as compared with placebo

* Assessment of whether the criteria has been met should be made according to one of the following descriptors

Well covered
Adequately addressed
Poorly addressed
Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
Not applicable.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: lipids			**Question number: 14-15**
Characteristics of study			
Checklist completed by: Jonathan Ucinek			
Study citation	ROBINSON, J. G., WANG, S., SMITH, B. J. & JACOBSON, T. A. (2009) Meta-analysis of the relationship between non-high-density lipoprotein cholesterol reduction and coronary heart disease risk. J Am Coll Cardiol, 53, 316-22.		
Study design	**Systematic review**	**N (total)**	23 trials: 14 statin (n =100,827), 7 fibrate (n =21,647), 6 niacin (n =4,445) trials, and 1 trial each of bile acid sequestrant (n =3,806), diet (n = 458), and ileal bypass surgery (n = 838).
Search strategy	Articles were identified by a literature search of the MEDLINE database (1966 to May 8, 2008), English language journals, a manual search of the author's reference files, and reference lists of original articles, reviews, and meta analyses		
Selection criteria	Criteria: 1) Studies were designed to evaluate the effect of diet, statins, niacin, fibrates, bile acid sequestrants, or surgery compared with an active or placebo control. 2) Studies had random, blinded (except for diet studies) allocation of study participants to the treatment or control group. 3) Total cholesterol and HDL-C, or non–HDL-C, were measured at least once after baseline; measured non– HDL-C was used in the few studies in which it was available, otherwise non–HDL-C was calculated from total cholesterol minus HDL-C; measured and calculated non– HDL-C were within 1 mg/dl for every study in which non–HDL-C was measured; the interval for lipid measurement was not fixed, and in some cases the values could		

	represent the average during the trial. 4) For the statin trials, primary outcomes of the trial were clinical events; a previous analysis found a similar relationship between LDL-C and CHD risk reduction in statin trials with imaging as the primary end point compared with those trials with cardiovascular events as the primary end point (5); statin trials of 2 or more years, duration were included to provide a stable estimate of relative risk reduction (6). 5) Study population did not have serious noncardiovascular diseases or conditions (e.g., renal or heart failure, organ transplantation). 6) The CHD end points were blindly adjudicated according to standardized criteria; coronary revascularization and unstable angina diagnoses were excluded because of greater temporal and regional variability in utilization and classification (7). The analysis was confined to CHD events because earlier trials did not report stroke outcomes. NOT PRIMARY PREVENTION SPECIFIC		
Intervention	Statin, Fibrate, Niacin, Bile acid, Sequestrant, Diet, Ileal bypass surgery		
Comparison	placebo or active-controlled		
Outcomes	The analysis was confined to CHD events because earlier trials did not report stroke outcomes.		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		WC	To determine the relationship between non–high-density lipoprotein cholesterol (HDL-C) lowering and coronary heart disease (CHD) risk reduction for various lipid-modifying therapies
Description of the methodology used is included		WC	
The literature search was sufficiently rigorous to identify all the relevant studies		AC	Medline only
Study quality was addressed and taken into account?		WC	
There were enough similarities between the studies to justify combining them.		AC	
SECTION 2: Overall assessment of the study			
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.			++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+	+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
			- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?			
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**			
Non–HDL-C is an important target of therapy for CHD prevention. Most lipid-modifying drugs used as mono therapy have an approximately 1:1			

relationship between percent non–HDL-C lowering and CHD reduction. Along with LDL-C, non–HDL-C is an important target of therapy for CHD prevention. The relationship between non–HDL-C lowering and CHD risk reduction is similar for statins and fibrates. Most lipid-modifying drugs used as monotherapy appear to have an ≈1:1 relationship between percent non–HDL-C lowering and CHD reduction. Small trial sizes and design issues limit conclusions regarding niacin used in combination. Definitive conclusions regarding greater efficacy for niacin used in combination with statins await the results of ongoing trials .

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: lipids		**Question number: 14 and 15**	
Characteristics of study			
Checklist completed by: Jonathan Ucinek			
Study citation	SAHA, S. A., KIZHAKEPUNNUR, L. G., BAHEKAR, A. & ARORA, R. R. (2007) The role of fibrates in the prevention of cardiovascular disease--a pooled meta-analysis of long-term randomized placebo-controlled clinical trials. Am Heart J, 154, 943-53.		
Study design	**Systematic review**	**N (total)**	36489 patients from 10 trials
Search strategy	Search of the Index Medicus/MEDLINE database (1966-July 2006, National Library of Medicine, Bethesda, MD)		
Selection criteria	The inclusion criteria used for selection of clinical trials for pooled meta-analysis were the following: (1)randomized placebo-controlled trial design; (2) study sample size of ≥30 patients in each arm of the study; (3) mean duration of follow-up ≥1 year (long-term); and (4) clinical end points having been predefined and recorded for patients enrolled in the study. (5) both in patients without (primary prevention) and with (secondary prevention) known history of cardiovascular disease (Only 2 trials completely primary prevention, and 2 others partly)		
Intervention	Fibrates		
Comparison	Placebo control		
Outcomes	Prevention of cardiovascular disease (not all had appropriate endpoints for guideline question)		
Quality of study			
Quality criteria (from SIGN)	***Met?**	**Comments**	
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question	WC	systematic review and pooled meta-analysis of long-term randomized placebo-controlled trials using fibrates for the prevention of cardiovascular disease	
Description of the methodology used is included	WC		
The literature search was sufficiently rigorous to identify	WC		

all the relevant studies		
Study quality was addressed and taken into account?	WC	
There were enough similarities between the studies to justify combining them.	WC	
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		
In conclusion, our meta-analysis revealed that the long-term use of fibrates significantly reduces the occurrence of nonfatal MI but has no significant effect on other adverse cardiovascular outcomes. Fibrates effectively reduce plasma total cholesterol and TG levels, raise plasma HDL-C levels, and shift the LDL-C profile to a larger, less atherogenic particle species, and have recently been shown to have pleiotropic effects on inflammation and endothelial function. However, pooled meta-analysis of randomized placebo-controlled clinical trials demonstrated no significant benefit of using fibrates on mortality, fatal MI, or stroke—all of which are significantly reduced by statins. On the other hand, the use of fibrates reduced the incidence of nonfatal MI in patients with non-LDL dyslipidemia to a comparable extent with that seen with statins in patients with high LDL-C levels. Increase in non CVD deaths were reported (here and in previous reviews). However, after elimination of the clofibrate trials (agent is no longer used/available) , there was no significant increase in all-cause (pooled odds ratio 1.04, P = .44) (Figure 3, A) or noncardiovascular mortality (pooled odds ratio 1.08, P = .20). No effect on CVD outcomes without the clofibrate trials were found. Limitations Not consistently primary prevention and data not separated out. The current meta-analysis used pooled results from the selected trials, and analyses were restricted by the lack of individual patient data. This article did not include trials that may have been presented at symposia or conferences or published in abstract form in media not indexed in the sources we used. In addition, publication bias may have also affected the results of our analysis because trials with neutral or negative results are less likely to see the light of publication		

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS	
Guideline topic: Lipids	**Question number: 15**
Characteristics of study	

Checklist completed by: Jonathan Ucinek			
Study citation	STUDER, M., BRIEL, M., LEIMENSTOLL, B., GLASS, T. R. & BUCHER, H. C. (2005) Effect of different anti lipidemic agents and diets on mortality: a systematic review. Arch Intern Med, 165, 725-30.		
Study design	**Systematic review**	**N (total)**	97 studies, with 137140 individuals in intervention and 138 976 individuals in control groups.
Search strategy	Included references from previous metaanalyses + searched MEDLINE, EMBASE, PASCAL, and the Cochrane Controlled Trials Register between 1965 and June 2003 that compared lipid-lowering agents or dietary interventions with placebo or usual care. No language restrictions were imposed.		
Selection criteria	Eligible if compared any lipid lowering intervention with placebo or usual care, used random allocation, had a follow-up of at least 6months, and reported mortality data. Excluded trials that were restricted to heart transplant recipients; trials in coronary artery bypass grafts or acute coronary syndromes; trials using hormone therapy in men or those using postmenopausal hormone therapies (because these therapies were shown to be harmful for CHD prevention); trials using any combination of lipid-lowering intervention (not allowing us to classify the intervention to 1 drug); and trials with outdated interventions such as ileal bypass surgery.		
Intervention	Lipid lowering interventions: Statins (all trials), Fibrates (all trials), Resins (all trials), Niacin (all trials), n-3 Fatty acids (all trials), Diet (all trials)		
Comparison	placebo or usual care		
Outcomes	Outcome measures were mortality from all, cardiac, and non cardiovascular causes		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		WC	The goal of the present meta-analysis is to investigate the efficacy and safety of different lipid lowering interventions in the primary and secondary prevention of CHD based on mortality data.
Description of the methodology used is included		WC	
The literature search was sufficiently rigorous to identify all the relevant studies		WC	
Study quality was addressed and taken into account?		WC	
There were enough similarities between the studies to justify combining them.		AC	
SECTION 2: Overall assessment of the study			
How well was the study done to minimise bias?		++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.

Determine the methodological quality of the study according to this ranking, based on responses above.		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		

SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**

Comment

This systematic review of randomized controlled trials examines the association between different lipid lowering interventions and mortality from various causes and separated primary and secondary prevention studies.

Statins are the most favourable lipid-lowering interventions with reduced risks of overall and cardiac mortality. Any potential reduction in cardiac mortality from fibrates is offset by an increased risk of death from non cardiovascular causes.

In meta-regression analysis authors found the magnitude of the effect of a lipid-lowering intervention tends to increase in trials with a higher percentage of participants with established CHD and to decrease in trials of longer duration.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS

Guideline topic: Lipids		**Question number: 14**	
Characteristics of study			
Checklist completed by: Jonathan Ucinek			
Study citation	THAVENDIRANATHAN, P., BAGAI, A., BROOKHART, M. A. & CHOUDHRY, N. K. (2006) Primary prevention of cardiovascular diseases with statin therapy: a meta-analysis of randomized controlled trials. Arch Intern Med, 166, 2307-13.		
Study design	**Systematic review**	**N (total)**	N= 7 RCTs, n= 42 848 patients (21 409 to statin therapy and 21 439 to placebo).
Search strategy	Search of MEDLINE (1966 to June 2005), EMBASE (1980 to June 2005), Cochrane Collaboration (CENTRAL, DARE, and CDSR), and the American College of Physicians Journal Club databases using medical subject headings and keywords related to statins (ie, HMG-CoA reductase inhibitors, simvastatin, lovastatin, pravastatin, atorvastatin, cervistatin, fluvastatin, and rosuvastatin), cardiovascular disease (ie, heart disease, coronary artery disease, myocardial infarction, and cerebrovascular disease), cholesterol (ie, cholesterol, LDL, HDL, and triglycerides), and study types (ie, randomized-control-trial, placebo control- trial, and meta-analysis). English-language studies conducted in human subjects. Reviewed retrieved reference lists to identify other studies.		
Selection criteria	Randomized trials of statins compared with controls (placebo, active control, or usual care) with the following characteristics: a mean follow-up of at least 1 year; at least 100 reported cardiovascular disease outcomes (eg, major coronary events, strokes, all-cause mortality); no intervention difference between the treatment and control groups other than the use of statin; at least 80% of participants not known to have cardiovascular disease (ie, coronary artery disease, cerebrovascular disease, and peripheral vascular disease); and at least 1 of the primary outcomes for the primary prevention subgroup reported. Excluded studies with the following characteristics: examined only changes in serum cholesterol concentration or angiographic		

	outcomes; compared high- to low-dose statins; pre screened patients with ultrasound for the presence of atherosclerosis; targeted patients with disease states that are not traditional cardiovascular risk factors (eg, dialysis or post transplantation patients); and did not report the proportion of study participants receiving therapy as primary prevention.		
Intervention	statins		
Comparison	compared with controls (placebo, active control, or usual care)		
Outcomes	cardiovascular disease outcomes (eg, major coronary events, strokes, all-cause mortality);		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		WC	to clarify the role of statins for the primary prevention of cardiovascular events.
Description of the methodology used is included		WC	
The literature search was sufficiently rigorous to identify all the relevant studies		WC	
Study quality was addressed and taken into account?		WC	
There were enough similarities between the studies to justify combining them.		AC	
SECTION 2: Overall assessment of the study			
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
			+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
			- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?			
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**			
EFFECT OF STATINS ON OUTCOMES There were 924 and 1219 major coronary events in patients randomized to statin therapy and control, respectively. This represents a 29.2% (95% CI, 16.7%-39.8%) reduction in the RR of a major coronary event from statin therapy (P_.001) (Figure 2, Table 2). Major cerebrovascular events occurred in 440 statin-treated patients and 517 controls, representing a 14.4% reduction in the relative risk of major cerebrovascular			

events from statin therapy (95% CI, 2.8%-24.6%) (P=.02) (Figure 3, Table 2). Statin therapy produced a non significant 22.6% RR reduction in CHD mortality (95% CI, 0.56- 1.08) (P=.13) (Figure 4, Table 2). There was no statistically significant reduction in overall mortality (RR, 0.92 [95% CI, 0.84-1.01]) (P=.09) (Figure 5, Table 2). Statin treatment was associated with a 31.7% RR reduction in NFMI (95% CI, 16.9%-43.9%) (P_.001) and a 33.8% RR reduction in the number of revascularization procedures (95% CI, 19.6%-45.5%) (P_.001). Fatal and nonfatal cancers were not reported by all studies (Table 2). The ALLHAT-LLT,13 ASCOT-LLA,14 PROSPER,15 and HPS11 trials did not provide sufficient information regarding CK and liver enzyme level changes for the primary prevention population. In the available studies, statin therapy was not associated with elevations of CK (RR, 0.51 [95% CI, 0.16-1.60]) (P=.25) or liver enzymes (RR, 1.37 [95% CI, 0.90- 2.09]) (P=.15). Similarly, statin therapy was not associated with a significant increase in the incidence of fatal or nonfatal cancers (RR, 1.02 [95% CI, 0.92-1.13]) (P=.74).

In patients without CV disease, statin therapy decreases the incidence of major coronary and cerebrovascular events and revascularizations but not coronary heart disease or overall mortality

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS

Guideline topic: Lipid modification		**Question number: Q14**	
Characteristics of study			
Checklist completed by: Janine Dizon			
Study citation	Vijan, and Hayward 2004, Pharmacologic Lipid-Lowering Therapy in Type 2 Diabetes Mellitus: Background Paper for the American College of Physicians Annals of Internal Medicine 140:650-658		
Study design	**Systematic review**	**N (total) 10 studies**	6 on primary prevention and 8 on secondary prevention
Search strategy	Search terms: *exp diabetes mellitus* and *exp lipids* (therapy or prevention and control) to identify studies from Cochrane Library and MEDLINE. Search was limited to randomized controlled trials and humans. Consultation with experts and list of reference lists of studies were also done as part of the search.		
Selection criteria	RCTs which included patients with diabetes		
Intervention	Pharmacologic lipid lowering therapy		
Comparison	Control group		
Outcomes	Cardiovascular mortality, myocardial infarction, stroke		
Quality of study			
Quality criteria (from SIGN)	***Met?**	**Comments**	
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question	Well covered	This paper focuses on the evidence behind the use of lipid-lowering agents in type 2 diabetes.	

Description of the methodology used is included	Adequately addressed	This review was able to report how analysis was done for both primary and secondary prevention of stroke.
The literature search was sufficiently rigorous to identify all the relevant studies	Well covered	Electronic search of databases was done as well as searching of reference lists and contact experts
Study quality was addressed and taken into account?	Not addressed	
There were enough similarities between the studies to justify combining them.	Well covered	There was no statistical heterogeneity found from the studies that were included for analysis.
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		
This review found evidence from homogenous studies that aggressive use of lipid-lowering therapy, particularly with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), is effective in the prevention of cardiovascular disease in patients with type 2 diabetes. This review was able to pool results from RCTs to answer Q14.		

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Lipid modification		**Question number: Q14, Q15 plus subgroups with T2D and FH**	
Characteristics of study			
Checklist completed by: Jonathan Ucinek			
Study citation	WARD, S., LLOYD JONES, M., PANDOR, A., HOLMES, M., ARA, R., RYAN, A., YEO, W. & PAYNE, N. (2007) A systematic review and economic evaluation of statins for the prevention of coronary events. *Health Technol Assess,* 11**,** 1-160, iii-iv.		
Study design	**Systematic review and economic evaluation (UK)**	**N (total)**	157 papers; 31 RCTS
Search strategy	Electronic literature searches November 2003 and April 2004: MEDLINE, EMBASE, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CCTR), Database of Abstracts of Reviews of Effectiveness (DARE), Science Citation Index, NHS Economic Evaluation Database (NHS EED), Health Technology Assessment Database (NHS HTA) and CINAHL. Reference lists of relevant articles and sponsor submissions were hand searched.		

Selection criteria	**Inclusion criteria** • Participants: adults (defined as age >18 years) with, or at risk of, CHD • Studies using other interventions in addition to statin therapy were included only if the treatment received by the intervention and control groups was identical in all respects other than the use of statin therapy. • RCTs of at least 6 months' duration. Trials were accepted as RCTs if the allocation of subjects to treatment groups was described by the authors as either randomised or double-blind. **Exclusion criteria** • Studies considered methodologically unsound • studies of multi-interventional therapies where the effect of the statin could not be separated out.		
Intervention	Statins: – atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin.		
Comparison	Placebo, other statins, 'usual care', 'no statin treatment'		
Outcomes	all-cause mortality, cardiovascular mortality, CHD mortality, stroke mortality, other cardiovascular events (e.g. non-fatal MI, angina, surgical revascularisation, non-fatal stroke), adverse events (including cancer and trauma), health-related quality of life (HRQoL), cost. Data relating to surrogate end-points (such as total cholesterol, LDL-C and HDL-C) were used only where information on clinical end-points was unavailable.		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		wc	To evaluate the clinical effectiveness and cost-effectiveness of statins for the primary and secondary prevention of cardiovascular events in adults with, or at risk of, coronary heart disease (CHD)
Description of the methodology used is included		wc	
The literature search was sufficiently rigorous to identify all the relevant studies		wc	
Study quality was addressed and taken into account?		wc	The quality of RCTs was assessed according to criteria based on those proposed by the NHS CRD.
There were enough similarities between the studies to justify combining them.		wc	
SECTION 2: Overall assessment of the study			
How well was the study done to minimise bias? Determine the methodological quality of the study		++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
			+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.

according to this ranking, based on responses above.		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		

SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**

Statins vs placebo control
meta-analysis of data from all studies that provided such data in usable form indicates that statins are associated with a reduction in the risk of all-cause mortality, cardiovascular mortality, CHD mortality and fatal MI, but not of stroke mortality (*Figures 2–4)*
meta-analysis of data from all studies that provided such data in usable form indicates that statins are associated with a reduction in the risk of non-fatal stroke, TIA, nonfatal MI (*Figure 5*), unstable angina and hospitalisations for unstable angina.
On the evidence available from the placebo controlled trials, it is barely possible to differentiate between the different statins in relation to any outcome: although the point estimates of their effect sizes may vary, the confidence intervals overlap in each case except for non-fatal MI, where simvastatin can just be differentiated from pravastatin (*Figure 5*). Head-to-head comparisons of one statin with another are reviewed in the section 'Direct statin–statin comparisons' (p. 42).
Reported absolute risk reduction for primary CVD prevention (table 17,page 43)-
All-cause mortality: risk of event in placebo arm - 4.13%; Absolute risk reduction (95%CI) - 0.55% (–0.20 to 1.29); NNT for 3 years - 183.
CHD mortality NR
Total stroke: risk of event in placebo arm - 2.36%; Absolute risk reduction (95%CI) - 0.63% (0.09 to 1.18); NNT for 3 years- 158 (84.8 to 1141.4)
CHD mortality + non-fatal MI: risk of event in placebo arm- 3.00%; Absolute risk reduction (95%CI) - 1.06% (0.46 to 1.66); NNT for 3 years- 95 (60.2 to 215.5)
Diabetes subgroup – table 23 has absolute risk and NNT data. No evidence statins are more/less effective in people with T2D that those without.
Familial hypercholesterolaemia – no trials found indeed unethical to not treat lipid levels in this population.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS

Guideline topic: lipids			**Question number: 15**
Characteristics of study			
Checklist completed by: Jonathan Ucinek			
Study citation	ZHOU, Z., RAHME, E. & PILOTE, L. (2006) Are statins created equal? Evidence from randomized trials of pravastatin, simvastatin, and atorvastatin for cardiovascular disease prevention. Am Heart J, 151, 273-81.		
Study design	**Systematic review**	**N (total)**	Eight trials, including 4 pravastatin trials (n = 25572), 2 simvastatin trials (n = 24980), and 2 atorvastatin trials (n = 13143).
Search strategy	Search in the MEDLINE and the Cochrane Controlled Trials Register databases (Update Software Ltd, Oxford, UK, 2004) between 1980 and 2004 for English-language studies using the keywords atorvastatin, simvastatin, and pravastatin in combination with any of the following words: cholesterol, prevention, cardiovascular disease, myocardial infarction, coronary heart disease,		

	ischemic heart disease, stroke, mortality in the title or abstract.		
Selection criteria	Studies were restricted to RCTs comparing statin vs placebo. In addition, trials that evaluated a statin vs usual care were also identified. Use of additional medications by the trial participants was considered acceptable, if the medications were applied equally in both arms. No age and sex restrictions were applied. Completed RCTs were included if they measured CVD or mortality as the outcome, enrolled ≥1000 participants, and had a minimum follow-up of 1 year.		
Intervention	Statin (pravastatin, atorvastatin, simvastatin)		
Comparison	placebo		
Outcomes	Four outcomes were compared between statins: (1) major coronary events, defined as fatal coronary heart disease (CHD) and nonfatal MI; (2) major cerebrovascular events (fatal and nonfatal strokes); (3) all cardiovascular deaths (coronary and cerebrovascular); and (4) all-cause mortality		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		WC	to determine the relative effect of 3 major statins (ie, pravastatin, simvastatin, and atorvastatin) based on adjusted indirect comparison. We used data from published large-scale RCTs that compare these statins to placebo for long-term CVD prevention
Description of the methodology used is included		WC	
The literature search was sufficiently rigorous to identify all the relevant studies		Wc	
Study quality was addressed and taken into account?		Wc	
There were enough similarities between the studies to justify combining them.		wc	
SECTION 2: Overall assessment of the study			
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
			+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
			- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?			
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your**			

own view of its strengths and weaknesses, and how it will help to answer the key question.
Statin treatment resulted in a significant reduction in the event rate of the primary cardiovascular outcomes, except for the ALLHAT-LLT trial, where the reduction did not reach a statistical significance. Evidence from published statin randomized placebo-controlled trials suggests that pravastatin, simvastatin, and atorvastatin, when used at their standard dosages, show no statistically significant difference in their effect on long-term cardiovascular prevention.

FORM framework Question 14

Key question(s): Q14 Does pharmacological lipid modification reduce CVD events and all cause mortality compared to control?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Multiple high quality (level I) studies	A	**One or more level I studies with a low risk of bias or several level II studies with a low risk of bias**
	B	**One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias**
	C	**One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias**
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
All papers confirm that lowering lipids using pharmacology reduces CVD events and mortality compared to control groups, and more recent SRs confirm also reduces all cause and stroke mortality. The majority of reviews make the point that the effect appears to be related to LDL reduction. Earlier SRs are less confirming for specific types of mortality prevention but the later SRs are consistent.	A	**All studies consistent**
	B	**Most studies consistent and inconsistency can be explained**
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
	NA	**Not applicable (one study only)**
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could*		
Evidence applies to a large patient population, is associated with substantial potential benefits, but no harms reported and has significant resource and organisational implications.	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Large amount of data related to diverse populations, international trials	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Highly applicable.	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

There is a substantial and consistent body of literature over time that confirms that pharmacological lipid modification reduces cardiovascular disease. However, no studies were conducted which included patients for treatment based on absolute risk assessment at entry. There appears to be consistent relative risk reduction with statins which the EWG may wish to consider based on applied benefits in different absolute risk categories. NOTE: on discussion the EWG felt the only group they were comfortable applying relative risk literature to absolute risk framework was high risk. Hence moderate and low risk are consensus based recommendations. BP lowering and lipid lowering therapy are both recommended for those assessed as high absolute risk. Therefore for ease of use the EWG agreed to combine this recommendation.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1.Evidence base	A	High quality, low risk reviews
2.Consistency	A	with consistent findings at 2003 and 2007 and 2009
3.Clinical impact	A	Remains high
4. Generalisability	A	High
5. Applicability	A	High

Evidence statement

Pharmacological lipid modification reduces CVD events and all cause mortality compared to controls.

Indicate any dissenting opinions

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE OF RECOMMENDATION**	

a) Adults at high absolute risk of CVD should be simultaneously treated with lipid and blood pressure lowering pharmacotherapy in addition to lifestyle intervention unless contraindicated or clinically inappropriate. (Grade B –downgraded from A due to assumptions of transferring from relative risk studies to absolute risk framework)

b) Adults at moderate absolute risk of CVD may treated with pharmacotherapy for blood pressure and/or lipid lowering in addition to lifestyle intervention if one or more of the following applies:

- Persistent blood pressure ≥ 160/100 mmHg;
- Family history of premature CVD;

- Aboriginal and Torres Strait Islander peoples;
- Other populations where FRE is known to underestimate risk (South Asians, Maori and Pacific Islanders, people from the Middle East). (Practice point)

c) Pharmacotherapy for blood pressure and lipid lowering is not routinely recommended for adults at low absolute risk of CVD. (Practice point)

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up*	
The questions do not identify adverse events for treatment. Of note is one recent RCT (Sattar 2010) that looks at risk of developing diabetes after statin use and found: Treatment of 255 (95% CI 150–852) patients with statins for 4 years resulted in one extra case of diabetes that is a small increased risk of developing diabetes predominantly in the trials with older participants. Also other risk factors may contribute such as previous history or groups where FRE is known to underestimate risk.	
IMPLEMENTATION OF RECOMMENDATION	
Will this recommendation result in changes in usual care? Absolute framework irrespective of lipid levels from those at high risk. But those at low or moderate risk could come off pharmacotherapy.	**YES**
Are there any resource implications associated with implementing this recommendation?	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation? Change in practice as noted above.	**YES**

FORM framework Question 15

Key question(s): Q15 What is the evidence for one lipid modifying drug class or any combination of drug classes being more effective than any other for reducing CVD events and all cause mortality. Secondary outcome – reduction of blood lipids		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Multiple high quality Level I studies (mostly re: statins but also Fibrates, n-3 fatty acids, resins, niacin)		**One or more level I studies with a low risk of bias or several level II studies with a low risk of bias**
	B	**One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias**
	C	**One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias**
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Of all methods to modify lipids, statins are superior. Of the statins (atorvastatin, cerivastatin, fluvastatin, lovastatin, provastatin, rosuvastatin and simvastatin) all similar (all reviews) only one clear differential effect between simvastatin and pravastatin for stroke prevention (reported in one review).	A	**All studies consistent**
	B	**Most studies consistent and inconsistency can be explained**
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could*		
	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to**
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Consideration of drug class availability is required for Australian healthcare sector.	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Differential effects between statins for stroke prevention only. Could compare risk reduction statistics across trials for different pharmacology but not recommended due to heterogeneity. Many reviews don't differentiate primary and secondary trials. Limited trial data for all groups except statins.
Where statin therapy may not be tolerated or where lipid levels remain high with maximum statin therapy other agents may need to be considered. Hence recommendations have been added along with evidence matrix summary.

EVIDENCE STATEMENT MATRIX

Component	Rating	Description
Evidence base	A	High quality, low risk reviews over last 8 years
Consistency	A	Strongest consistency is for classes to have no clear advantage except for specific prevention effects (eg stroke)
Clinical impact	A	Remains high
Generalisability	A	Diverse, large international populations
Applicability	A	

Evidence statement
There is strong evidence for statins being more effective than any other for reducing LDL (several reviews). For reducing CVD events and all cause mortality generally all the different statins have similar effects except in the case of stroke prevention where simvastatin is superior to pravastatin. Choice of statin may relate to dosage required for lowering. Combination therapies can be considered when target LDL levels are not being reached with statins alone (eg Statins and ezetimibe). Other options are reviewed (see question 14) but rarely head to head to allow meaningful comparison.

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE OF RECOMMENDATION**	

a) Statins should be used as first line therapy. (Grade A)
b) If LDL-C levels are not sufficiently reduced on maximally tolerated dose of statin, one or more of the following may be added:
   - Ezetimibe (Grade C [Evidence base B –SR with surrogate outcomes and SHARP trial; Consistency B (for surrogate outcomes); Clinical impact B; Generalisability C; Applicability B]);
   - Bile acid binding resins; (Grade D [Evidence base C; Consistency NA; Clinical impact B; Generalisability C; Applicability C])
   - Nicotinic acid. (Grade D [Evidence base B; Consistency B; Clinical impact D; Generalisability C; Applicability B])
c) Where statins cannot be tolerated at all, one or more of the following can be used:
   - Ezetimibe; (Grade D [Evidence base B —SR with surrogate outcomes and SHARP trial; Consistency B; Clinical impact B; Generalisability C; Applicability B])
   - Bile acid binding resin; (Grade D [Evidence base C; Consistency NA; Clinical impact B; Generalisability B; Applicability C])

- Nicotinic acid. (Grade D [Evidence base B; Consistency B; Clinical impact D; Generalisability C; Applicability B])

d) If triglyceride levels remain elevated, treatment with one of the following may be considered.
   - Fenofibrate (especially if HDL is below target); (Grade C [Evidence base B –particularly two large trials FIELD & ACCORD; Consistency C; Clinical impact C; Generalisability B; Applicability A])
   - Nicotinic acid; (Grade C [Evidence base B; Consistency B; Clinical impact D; Generalisability C; Applicability B])
   - Fish oil. (Grade C [Evidence base B; Consistency B; Clinical impact C; Generalisability C; Applicability C])

e) Treatable secondary causes of dyslipidaemia should be considered before commencing lipid lowering pharmacotherapy. (Practice point)

UNRESOLVED ISSUES

If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up

For this question we have not reviewed individual studies ie looking at individual drugs/classes published after the SRs as this would lead to potentially giving greater strength to the individual drug class than the collective.

IMPLEMENTATION OF RECOMMENDATION

Will this recommendation result in changes in usual care?	**NO**
Are there any resource implications associated with implementing this recommendation?	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**NO**

FORM framework Question 16

Key question(s): Q16 Should lipid lowering therapy employ drugs at fixed doses or should individuals always be titrated to target lipid levels?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One high quality systematic review: - Edwards 2003 looked at fixed dose versus titrated at different doses and found no significant different particularly in the longer duration studies (see page 17).		**One or more level I studies with a low risk of bias or several level II studies with a low risk of bias**
	B	**One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias**
	C	**One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias**
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Acceptable heterogeneity.	A	**All studies consistent**
	B	**Most studies consistent and inconsistency can be explained**
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could*		
	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to**
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Consideration of drug class availability is required for Australian healthcare sector.	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Study numbers for titrated trials are low and therefore not as conclusive as for fixed dose trials.

EVIDENCE STATEMENT MATRIX

Component	Rating	Description
16. Evidence base	A	High quality, low risk review
17. Consistency	A	
18. Clinical impact	A	Remains high
19. Generalisability	A	Diverse, large international populations
20. Applicability	A	

Evidence statement

There is no difference between fixed doses and titrated in the long term.

Indicate any dissenting opinions

RECOMMENDATION	**GRADE OF RECOMMENDATION**	
No recommendation made		

FORM framework Question 17

Key question(s): Q17 Does more intensive lipid modification treatment produce greater reductions in CVD events and all cause mortality.		**Evidence table ref:**
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Multiple level I studies		**One or more level I studies with a low risk of bias or several level II studies with a low risk of bias**
	B	**One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias**
	C	**One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias**
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Each review addresses this question slightly differently but the findings are congruent.	A	**All studies consistent**
	B	**Most studies consistent and inconsistency can be explained**
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could*		
	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to**
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Consideration of drug class availability is required for Australian healthcare sector.	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Cannon 2006 (SR) also looked at intensive versus moderate statin therapy but on trials with subjects who had either stable CHD or ACS – they also reported in favour of intensive: a highly significant 16% reduction of coronary death or MI ($p < 0.00001$) and, similarly, a 16% reduction in coronary death or any cardiovascular events in patients receiving high-dose statin therapy versus those receiving standard-dose therapy ($p < 10^{-12}$) and concluded "Intensive lipid lowering with high-dose statin therapy provides a significant benefit over standard-dose therapy for preventing predominantly non-fatal cardiovascular events".
However evidence for less v more is inferred from trial results. NOTE: Additional MA (see appendix A) from Cholesterol trialists collaboration (2010) found in the primary prevention cohort a 25% relative risk reduction for each 1mmol/L reduction in LDL-C.

However actual targets for more intensive therapy is derived from trials and thus is determined as guide to practice rather than direct evidence based recommendation.

EVIDENCE STATEMENT MATRIX

Component	Rating	Description
6. Evidence base	A	High quality, low risk reviews over 7 years
7. Consistency	A	
8. Clinical impact	A	Remains high
9. Generalisability	A	Diverse, large international populations
10. Applicability	A	

Evidence statement
More intensive lipid modification produces greater reduction in CVD events (stroke) although targets are derived from trials and there is little direct evidence for targets. LDL-C levels appear to be the most useful surrogate measure and there is a dose response relationship up to a point. Other cholesterol measures may also be useful in some cases (e.g. triglycerides).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE OF RECOMMENDATION**	

Pharmacotherapy for lipid lowering should aim towards the following targets while balancing the risks/benefits:

TC< 4.0 mmol/L
HDL-C ≥1.0 mmol/L
LDL-C <2.0 mmol/L
Non HDL<2.5 mmol/L
TG < 2.0 mmol/L

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up*	
IMPLEMENTATION OF RECOMMENDATION	
Will this recommendation result in changes in usual care?	**NO**
Are there any resource implications associated with implementing this recommendation?	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**NO**

Subgroup evidence for Lipid questions:

a. Those deemed clinically high risk as outlined in the assessment guidelines (those with SBP >180 or DBP>110mmHg, diabetes >60yrs, diabetes with microalbuminuria, CKD [see levels below], familial hypercholesterolaemia, cholesterol >7.5mmol/L)

Q14. Does pharmacological lipid modification reduce CVD events and all cause mortality compared to 'control'?
General evidence statement: Pharmacological lipid modification reduces CVD events and all cause mortality compared to controls (but not stroke mortality).
There is no evidence to support a different approach for those deemed as clinically high risk.
Ward 2007 reported that people with familial hypercholesterolaemia were not investigated specifically in trials and that this was not surprising given their obvious high risk and therefore need for modification (p50).
Corvol 2003 report an effect model analysis that suggests the effectiveness of LLT is irrespective of level of risk for stroke.
Brugt 2009 confirmed people at high risk should be treated as usual, and similarly for those with Diabetes mellitus.
Jun 2010 suggest the use of fibrates, though the magnitude of effect is moderate, but in high-risk individuals and in those with combined dyslipidaemia, clinically meaningful reductions in risk could be achieved.

Q15. What is the evidence for one lipid modifying drug class or any combination of drug classes being more effective than any other drug class or combination for reducing CVD events and all cause mortality? Report evidence for secondary outcome defined as: Reduction of …….
General: There is strong evidence for one lipid modifying drug class being more effective than any other for reducing LDL (this is statins); and for reducing CVD events and all cause mortality generally all the different statins (7) have similar effects except in the case of stroke prevention where simvastatin is superior to pravastatin. Choice of statin may relate to dosage required for lowering.
There is no evidence to support a different approach for those deemed as clinically high risk; treating to target levels is the key. *Note though that Robinson 2009 cited non–HDL-C was a better measure than LDL-C for identifying patients at high risk who had multiple cardiometabolic risk factors.*

Q16. Should lipid lowering therapy employ drugs at fixed doses or should individuals always be titrated to target blood pressure levels?
General: There is no difference between fixed doses and titrated in the long term.
No reported evidence

Q17. Does more intensive blood pressure lowering produce greater reductions in CVD events and all cause mortality?
General: More intensive lipid modification produces greater reduction in CVD events (stroke) and a lowering of cholesterol,with the optimum level < 232mg/dL (6.0 mmol/L). LDL-C levels appear to be the most useful surrogate measure and there is a dose response relationship up to a point.
No reported evidence

b. Those with atrial fibrillation

No studies found to differentiate those with AF from the general population in lipid management

c. High, medium and low absolute risk of CVD

No studies found reporting between different levels of absolute risk in regard to lipid management.

d. Abnormal BP and normal BP

No studies found which differentiated between abnormal and normal BP for lipid management

e. Hypercholesterol and normal cholesterol

No studies found which investigated lipid modification for those with normal cholesterol.

f. Diabetes and no diabetes

No studies directly compared effects of lipid management for people with and without diabetes however studies did look exclusively at response to lipid modification of people with type II diabetes.
Ward 2007 (SR) stated that there is no evidence that statins are more or less effective in people with diabetes than in those without (see Table 23 for absolute risk reduction and NNT for diabetes).
An earlier high quality systematic review by Vijan (2004) also confirmed the effectiveness of statins in the prevention of CVD in people with T2D.
Brugt 2009 (SR) confirmed people with diabetes gain the same benefits from statin therapy as people without.
Alleman 2006 (SR) confirmed there is a reduction in CHD events people with T2D taking fibrates, and non-significant reductions in risk for MI and stroke.
Ginsberg 2010 (ACCORD- RCT) found the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke, as compared with simvastatin alone. These results do not support the routine use of combination therapy with fenofibrate and simvastatin to reduce cardiovascular risk in the majority of high-risk patients with type 2 diabetes.
Keech 2005 (FIELD RCT) found that Fenofibrate did not significantly reduce the risk of the primary outcome of coronary events. It did reduce total cardiovascular events, mainly due to fewer non-fatal myocardial infarctions and revascularisations. The higher rate of starting statin therapy in patients allocated placebo might have masked a moderately larger treatment benefit.

g. Chronic kidney disease and no chronic kidney disease (break down into GFR <45 ml/min, GFR 45-60 ml/min and GFR >60 ml/min)

One study directly compared effects of lipid management for people with and without CKD:
Ridker 2010 (RCT – secondary analysis of Jupiter participants, investigating the effectiveness of rosuvastatin). They reported:

- Compared with those with eGFR ≥60 ml/min/1.73 m2, JUPITER participants with moderate CKD had higher vascular event rates (hazard ratio [HR]: 1.54, 95% confidence interval [CI]: 1.23 to 1.92, p = 0.0002).
- Among those with moderate CKD, rosuvastatin was associated with a 45% reduction in risk of myocardial infarction, stroke, hospital stay for unstable angina, arterial revascularization, or confirmed cardiovascular death (HR: 0.55, 95% CI: 0.38 to 0.82, p = 0.002) and a 44% reduction in all-cause mortality (HR: 0.56, 95% CI: 0.37 to 0.85, p = 0.005).
- Median LDL-C and hsCRP reductions as well as side effect profiles associated with rosuvastatin were similar among those with and without CKD. Median eGFR at 12 months was marginally improved among those allocated to rosuvastatin as compared with placebo

Navaneethan 2009 (Cochrane systematic review) showed in patients with non-dialysis dependent CKD, that Statins decreased all-cause mortality and cardiovascular mortality along with lowering lipid levels to an extent which is similar to that found in the general population. Statins also reduce protein excretion in urine but the impact of this on the risk of needing renal replacement therapy needs to be studied further. Statins were not found to have serious adverse effects in this group of people.

7. Antiplatelet therapy (Q18-19)

Search results

Sources	Dates	Total hits	Retrieval list	Final inclusions
Databases Medline; Embase ; Cinahl; PsychINFO Cochrane Library, including CENTRAL Cochrane Controlled Trial Register (CCTR) **Other sources:** pearling; expert working group.	**2002-2010**	**1761**	**85**	**16** AACTIVE – A 2009 Aguilar 2005 + 2005 Aguilar 2007 ATT 2009 Berger 2006 Calvin 2009 Connolly 2009 De Berardis 2009 Fowkes 2010 Mant 2007 Pignone 2010 Wang 2008 Wolf 2009 Yerman 2007 Zhang 2010
Search terms:	Aspirin; Platelet Aggregation Inhibitors; Clopidogrel; dipyridamole acetylsalicylic acid; antiplatelet; Warfarin; Antithrombotic agents Thrombin inhibitors; Thrombin receptor antagonists; Heparinoids **Added:** Clopidogrel; Dipyridamole			

Literature Included

Question 18. Does antiplatelet therapy compared to control reduce CVD events and all cause mortality?	
References	**Comments / quality**
Antithrombotic Trialists' (ATT) Collaboration et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009 May 30;373(9678):1849-60.	High quality SR. Includes modeling on basis of absolute

	risk of CHD.
Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. JAMA. 2006; 295:306-13.	High quality SR
Fowkes FG, Price JF, Stewart MC, Butcher I, Leng GC, Pell AC, Sandercock PA, Fox KA, Lowe GD, Murray GD; Aspirin for Asymptomatic Atherosclerosis Trialists. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. JAMA. 2010 Mar 3;303(9):841-8.	Good quality RCT. Underpowered.
Jardine MJ, Ninomiya T, Perkovic V, et al. Aspirin is beneficial in hypertensive patients with chronic kidney disease: a post-hoc subgroup analysis of a randomized controlled trial. J Am Coll Cardiol 2010;56:956–65.	Subgroup analysis (post-hoc) to be considered exploratory only
Wolff T, Miller T, Ko S. Aspirin for the primary prevention of cardiovascular events: an update of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2009 Mar 17;150(6):405-10.	Good quality SR for guideline
Yerman T, Gan WQ, Sin DD. The influence of gender on the effects of aspirin in preventing myocardial infarction. BMC Med 2007; 5:29.	Moderate quality SR. Includes primary and secondary trials
References specific for DIABETES	
Calvin et al. Aspirin for the primary prevention of cardiovascular events: a systematic review and meta-analysis comparing patients with and without diabetes. Diabetes Care. 32(12):2300-6, 2009 Dec.	High quality SR
De Berardis et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials.BMJ. 2009 Nov 6;339:b4531. Erratum in: BMJ. 2010;340:c374.	High quality SR
Zhang C et al. Aspirin for primary prevention of cardiovascular events in patients with diabetes: A meta-analysis. Diabetes Res Clin Pract. 2010 Feb;87(2):211-8. Epub 2009 Oct 23.	Moderate quality SR
Pignone et al 2010. Aspirin for primary prevention of cardiovascular events in people with diabetes. American Diabetes Association statement. Diabetes Care. 2010 June;33(6):1395-1402.	Moderate quality SR
References specific for those with AF	

Active Investigators, Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M. Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation. N Engl J Med. 2009;360(20):2066-78.	Good quality RCT
Aguilar M, Hart R. Antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD001925.	High quality SR.
Aguilar MI, Hart R, Pearce LA. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD006186.	High quality SR. Anticoagulant vs antiplatelet
Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;361(12):1139-51. Epub 2009 Aug 30.	Good quality RCT. Anticoagulant rather than antiplatelet
Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, Murray E; BAFTA investigators; Midland Research Practices Network (MidReC). Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet. 2007 Aug 11;370(9586):493-503.	Good quality RCT. Antiplatelet v anticoagulant

Question 19. What is the evidence for one antiplatelet therapy or dose or any combination of therapy/doses being more effective than any other antiplatelet therapy/dose or combination for the reduction of CVD events and all cause mortality?	
References -DOSE	**Summary**
Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002 Jan 12;324(7329):71-86. (included in SIGN)	Indirect evidence from the ATT collaboration suggests that the risk reductions achieved with low doses (75–162 mg/day) are as large as those obtained with higher doses (500–1,500 mg/day) and larger than those in the few trials that have used doses below 75 mg/day. Most trials in last 15 years have used 75-150mg doses.
References -AGENT	**Summary**
Wang et al. An analysis of mortality rates with dual-antiplatelet therapy in the primary prevention population of the CHARISMA trial. European Heart Journal. 28(18):2200-2207.	Only one good quality RCT (CHARISMA) compared dual antiplatelet therapy (ASA + Clopidogrel) –approx 2000 of the 15,000 participants were free of existing CVD and reported

	separately.

Evidence details

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Antiplatelets	**Question number: Q18**		
Characteristics of study			
Checklist completed by: Kelvin Hill			
Study citation	Aguilar MI, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD001927.		
Study design	**Systematic review**	**N (total)**	5 trials (N= 2313)
Search strategy	We searched the Cochrane Stroke Group Trials Register which was last searched by the Review Group Co-ordinator in August 2004. In addition, we searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 1, 2005), and MEDLINE (1966 to June 2004), not restricted to any languages, using the text words of 'atrial fibrillation' and stroke combined individually with anticoagulation, antithrombotic, clinical trial, and embolism.. In addition, we contacted the Atrial Fibrillation Investigators Collaboration and experts working in the field seeking information about trials currently in progress.		
Selection criteria	all unconfounded, randomized trials in which long-term treatment (more than four weeks) with OACs was compared with control or placebo in patients with chronic non-valvular AF. The overall mean age was 69 years, with 20% of participants over 75 years old		
Intervention	OAC (warfarin in all five trials)		
Comparison	Placebo (or control)		
Outcomes	(1) All strokes (ischemic and hemorrhagic) was the primary outcome. (2) Ischemic strokes (including both fatal and non-fatal). (3) All disabling or fatal stroke (ischemic and hemorrhagic). (4) MI (fatal and non-fatal). (5) Systemic (that is, non CNS) emboli. (6) All intracranial hemorrhage. (7) Major extracranial hemorrhage. (8) Vascular death. These consisted of death due to stroke, heart disease, hemorrhage, and sudden deaths of unknown cause. (9) Composite outcome: all stroke (disabling and non-disabling, hemorrhagic and ischemic), MI or vascular death. (10) All cause mortality: death from any cause (vascular and non-vascular) within 30 days from onset of stroke symptoms.		
Results	Participant features and study quality were similar between trials: the OAC in all five trials was warfarin. About half of participants (N = 1154) were randomized to adjusted-dose warfarin with mean achieved INRs ranging between 2.0 to 2.6. During 1.5 years mean follow up, warfarin was associated with large, highly statistically significant reductions in all strokes (odds ratio (OR) 0.39, 95% CI 0.26 to 0.59), ischemic stroke (OR 0.34, 95% CI 0.23 to 0.52), all disabling or fatal stroke (OR 0.47, 95% CI 0.28		

	to 0.80), death (OR 0.69, 95% CI 0.50 to 0.94) and the combined endpoint of all stroke, myocardial infarction or vascular death (OR 0.56, 95% CI 0.42 to 0.76). The observed rates of intracranial and extracranial hemorrhage were not significantly increased by OAC therapy, but the confidence intervals were wide.		
Quality of study			
Quality criteria (from SIGN)	***Met?**	**Comments**	
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question	WC		
Description of the methodology used is included	WC		
The literature search was sufficiently rigorous to identify all the relevant studies	WC		
Study quality was addressed and taken into account?	WC		
There were enough similarities between the studies to justify combining them.	WC		
SECTION 2: Overall assessment of the study			
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.	
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.	
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.	
If coded as +, or - what is the likely direction in which bias might affect the study results?			
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**			
Robust systematic review of RCTs which found clear benefits of warfarin for preventing stroke and all cause mortality and combined endpoints (but not vascular death alone). About 12 serious stroke events would be prevented yearly for every 1000 participants given warfarin.			

* Assessment of whether the criteria has been met should be made according to one of the following descriptors
Well covered
Adequately addressed
Poorly addressed
Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
Not applicable.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Antiplatelets		**Question number: Q18**	
Characteristics of study			
Checklist completed by: Kelvin Hill			
Study citation	Aguilar M, Hart R. Antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD001925.		
Study design	**Systematic review**	**N (total)**	3 trials (N=1965)
Search strategy	We searched the Cochrane Stroke Group Trials Register which was last searched by the Review Group Co-ordinator in August 2004. In addition, we searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 1, 2005), and MEDLINE (1966 to June 2004), not restricted to any languages, using the following text words: atrial fibrillation, stroke, aspirin, APT, antithrombotic, clinical trial, cerebrovascular disease, embolism. In addition, we contacted the Atrial Fibrillation Investigators Collaboration and experts working in the field seeking information about trials currently in progress.		
Selection criteria	all unconfounded, randomized trials in which long-term APT (more than four weeks) was compared to placebo or control in patients with chronic non-valvular AF. Participants with AF documented by electrocardiogram (ECG), either intermittent (that is, paroxysmal) or sustained (that is, constant) were included. Those with mitral stenosis or prosthetic cardiac valves were not included.		
Intervention	APT (Aspirin, clopidogrel etc) –all three trials used aspirin		
Comparison	Placebo (or control)		
Outcomes	(1) All strokes (ischemic and hemorrhagic) was the primary outcome. (2) Ischemic strokes (including both fatal and non-fatal). (3) All disabling or fatal stroke (ischemic and hemorrhagic). (4) MI (fatal and non-fatal). (5) Systemic (that is, non CNS) emboli. (6) All intracranial hemorrhage. (7) Major extracranial hemorrhage. (8) Vascular death. These consisted of death due to stroke, heart disease, hemorrhage, and sudden deaths of unknown cause. (9) Composite outcome: all stroke (disabling and non-disabling, hemorrhagic and ischemic), MI or vascular death. (10) All cause mortality: death from any cause (vascular and non-vascular) within 30 days from onset of stroke symptoms.		
Results	Aspirin was associated with non-significant lower risks of all stroke (odds ratio (OR) 0.70, 95% confidence interval (CI) 0.47 to 1.07), ischemic stroke (OR 0.70, 95% CI 0.46 to 1.07), all disabling or fatal stroke (OR 0.86, 95% CI 0.50 to 1.49) and all-cause death (OR 0.75, 95% CI 0.54 to 1.04). The combination of stroke, myocardial infarction or vascular death was significantly reduced (OR 0.71, 95% CI 0.51 to 0.97). No increase in intracranial hemorrhage or major extracranial hemorrhage was observed.		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**

SECTION 1: Internal validity		
Study addresses an appropriate and clearly focused question	WC	
Description of the methodology used is included	WC	
The literature search was sufficiently rigorous to identify all the relevant studies	WC	
Study quality was addressed and taken into account?	WC	
There were enough similarities between the studies to justify combining them.	WC	
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		
SECTION 3: Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.		
Aspirin was associated with consistent, but modest reductions in stroke and other ischemic events that were of marginal statistical significance. The combination of stroke, myocardial infarction or vascular death was significantly reduced (OR 0.71, 95% CI 0.51 to 0.97). No statistically significant reduction in vascular death 0.82 [0.54, 1.25]. No increase in intracranial hemorrhage or major extracranial hemorrhage was observed.		

* Assessment of whether the criteria has been met should be made according to one of the following descriptors
Well covered
Adequately addressed
Poorly addressed
Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
Not applicable.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS	
Guideline topic: Antiplatelets	**Question number: Q18**
Characteristics of study	
Checklist completed by: Kelvin Hill	

Study citation	Aguilar MI, Hart R, Pearce LA. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD006186.		
Study design	**Systematic review**	**N (total)**	8 trials (N= 9598 patients)
Search strategy	We searched the Cochrane Stroke Group Trials Register (June 2006). We also searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 2, 2006), MEDLINE (1966 to June 2006) and EMBASE (1980 to June 2006). We contacted the Atrial Fibrillation Collaboration and experts working in the field to identify unpublished and ongoing trials.		
Selection criteria	All unconfounded, randomized trials in which long-term (more than four weeks) adjusted-dose oral anticoagulant treatment was compared with antiplatelet therapy in patients with chronic non-valvular AF.		
Intervention	adjusted-dose warfarin		
Comparison	APT (mostly aspirin in dosages ranging from 75 to 325 mg/day)		
Outcomes	(1) All strokes (ischemic and hemorrhagic) was the primary outcome. (2) Ischemic strokes (including both fatal and non-fatal). (3) All disabling or fatal stroke (ischemic and hemorrhagic). (4) MI (fatal and non-fatal). (5) Systemic (that is, non CNS) emboli. (6) All intracranial hemorrhage. (7) Major extracranial hemorrhage. (8) Vascular death. These consisted of death due to stroke, heart disease, hemorrhage, and sudden deaths of unknown cause. (9) Composite outcome: all stroke (disabling and non-disabling, hemorrhagic and ischemic), MI or vascular death. (10) All cause mortality: death from any cause (vascular and non-vascular) within 30 days from onset of stroke symptoms.		
Results	The mean overall follow up was 1.9 years/participant. Oral anticoagulants were associated with lower risk of all stroke (odds ratio (OR) 0.68, 95% CI 0.54 to 0.85), ischemic stroke (OR 0.53, 95% CI 0.41 to 0.68) and systemic emboli (OR 0.48, 95% CI 0.25 to 0.90). All disabling or fatal strokes (OR 0.71, 95% CI 0.59 to 1.04) and myocardial infarction (OR 0.69, 95% CI 0.47 to 1.01) were substantially but not significantly reduced by oral anticoagulants. Vascular death (OR 0.93, 95% CI 0.75 to 1.15) and all cause mortality (OR 0.99, 95% CI 0.83 to 1.18), were similar with these treatments. Intracranial hemorrhages (OR 1.98, 95% CI 1.20 to 3.28) were increased by oral anticoagulant therapy.		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		WC	
Description of the methodology used is included		WC	
The literature search was sufficiently rigorous to identify all the relevant studies		WC	

Study quality was addressed and taken into account?	WC	
There were enough similarities between the studies to justify combining them.	WC	
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		
Robust systematic review of RCTs which found clear benefits (~30%) of warfarin over APT for preventing stroke and all cause mortality and combined endpoints (but not vascular death alone, all cause mortality or MI alone). OAC doubled heamorhage rates but was relatively infrequent (41 v 20).		

* Assessment of whether the criteria has been met should be made according to one of the following descriptors
Well covered
Adequately addressed
Poorly addressed
Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
Not applicable.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS

Guideline topic: Antiplatelets		**Question number: Q18**	
Characteristics of study			
Checklist completed by: Kelvin Hill			
Study citation	Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, Meade T, Patrono C, Roncaglioni MC, Zanchetti A. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009 May 30;373(9678):1849-60.		
Study design	**Systematic review**	**N (total)**	6 studies
Search strategy	Not covered –simply state no further trials found since 2002 (last review –states: We identified relevant trials by searching several electronic databases (Medline, Embase, Derwent, Scisearch, and Biosis; search strategy available on request); searching the trials registers of the Cochrane Stroke and Peripheral Vascular Disease Groups; manual searching of journals, abstracts, and proceedings		

	of meetings; scrutinising the reference lists of trials and review articles; and inquiry among many colleagues, including representatives of pharmaceutical companies.		
Selection criteria	Inclusion criteria: 1. RCT 2. >1000 non diabetic patients without CVD (although 2% were found to have some) 3. >2year follow up		
Intervention	Aspirin		
Comparison	Placebo (no treatment)		
Outcomes	Primary: Serious vascular event, defined as myocardial infarction, stroke, or death from a vascular cause (including sudden death,pulmonary embolism, haemorrhage) Secondary: major coronary event (myocardial infarction, coronary death, or sudden death); any stroke (haemorrhagic or probably ischaemic [ie, definitely ischaemic or of unknown type]); death from any cause; and major extracranial bleed (mainly gastrointestinal and usually defined as a bleed requiring transfusion or resulting in death). In the primary prevention trials, myocardial infarctions and strokes were classified as fatal or non-fatal in accordance with each trial's definitions. For the purposes of discussion, we calculated what the absolute effects of aspirin allocation would be on outcome at 5 years (only two trials had much longer follow up) if the yearly event rates were constant and the proportional effects of aspirin were independent of age, sex, and other risk factors. Additionally, regression model for major coronary events in control participants only, together with the absolute event rates in the controls of each trial, were used to classify the baseline risks of all participants (including those allocated aspirin) as very low (predicted 5-year risk of coronary heart disease without aspirin <2·5%), low (2·5–5%), moderate (5–10%), or high (≥10%).		
Results	Six primary prevention trials (95 000 individuals at low average risk, 660 000 person-years, 3554 serious vascular events) Aspirin allocation yielded a 12% proportional reduction in serious vascular events (0·51% aspirin vs 0·57% control per year, p=0·0001), due mainly to a reduction of about a fifth in non-fatal myocardial infarction (0·18% vs 0·23% per year, p<0·0001). The net effect on stroke was not significant (0·20% vs 0·21% per year, p=0·4: haemorrhagic stroke 0·04% vs 0·03%, p=0·05; other stroke 0·16% vs 0·18% per year, p=0·08). Vascular mortality did not differ significantly (0·19% vs 0·19% per year, p=0·7). Aspirin allocation increased major gastrointestinal and extracranial bleeds (0·10% vs 0·07% per year, p<0·0001), and the main risk factors for coronary disease were also risk factors for bleeding. No difference found based on 5 year risk of coronary disease although there were small numbers at the highest risk making comparison difficult.		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		WC	
Description of the methodology used is included		Adequately addressed	Although little info for lit search

The literature search was sufficiently rigorous to identify all the relevant studies	Poorly addressed	Little information provided –electronic searches conducted only
Study quality was addressed and taken into account?	Not addressed	No further trials identified from 2002
There were enough similarities between the studies to justify combining them.	Adequately addressed	
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
	+	+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?	Large studies included so smaller trials unlike to change results.	
SECTION 3: Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.		
Aspirin has only a small absolute benefit (0.07% per year) of serious vascular event (no difference in mortality) without heterogeneity (although no difference for those who smoke). Most of the benefit came from reduction in non-fatal MI. Appears different effects for men and women –men have reduced MI but no change in IS whereas women have the reverse (hence no difference overall). But there is an increased risk of major gastrointestinal and other extracranial bleeds by about half (10% v 7%). There is also increase in haemorrhagic stroke. No association was found in the effect of aspirin for low, medium and high risk of CHD –although numbers are small in high risk groups. Overall this is a quality meta-analysis which provides good evidence to answer the question. The weakness of the paper is lack of detail around the literature search which can only be assumed from previous reviews.		

* Assessment of whether the criteria has been met should be made according to one of the following descriptors
Well covered
Adequately addressed
Poorly addressed
Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
Not applicable.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS	
Guideline topic: Antiplatelets	**Question number: Q18**
Characteristics of study	

Checklist completed by: Kelvin Hill			
Study citation	Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. JAMA. 2006; 295:306-13.		
Study design	**Systematic review**	**N (total)**	6 studies
Search strategy	Medline (1966-2005) using terms: aspirin, primary prevention, myocardial infarction, stroke, and randomized controlled trials, as well as combinations of these terms. Cochrane database was mentioned in abstract but not in methods. Other appropriate strategies also used.		
Selection criteria	Inclusion criteria: 1. RCT 2. English language 3. No CVD 4. Outcomes reported		
Intervention	Aspirin		
Comparison	Placebo (no treatment)		
Outcomes	composite end point of any major cardiovascular event (cardiovascular mortality, nonfatal MI, or nonfatal stroke), each of the individual components of the composite end point separately, all cause mortality, and major bleeding.		

Quality of study		
Quality criteria (from SIGN)	***Met?**	**Comments**
SECTION 1: Internal validity		
Study addresses an appropriate and clearly focused question	WC	
Description of the methodology used is included	WC	Although little info for lit search
The literature search was sufficiently rigorous to identify all the relevant studies	Adequately addressed	Medline only main database used with follow up searches –unclear use of Cochrane
Study quality was addressed and taken into account?	Adequately addressed	
There were enough similarities between the studies to justify combining them.	Adequately addressed	
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.

If coded as +, or - what is the likely direction in which bias might affect the study results?	

SECTION 3: Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.

For women and men, aspirin therapy reduced the risk of a composite of cardiovascular events due to its effect on reducing the risk of ischemic stroke in women and MI in men. Aspirin significantly increased the risk of bleeding to a similar degree among women and men.

Overall this is a quality meta-analysis which provides good evidence. Provides same conclusions to ATT –No overall effect on mortality but reduced non-fatal events with increase in bleeding complications.

* Assessment of whether the criteria has been met should be made according to one of the following descriptors
Well covered
Adequately addressed
Poorly addressed
Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
Not applicable.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS

Guideline topic: Antiplatelets		**Question number: Q18**	
Characteristics of study			
Checklist completed by: Kelvin Hill			
Study citation	Bjorklund L. Wallander MA. Johansson S. Lesen E. Aspirin in cardiology--benefits and risk. International Journal of Clinical Practice. 63(3):468-77, 2009 Mar.		
Study design	**Systematic review**	**N (total)**	7 trials included 11,618 individuals
Search strategy	Searches were performed in the Current Contents Science Edition, EMBASE and Ovid MEDLINE databases..		
Selection criteria	Searches were limited to articles published in the English language between January 1996 and December 2006 and reporting studies in human subjects		
Intervention	Aspirin		
Comparison	Placebo (no treatment)		
Outcomes			
Results			
Quality of study			
Quality criteria (from SIGN)	***Met?**	**Comments**	

SECTION 1: Internal validity		
Study addresses an appropriate and clearly focused question		
Description of the methodology used is included		
The literature search was sufficiently rigorous to identify all the relevant studies		
Study quality was addressed and taken into account?		
There were enough similarities between the studies to justify combining them.		
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
	-	- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		
SECTION 3: Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.		
This study is written by pharma and is not robust and hence should be excluded. It only provides a narrative review and hence does not add to existing systematic reviews.		

* Assessment of whether the criteria has been met should be made according to one of the following descriptors
Well covered
Adequately addressed
Poorly addressed
Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
Not applicable.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS	
Guideline topic: Antiplatelets	**Question number: Q18**
Characteristics of study	
Checklist completed by: Kelvin Hill	
Study citation	Calvin AD. Aggarwal NR. Murad MH. Shi Q. Elamin MB. Geske JB. Fernandez-Balsells MM. Albuquerque FN. Lampropulos JF.

	Erwin PJ. Smith SA. Montori VM. Aspirin for the primary prevention of cardiovascular events: a systematic review and meta-analysis comparing patients with and without diabetes. Diabetes Care. 32(12):2300-6, 2009 Dec.		
Study design	**Systematic review**	**N (total)**	8 studies
Search strategy	MEDLINE, EMBASE, Cochrane Library, Web of Science, and Scopus, since their inceptions until November 2008. We used database-specific controlled language and terms that describe the key concepts: aspirin, diabetes, cardiovascular events, prevention, and randomized trials. We also reviewed the reference sections of identified reviews, published guidelines, and published manuscripts known to the authors.		
Selection criteria	Inclusion criteria: 1. RCT 2. Existing diabetes 3. Outcomes reported		
Intervention	Aspirin		
Comparison	Placebo (no treatment)		
Outcomes	Ischemic stroke, myocardial infarction, and all-cause mortality.		
Results	MI found RR 0.86 (95% CI 0.67–1.11) using the seven trials. For ischemic stroke, they found RR 0.62 (95% CI 0.31–1.24) using only the results of two trials.		
Quality of study			
Quality criteria (from SIGN)	***Met?**	**Comments**	
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question	WC		
Description of the methodology used is included	WC		
The literature search was sufficiently rigorous to identify all the relevant studies	WC		
Study quality was addressed and taken into account?	WC		
There were enough similarities between the studies to justify combining them.	WC		
SECTION 2: Overall assessment of the study			
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.	
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.	
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.	
If coded as +, or - what is the likely direction in which bias			

might affect the study results?	

SECTION 3: Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.
No difference in effect were found with aspirin with those with diabetes. Overall the diabetes trials are smaller than the overall trials and numbers are small. This study found that overall the effects of ASA were similar to those without diabetes and suggested similar conclusions should therefore be made for those with diabetes. No complications were reported. Overall this is a quality meta-analysis which provides mixed evidence (indirect) evidence for benefit of aspirin for those with diabetes.

* Assessment of whether the criteria has been met should be made according to one of the following descriptors
Well covered
Adequately addressed
Poorly addressed
Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
Not applicable.

METHODOLOGY CHECKLIST: RCT

Guideline topic: Antiplatelets	**Question number: Q19**
Characteristics of study	
Checklist completed by: checked by Kelvin (from previous Stroke guidelines review)	
REFERENCE Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;361(12):1139-51. Epub 2009 Aug 30.	
SOURCE OF FUNDING	
Boehringer Ingelheim	
METHOD	
Patient Eligibility Criteria	Confirmed atrial fibrillation on ECG within the previous 6 months of trial recruitment plus any one of stroke/TIA, left ventricular fraction < 40%, New York Heart Association class II or worse heart failure symptoms, or aged at least 75 years. Alternatively, those with AF and who were aged 65-74 years were eligible if they had additional risk factors of diabetes mellitus, hypertension or coronary heart disease. Exclusions were: severe heart valve disorder, stroke within the previous 14 days, or severe stroke within the past 6 months, a condition that increased the risk of bleeding, creatinine clearance < 30mls/min, active liver disease and pregnancy.
Study design	RCT of open warfarin versus two different (blinded) doses of dabigatran
Setting	Out-patients (presumed)

Intervention(s)	Tablets of either Warfarin (standard treatment Vitamin K antagonist) versus dabigatran (thrombin inhibitor)
Primary outcome measure	Stroke or systemic embolism
Additional outcome measures	Net clinical benefit composite outcome of: stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, major haemorrhage; stroke; death; major bleeding
Sample Size	18113
Main results	Numbers analysed:18113
	Study duration: 2005-7, median treatment 2 years
	Patients characteristics and group comparability: Mean age 71years, 63.6% men, half previously treated with Vit K antagonists, mean $CHADS_2$ score 2.1,
	Effect size – primary outcome: Both doses of dabigatran were statistically non-inferior to warfarin with primary event rates (stroke and systemic embolism) of 1.53% per year for those receiving 110mg of dabigatran twice daily, compared to 1.11% for those receiving 150mg of dabigatran twice daily and 1.69% for those receiving warfarin ($p<0.001$)
	Effect size – additional outcomes: Net clinical benefit: 7.09% per year for 110mg dabigatran dose, 6.91% per year for 150mg dabigatran dose and 7.64% per year for warfarin (relative risk reduction for 150mg dose p=0.04); stroke: 1.44% per year 110mg dabigatran dose, 1.01% per year 150mg dabigatran dose and 1.57% per year for warfarin (150mg dose statistically superior to warfarin and 110mg dabigatran dose); Ischaemic/unspecified stroke 1.34% per year for 110mg dabigatran dose, 0.92 for 150mg dabigatran dose and 1.20% per year for warfarin (150mg dose statistically superior to warfarin and 110mg dose); haemorrhagic stroke: 0.12% per year for 110mg dabigatran dose, 0.10%per year for 150mg dabigatran dose and 0.38% per year for warfarin (both doses of dabigatran statistically superior to warfarin); disabling or fatal stroke: 0.94% per year for 110mg dabigatran dose, 0.66% per year for 150mg dabigatran dose and 1.00 for warfarin (both doses of dabigatran superior to warfarin; non-disabling stroke: 0.50 for 110mg dabigatran dose, 0.37%per year for 150mg dabigatran dose and 0.58% per year for warfarin (dabigatran 150mg dose superior to warfarin); pulmonary embolism: 0.12% per year for 110mg of dabigatran, 0.15% per year for 150mg dabigatran and 0.09% per year for warfarin (no significant difference to warfarin); myocardial infarction: 0.72% per year for 110mg dabigatran, 0.74% per year for 150mg of dabigatran and 0.53% per year for warfarin (warfarin statistically superior to 150mg dabigatran dose); death(all cause): 3.75% per year 110mg dabigatran dose, 3.64% per year for 150mg dabigatran dose, and 4.13% per year for warfarin (non-significant difference); death (vascular): 2.43% per year for 110mg dabigatran dose, 2.28% per year for 150mg dabigatran dose, and 2.69% per year for warfarin (150mg dabigatran dose superior to warfarin); major bleeding: 2.71% per year for 110mg dabigatran, 3.11% per year for 150mg dabigatran, and 3.36% per year for warfarin (dabigatran 110mg dose superior to warfarin for all major bleeding, both doses of dabigatran statistically superior to warfarin for life threatening bleeding, and

	150mg dabigatran statistically inferior to 110mg dose and warfarin for gastrointestinal bleeding)		
QUALITY CHECK [3]			
Patient selection		YES/NO	Comment
Were the eligibility criteria specified?		Y	
Was a method of randomisation performed?		Y	
Was the treatment allocation concealed?		Y and N	The warfarin arm was open, the two dabigatran doses were given double blind
Were the groups similar at baseline regarding the most important prognostic indicators?		Y	
Interventions			
Were the index and control interventions explicitly described?		Y	
Was the care provider blinded for the intervention?		N	See above
Were co-interventions avoided or comparable?		Y	
Was the compliance acceptable in all groups?		Y	
Was the patient blinded to the intervention?		N	See above
Outcome measurement			
Was the outcome assessor blinded to the interventions?		Y	
Were the outcome measures relevant?		Y	
Were adverse effects described?		Y	
Was the withdrawal/drop-out rate described and acceptable?		Y and N	Statistically significant increase in discontinuation rates for dabigatran (15% and 16% versus 10% for warfarin after one year; 21% versus 17% for warfarin after 2 years)
Was a short-term follow-up measurement performed?		Y	
Was a long-term follow-up measurement performed?		Y	
Was the timing of the outcome assessment in both groups comparable?		Y	
Statistics			
Was the sample size for each group described?		Y	
Did the analysis include an intention-to-treat analysis?		Y	
Were point estimates and measures or variability presented for the primary outcome measures?		Y	
CLINICAL IMPLICATIONS			
Benefits	Both doses of dabigatran were shown to be statistically non-inferior to warfarin. There appeared to be statistically significant benefits from both doses of dabigatran for outcomes such as haemorrhagic stroke, life threatening major		

	bleeding, minor bleeding and intra-cranial bleeding
Harms	There was a statistically significant excess of MI in the 150mg dabigatran dose compared to warfarin, with the lower dabigatran dose also with a excess (non-significant). In addition there was a non-significant excess of pulomonary embolism in the dabigatran groups. There was a statistically significant excess of gastrointestinal bleeds in the 150mg dabigatran dose, with a non-significant excess in the 110mg dose, compared to warfarin.
Comments	This is a very important paper as it is the first real alternative to warfarin. However, there are several cautions: anticoagulation is given to millions of people, often for many years, and even small excess of events can multiply into many tens of thousands of excess events. However, the worrying excess of pro-thrombotic events are overwhelmed by the other advantages of dabigatran. The second point is that only in post-marketing surveillance will you pick up the adverse events related to many years of treatment. We know these for warfarin but we will not know these for dabigatran for some years.
REASON FOR EXCLUSION	
Must be included	
RELEVANCE TO AN AUSTRALIAN CONTEXT	
Dabigatran is very relevant to the Australian context and scientifically appears to be superior to warfarin for several important clinical outcomes, and inferior in others. It is likely to be approved but cost-effectiveness will crucially depend on the marketed cost and whether it will be approved for PBS subsidy.	
OVERALL CONCLUSIONS	
Dabigatran is an alternative to warfarin for secondary prevention of patients with ischaemic stroke/TIA and who have AF (paroxysmal, persistent or permanent). The excess of dyspepsia will limit acceptability for an important proportion of patients (6% in the first year), and together with the excess of gastrointestinal haemorrhage, myocardial infarction and pulmonary embolism, future post marketing surveillance for possible long-term GI, cardiac and venous thrombo-embolism (and other) adverse events needs to be undertaken. The important benefits of dabigatran over warfarin include not requiring regular blood tests, and the lower intracranial bleeding rate and lower haemorrhagic stroke rate. It's cost-effectiveness and TGA approval are not yet known for the Australian market. UNCLEAR POPULATION INCLUDED THOSE WITHOUT PRE EXISTING CVD.	

	Methodology Checklist 2: Controlled Trials	
Study identification Active Investigators, Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M. Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation. N Engl J Med. 2009;360(20):2066-78.		
Guideline topic:		Key Question No: 18
Checklist completed by: Kelvin **Hill**		
Section 1: Internal validity		
In a well conducted RCT study…		In this study this criterion is:
1.1	The study addresses an appropriate and clearly focused question.	Well covered

1.2	The assignment of subjects to treatment groups is randomised	Adequately addressed –previous paper
1.3	An adequate concealment method is used	Not reported in this paper
1.4	Subjects and investigators are kept 'blind' about treatment allocation	Well covered –double blind
1.5	The treatment and control groups are similar at the start of the trial	Well covered
1.6	The only difference between groups is the treatment under investigation	Adequately addressed –table only
1.7	All relevant outcomes are measured in a standard, valid and reliable way	Well covered
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	Poorly covered. Forty-three patients (<1%) were lost to follow-up. Breakdown in treatment arms not reported but small numbers.
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)	Well covered
1.10	Where the study is carried out at more than one site, results are comparable for all sites	Well covered
SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	How well was the study done to minimise bias? Code ++, +, or –	++ (considering info from previous publication on methods and baseline data)
2.2	If coded as +, or – what is the likely direction in which bias might affect the study results?	
2.3	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	Yes
2.4	Are the results of this study directly applicable to the patient group targeted by this guideline?	Possibly –unclear % without any pre-existing CVD –have emailed authors to clarify.
SECTION 3: DESCRIPTION OF THE STUDY (The following information is required to complete evidence tables facilitating cross-study comparisons. Please complete all sections for which information is available). PLEASE PRINT CLEARLY		
3.1	*Do we know who the study was funded by?*	□ Healthcare Industry (Sanofi-Aventis and Bristol-Myers Squibb)
3.2	*How many centres are patients recruited from?*	580 centers in 33 countries.
3.3	*From which countries are patients selected? (Select all those involved. Note additional countries after "Other")*	many
3.4	*What is the social setting (ie type of environment in which they live) of patients in the study?*	Unclear
3.5	*What criteria are used to decide who should be INCLUDED*	Atrial fibrillation at enrollment or had had at least two episodes of intermittent atrial

	in the study?	fibrillation in the previous 6 months. In addition, patients were required to have at least one of the following risk factors for stroke: an age of 75 years or more; systemic hypertension during treatment; previous stroke, transient ischemic attack, or non–central nervous system systemic embolism; a left ventricular ejection fraction of less than 45%; peripheral vascular disease; or an age of 55 to 74 years and diabetes mellitus or coronary artery disease.
3.6	What criteria are used to decide who should be EXCLUDED from the study?	Patients were excluded if they required a vitamin K antagonist or clopidogrel or had any of the following risk factors for hemorrhage: documented peptic ulcer disease within the previous 6 months; a history of intracerebral hemorrhage; significant thrombocytopenia (platelet count <50×109 per liter); or ongoing alcohol abuse.
3.7	*What intervention or risk factor is investigated in the study? (Include dosage where appropriate)*	Clopidogrel (75mg daily) plus aspirin (75-100mg daily)
3.8	*What comparisons are made in the study (ie what alternative treatments are used to compare the intervention with). Include dosage where appropriate.*	Aspirin (75-100mg daily)
3.9	*What methods were used to randomize patients, blind patients or investigators, and to conceal the randomization process from investigators?*	interactive telephone system, patients in ACTIVE A were randomly assigned in equal numbers, in blocks of varying sizes, to receive clopidogrel at a dose of 75 mg or matching placebo once daily, in a double-blind fashion.
3.10	*How long did the active phase of the study last?*	
3.11	*How long were patients followed-up for, during and after the study?*	Median 3.6 years
3.12	*List the key characteristics of the patient population. Note if there are any significant differences between different arms of the trial.*	AF plus risk factors (existing CVD, age etc). No difference between groups.
3.13	*Record the basic data for each arm of the study. If there are more than four arms, note data for subsequent arms at the bottom of the page.*	
major vascular events had occurred in 832 patients receiving clopidogrel (6.8% per year) and in 924 patients receiving placebo (7.6% per year) (relative risk with clopidogrel, 0.89; 95% confidence interval [CI], 0.81 to 0.98; P = 0.01). The difference was primarily due to a reduction in the rate of stroke with clopidogrel. Stroke occurred in 296 patients receiving clopidogrel (2.4% per year) and 408 patients receiving placebo (3.3% per year) (relative risk, 0.72; 95% CI, 0.62 to 0.83; P<0.001). Myocardial infarction occurred in 90 patients receiving clopidogrel (0.7% per year) and in 115 receiving placebo (0.9% per year) (relative risk, 0.78; 95% CI, 0.59 to 1.03; P = 0.08). Major bleeding occurred in 251 patients receiving clopidogrel (2.0% per year) and in 162 patients receiving placebo (1.3% per year) (relative risk, 1.57; 95% CI, 1.29 to 1.92; P<0.001).		
3.15	Notes. Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question. *{Much of this is likely to be contributed by GDG members).*	
	Good quality study demonstrating benefits of ASA+C for AF where warfarin is not considered appropriate. Reduction of stroke were partially offset by increase bleeding. The authors indirectly compared ASA+C to warfarin and noted that effect was smaller but bleeding was also less (but this is not direct comparision). For those not able to take warfarin ASA+C maybe recommended considering risk/benefits in each case.	

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS	
Guideline topic: Antiplatelets	Question number: Q18

Characteristics of study			
Checklist completed by: Kelvin **Hill**			
Study citation	De Berardis G, Sacco M, Strippoli GF, Pellegrini F, Graziano G, Tognoni G, Nicolucci A. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials.BMJ. 2009 Nov 6;339:b4531. Erratum in: BMJ. 2010;340:c374.		
Study design	Systematic review	N (total)	6 studies (N=10117)
Search strategy	Medline (1966-November 2008), the Cochrane central register of controlled trials (Cochrane Library 2008;issue 4), and reference lists of retrieved articles.		
Selection criteria	Inclusion criteria: RCT Existing diabetes English language only Trials >500 people Outcomes reported		
Intervention	Aspirin		
Comparison	Placebo (no treatment)		
Outcomes	all cause mortality, death from cardiovascular causes, non-fatal myocardial infarction, and non-fatal stroke.		
Results	No statistically significant reduction in the risk of major cardiovascularevents (five studies, 9584 participants; relative risk 0.90, 95% CI 0.81 to 1.00), cardiovascular mortality (four studies, n=8557, 0.94; 0.72 to 1.23), or all cause mortality (four studies, n=8557; 0.93, 0.82 to 1.05). For MI, RR 0.86 (95% CI 0.61–1.21) with moderate heterogeneity (I2=62.2%), mainly due to inclusion of WHS and PHS. For stroke, they included five trials (excluding PHS) and calculated a summary RR of 0.83 (95% CI 0.60 –1.14) and also noted moderate heterogeneity (I2=52.5%), mainly due to inclusion of WHS. Aspirin significantly reduced the risk of myocardial infarction in men (0.57, 0.34 to 0.94) but not in women (1.08, 0.71 to 1.65; P for interaction=0.056). No effect for preventing stroke for either men or women.		

Quality of study		
Quality criteria (from SIGN)	*Met?	Comments
SECTION 1: Internal validity		
Study addresses an appropriate and clearly focused question	Adequately Covered	
Description of the methodology used is included	WC	
The literature search was sufficiently rigorous to identify all the relevant studies	WC	
Study quality was addressed and taken into account?	WC	
There were enough similarities between the studies to justify combining them.	WC	

SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		
SECTION 3: Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.		
Similar to other SR's no difference in effect were found with aspirin with those with diabetes. GI or any bleeding was about 2-2.5 times more likely but CI were wide (and non significant). NNT ~1000! Hence such small benefits and potential risks suggest evidence for effect of ASA is currently negligible and results of ongoing studies needed before clearer conclusions can be made. Overall this is a quality meta-analysis which provides evidence NOT to recommend ASA for those with diabetes.		

* Assessment of whether the criteria has been met should be made according to one of the following descriptors
Well covered
Adequately addressed
Poorly addressed
Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
Not applicable.

Template for Intervention Study – Randomised Controlled Trial

KEY QUESTION(S)	
18 Antiplatelets	
COMPLETED BY:	
Kelvin **Hill**	
REFERENCE(S)	
Fowkes FG, Price JF, Stewart MC, Butcher I, Leng GC, Pell AC, Sandercock PA, Fox KA, Lowe GD, Murray GD; Aspirin for Asymptomatic Atherosclerosis Trialists. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. JAMA. 2010 Mar 3;303(9):841-8.	
METHOD	
Patient Eligibility Criteria	No CVD but low ABI (<0.95) aged 50-75 at baseline. Excludsion: history of

	myocardial infarction, stroke, angina, or peripheral artery disease; currently used aspirin, other antiplatelet or anticoagulant agents; had severe indigestion; had chronic liver or kidney disease; were receiving chemotherapy; had contraindications to aspirin; and had an abnormally high or low hematocrit value (measured after the screening).
Study design	Double blind RCT
Setting	Community setting in Scotland
Intervention(s)	Aspirin (100mg) v placebo
Primary outcome measure	Composite of initial (earliest) fatal or nonfatal coronary event or stroke or revascularization.
Additional outcome measures	(1) all initial vascular events, defined as a composite of a primary end point event or angina, intermittent claudication or transient ischemic attack; and (2) all-cause mortality.
Sample Size	165 795 invited, 28 980 screened, 4914 eligible, 3350 randomised
Main results	Numbers analysed: 1675 in each arm used in primary analysis (ITT)
	Study duration:
	Patients characteristics and group comparability:
	Effect size – primary outcome: No statistically significant difference was found between groups (13.7 events per 1000 person-years in the aspirin group vs 13.3 in the placebo group; hazard ratio [HR], 1.03; 95%CI, 0.84-1.27).
	Effect size – additional outcomes: A vascular event comprising the secondary end point occurred in 578 participants (22.8 per 1000 person-years;95%CI, 21.0-24.8) and no statistically significant difference between groups (22.8 events per 1000 person-years in the aspirin group vs 22.9 in the placebo group; HR, 1.00;95%CI, 0.85-1.17). There was no significant difference in all-cause mortality between groups (176 vs 186 deaths, respectively; HR, 0.95; 95% CI, 0.77-1.16). An initial event of major hemorrhage requiring admission to hospital occurred in 34 participants (2.5 per 1000 person-years) in the aspirin group and 20 (1.5 per 1000 person-years) in the placebo group (HR, 1.71; 95% CI, 0.99-2.97).

QUALITY CHECK [3]		
Patient selection	YES/NO	Comment
Were the eligibility criteria specified?	y	
Was a method of randomisation performed?	y	

Was the treatment allocation concealed?	y	
Were the groups similar at baseline regarding the most important prognostic indicators?	y	
Interventions		
Were the index and control interventions explicitly described?	Y	
Was the care provider blinded for the intervention?	Y	
Were co-interventions avoided or comparable?	Y	
Was the compliance acceptable in all groups?	Y	
Was the patient blinded to the intervention?	Y	
Outcome measurement		
Was the outcome assessor blinded to the interventions?	Y	
Were the outcome measures relevant?	Y	
Were adverse effects described?	y	
Was the withdrawal/drop-out rate described and acceptable?	N	Only ~15% still taking ASA at 5years although 85% took it for 6months or more.
Was a short-term follow-up measurement performed?	Y	
Was a long-term follow-up measurement performed?	Y	
Was the timing of the outcome assessment in both groups comparable?	Y	
Statistics		
Was the sample size for each group described?	Y	
Did the analysis include an intention-to-treat analysis?	Y	
Were point estimates and measures or variability presented for the primary outcome measures?	Y	

CLINICAL IMPLICATIONS	
Benefits	Non
Harms	Increase risk of major bleeding
Comments	Would need 500-600 people screened and started treatment to prevent just one CVD event over 8 years making the treatment not clinically or economically useful. But authors note underpowered to detect small benefits in aspirin.
REASON FOR EXCLUSION	
include	
SOURCE OF FUNDING	
British Heart Foundation and Chief Scientist's Office, Scotland. Bayer HealthCare provided the aspirin and placebo	

tablets and funds for packaging, dispensing, and some statistical analysis.	
RELEVANCE TO AN AUSTRALIAN CONTEXT	
Should be relevant even though Scottish population	
OVERALL CONCLUSIONS	
Decision to commence aspirin in those without CVD should not be based on ABI.	

Template for Intervention Study – Randomised Controlled Trial

KEY QUESTION(S)	
18 Antiplatelets	
COMPLETED BY:	
Kelvin Hill	
REFERENCE(S)	
Jardine MJ, Ninomiya T, Perkovic V, et al. Aspirin is beneficial in hypertensive patients with chronic kidney disease: a post-hoc subgroup analysis of a randomized controlled trial. J Am Coll Cardiol 2010;56:956–65.	
METHOD	
Patient Eligibility Criteria	No CVD but CKD identified on assessment
Study design	Double blind RCT
Setting	
Intervention(s)	Aspirin (100mg) v placebo
Primary outcome measure	Composite of initial (earliest) fatal or nonfatal coronary event or stroke or revascularization.
Additional outcome measures	(1) all initial vascular events, defined as a composite of a primary end point event or angina, intermittent claudication or transient ischemic attack; and (2) all-cause mortality.
Sample Size	
Main results	Numbers analysed:
	Study duration:
	Patients characteristics and group comparability:
	Effect size – primary outcome:
	Effect size – additional outcomes:

QUALITY CHECK [3]		
Patient selection	YES/NO	Comment
Were the eligibility criteria specified?	y	

Was a method of randomisation performed?	y	
Was the treatment allocation concealed?	y	
Were the groups similar at baseline regarding the most important prognostic indicators?	y	
Interventions		
Were the index and control interventions explicitly described?	Y	
Was the care provider blinded for the intervention?	Y	
Were co-interventions avoided or comparable?	Y	
Was the compliance acceptable in all groups?	Y	
Was the patient blinded to the intervention?	Y	
Outcome measurement		
Was the outcome assessor blinded to the interventions?	Y	
Were the outcome measures relevant?	Y	
Were adverse effects described?	y	
Was the withdrawal/drop-out rate described and acceptable?	N	Only ~15% still taking ASA at 5years although 85% took it for 6months or more.
Was a short-term follow-up measurement performed?	Y	
Was a long-term follow-up measurement performed?	Y	
Was the timing of the outcome assessment in both groups comparable?	Y	
Statistics		
Was the sample size for each group described?	Y	
Did the analysis include an intention-to-treat analysis?	Y	
Were point estimates and measures or variability presented for the primary outcome measures?	Y	

CLINICAL IMPLICATIONS	
Benefits	Apparent reduction in CVD events with more severe CKD
Harms	Increase risk of major bleeding
Comments	
REASON FOR EXCLUSION	

Include clearly noting limitations. Note (From David Sullivan:There had been an earlier re-analysis of the HOT study by Ruilope et al (J Am Soc Nephrol 12:218-225, 2001), which had not found a statistically significant benefit of aspirin therapy for primary prevention of cardiovascular events in patients with a Cockcroft-Gault estimated creatinine clearance < 60 mL/min (although there was a lower point estimate of effect for CVEs in the aspirin

group).	
SOURCE OF FUNDING	
RELEVANCE TO AN AUSTRALIAN CONTEXT	
Should be relevant	
OVERALL CONCLUSIONS	
Recent subgroup re-analysis of HOT study (N=3619 with high BP and CKD) found low-dose aspirin (75mg daily) resulted in an absolute risk reduction of major CVD events by 0.28%, 0.74%, and >7% in the different eGFR groups (>60, 45 to 59, and <45 ml/min/1.73 m2), respectively. Those with the most severe CKD (<45 ml/min/1.73 m2) were found to reduce all-cause mortality, cardiovascular mortality, and strokes but numbers were small making conclusions unreliable. Use of low-dose aspirin was associated with major bleeding in 27 per 1,000 persons and minor bleeding in 12 per 1,000 persons in the low eGFR group. This post-hoc analysis should not be considered hard evidence but used to develop further appropriate trials.	

Template for Intervention Study – Randomised Controlled Trial

KEY QUESTION(S)	
18 Antiplatelets	
COMPLETED BY:	
Kelvin	
REFERENCE(S)	
Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, Murray E; BAFTA investigators; Midland Research Practices Network (MidReC). Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet. 2007 Aug 11;370(9586):493-503.	
METHOD	
Patient Eligibility Criteria	aged 75 years or over and had atrial fi brillation or atrial fl utter demonstrated by a study electrocardiogram (ECG) or by an ECG done within the previous two years. Patients were excluded if they had any of the following: rheumatic heart disease; a major non-traumatic haemorrhage within the previous 5 years; intracranial haemorrhage; endoscopically proven peptic ulcer disease in the previous year; oesophageal varices; allergic hypersensitivity to either of the study drugs; a terminal illness, as judged by their primary care physician; surgery within the past 3 months; or blood pressure greater than 180/110 mm Hg. Patients were also excluded if their primary care physician judged, on the basis of risk factors for stroke and haemorrhage, that the patient either should or should not be on warfarin.
Study design	Single blind RCT
Setting	Patients were recruited from 260 general practices in England and Wales between April, 2001, and November, 2004.
Intervention(s)	Aspirin (75mg) v warfarin (INR 2-3)
Primary outcome measure	fi rst occurrence of fatal or non-fatal disabling stroke (ischaemic or haemorrhagic), other intracranial haemorrhage, or clinically signifi cant arterial embolism.

Additional outcome measures	major extracranial haemorrhage (defi ned as a fatal haemorrhage, or one that resulted in the need for transfusion or surgery), other admissions to hospital for haemorrhage, hospital admission or death as a result of a non-stroke vascular event, and all-cause mortality.
Sample Size	4639
Main results	Numbers analysed: 485 and 488
	Study duration: mean follow up 2.7 years
	Patients characteristics and group comparability: yes
	Effect size – There were 24 primary events (21 strokes, two other intracranial haemorrhages, and one systemic embolus) in people assigned to warfarin and 48 primary events (44 strokes, one other intracranial haemorrhage, and three systemic emboli) in people assigned to aspirin (yearly risk 1·8% *vs* 3·8%, relative risk 0·48, 95% CI 0·28–0·80, p=0·003; absolute yearly risk reduction 2%, 95% CI 0·7–3·2). Yearly risk of extracranial haemorrhage was 1·4% (warfarin) versus 1·6% (aspirin) (relative risk 0·87, 0·43–1·73; absolute risk reduction 0·2%, –0·7 to 1·2).

QUALITY CHECK [3]		
Patient selection	YES/NO	Comment
Were the eligibility criteria specified?	y	
Was a method of randomisation performed?	y	
Was the treatment allocation concealed?	?	Previous publication
Were the groups similar at baseline regarding the most important prognostic indicators?	y	
Interventions		
Were the index and control interventions explicitly described?	Y	
Was the care provider blinded for the intervention?	N	Open labelled trial
Were co-interventions avoided or comparable?	Y	
Was the compliance acceptable in all groups?	Y	
Was the patient blinded to the intervention?	N	
Outcome measurement		
Was the outcome assessor blinded to the interventions?	Y	
Were the outcome measures relevant?	Y	
Were adverse effects described?	y	
Was the withdrawal/drop-out rate described and acceptable?	Y	66/973
Was a short-term follow-up measurement performed?	Y	
Was a long-term follow-up measurement performed?	Y	
Was the timing of the outcome assessment in both groups comparable?	Y	

Statistics		
Was the sample size for each group described?	Y	
Did the analysis include an intention-to-treat analysis?	Y	
Were point estimates and measures or variability presented for the primary outcome measures?	Y	

CLINICAL IMPLICATIONS	
Benefits	Lower CVD events and less bleeding complications
Harms	
Comments	

REASON FOR EXCLUSION
include
SOURCE OF FUNDING
Medical Research Council
RELEVANCE TO AN AUSTRALIAN CONTEXT
Would appear relevant
OVERALL CONCLUSIONS
This trial confirms benefits of warfarin for those >75years over aspirin for preventing CVD in AF. The studiy does not separate those without existing CVD and there was 10%MI, 20% heart failure, 15% angina and 12% previous stroke (unsure of overlap). Hence caution is needed to generalise findings to primary prevention only.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Antiplatelets		Question number: Q18	
Characteristics of study			
Checklist completed by: Kelvin Hill			
Study citation	Pignone et al 2010. Aspirin for primary prevention of cardiovascular events in people with diabetes. American Diabetes Association statement. Diabetes Care. 2010 June;33(6):1395-1402.		
Study design	Systematic review	N (total)	9 studies
Search strategy	Not reported		
Selection criteria	Not reported		
Intervention	Aspirin		
Comparison	Placebo (no treatment)		
Outcomes	Not specified but discussed myocardial infarction, and stroke.		

Results	9% decrease in risk of CHD events (nonfatal and fatal MI) that was not statistically significant (RR 0.91, 95% CI 0.79 –1.05). We did not identify important heterogeneity (X2=8.71, P=0.367, I2=8.2%), but a large portion of the summary estimate depended on the ETDRS trial. 15% reduction in the risk of stroke (RR 0.85, 95% CI 0.66 –1.11) that was not statistically significant. There was some heterogeneity (X2=12.48, P=0.131, I2=35.9%).		
Quality of study			
Quality criteria (from SIGN)		*Met?	Comments
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		Adequately Covered	
Description of the methodology used is included		Not addressed	
The literature search was sufficiently rigorous to identify all the relevant studies		Not addressed	
Study quality was addressed and taken into account?		Poorly addressed	
There were enough similarities between the studies to justify combining them.		Adequately Covered	
SECTION 2: Overall assessment of the study			
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.			++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+	+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
			- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		All main studies included similar to other SR's but methods not reported.	
SECTION 3: Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.			
Similar to other SR's no difference in effect were found with aspirin with those with diabetes. Authors suggest this represents small effect which requires larger numbers to narrow confidence intervals. Overall this is a practice guideline that suggestions that ASA (75-162mg) should be considered with patients at high risk of CVD (>10% 10 year risk) without previous bleeding indications but not in those at low risk. Those at intermediate risk may consider ASA depending on factors and current treatments.			

* Assessment of whether the criteria has been met should be made according to one of the following descriptors
Well covered
Adequately addressed
Poorly addressed
Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
Not applicable.

Template[1] for Intervention [2] Study – Randomised Controlled Trial

KEY QUESTION(S) 18 Antiplatelets	
COMPLETED BY: Kelvin Hill	
REFERENCE(S) Wang T.H. Bhatt D.L. Fox K.A.A. Steinhubl S.R. Brennan D.M. Hacke W. Mak K.-H. Pearson T.A. Boden W.E. Steg P.G. Flather M.D. Montalescot G. Topol E.J. An analysis of mortality rates with dual-antiplatelet therapy in the primary prevention population of the CHARISMA trial. European Heart Journal. 28(18):2200-2207. Orignial paper: Bhatt et al 2006 N Engl J Med 354;16, 1704-17.	
METHOD	
Patient Eligibility Criteria	45 years of age or older and had one of the following conditions: multiple atherothrombotic risk factors, documented coronary disease, documented cerebrovascular disease, or documented symptomatic peripheral arterial disease. Patients were excluded from the trial if they were taking oral antithrombotic medications or nonsteroidal antiinflammatory drugs on a longterm basis (although cyclooxygenase-2 inhibitors were permitted). Patients were also excluded if, in the judgment of the investigator, they had established indications for clopidogrel therapy (such as a recent acute coronary syndrome).
Study design	Double blind RCT
Setting	multiple
Intervention(s)	Aspirin (75-162mg) plus clopidogrel (75mg) v placebo plus ASA (75-162mg)
Primary outcome measure	composite of myocardial infarction, stroke, or CVD.
Additional outcome measures	(1) all-cause mortality; (2) CV mortality (3) bleeding/complications
Sample Size	15603 total cohort
Main results	Numbers analysed: 2289 primary prevention cohort (including 163 with PVD only)
	Study duration: mean follow up 28 months
	Patients characteristics and group comparability: yes
	Effect size – primary outcome: Compared with aspirin alone, a significant increase in CV death (P = 0.01) was observed in patients receiving dual-antiplatelet therapy in the asymptomatic population. Within the primary prevention cohort, this excess

	CV death was not significant (P = 0.07). Multivariate analysis of the primary prevention group showed a trend towards excess CV death (P = 0.054; HR 1.72; CI 0.99–2.97) with dual-antiplatelet therapy (aspirin plus clopidogrel). Other independent predictors of CV death included increasing age, hypertension, atrial fibrillation, and a history of heart failure.
	Effect size – additional outcomes: There was a non-significant increase in moderate or severe bleeding (P = 0.218) with dual-antiplatelet therapy; thus, bleeding was an unlikely explanation for the excess event rate.

QUALITY CHECK [3]		
Patient selection	YES/NO	Comment
Were the eligibility criteria specified?	y	
Was a method of randomisation performed?	y	
Was the treatment allocation concealed?	?	Previous publication
Were the groups similar at baseline regarding the most important prognostic indicators?	y	
Interventions		
Were the index and control interventions explicitly described?	Y	
Was the care provider blinded for the intervention?	Y	
Were co-interventions avoided or comparable?	Y	
Was the compliance acceptable in all groups?	Y	
Was the patient blinded to the intervention?	Y	
Outcome measurement		
Was the outcome assessor blinded to the interventions?	Y	
Were the outcome measures relevant?	Y	
Were adverse effects described?	y	
Was the withdrawal/drop-out rate described and acceptable?	Y	5% each
Was a short-term follow-up measurement performed?	Y	
Was a long-term follow-up measurement performed?	Y	
Was the timing of the outcome assessment in both groups comparable?	Y	
Statistics		
Was the sample size for each group described?	Y	
Did the analysis include an intention-to-treat analysis?	Y	
Were point estimates and measures or variability presented for the	Y	

primary outcome measures?			
CLINICAL IMPLICATIONS			
Benefits	Non		
Harms	No increase in bleeding but non significant trend to increase CVD mortality (p=0.07)		
Comments			
REASON FOR EXCLUSION			
include			
SOURCE OF FUNDING			
Sanofi-Aventis and Bristol-Myers Squibb.			
RELEVANCE TO AN AUSTRALIAN CONTEXT			
Includes Australian patients in cohort			
OVERALL CONCLUSIONS			
Unexplained increase in CV death with dual treatment without increase in bleeding. Currently suggest not recommended for primary prevention.			

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Antiplatelets		Question number: Q18	
Characteristics of study			
Checklist completed by: Kelvin Hill			
Study citation	Wolff T, Miller T, Ko S. Aspirin for the primary prevention of cardiovascular events: an update of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2009 Mar 17;150(6):405-10.		
Study design	Systematic review	N (total)	6 trials and 2 sub-analysis of 2 of these trials
Search strategy	MEDLINE and Cochrane Library (search dates, 1 January 2001 to 28 August 2008), recent systematic reviews, reference lists of retrieved articles, and suggestions from experts.		
Selection criteria	English-language studies, human studies, and studies of non-pregnant adults and to the following study types for benefits: RCT, meta-analysis, and systematic review. For evidence on harms, we limited our search to RCTs, case– control studies, meta-analyses, and systematic reviews.		
Intervention	Aspirin		
Comparison	Placebo (no treatment)		
Outcomes	myocardial infarction, stroke, death from myocardial infarction or stroke, or all-cause mortality for benefits and gastrointestinal bleeding, serious bleeding episodes, hemorrhagic stroke, or cerebral hemorrhage for harms.		
Results	aspirin use reduces the number of CVD events in patients without known CVD. Men experienced fewer myocardial infarctions and women experienced fewer ischemic strokes. Aspirin does not seem to affect CVD mortality or all-cause mortality in either		

	men or women. The use of aspirin for primary prevention increases the risk for major bleeding events, primarily gastrointestinal bleeding events, in both men and women. Men have an increased risk for hemorrhagic strokes with aspirin use. A new RCT and meta-analysis suggest that the risk for hemorrhagic strokes in women is not statistically significantly increased.	
Quality of study		
Quality criteria (from SIGN)	*Met?	Comments
SECTION 1: Internal validity		
Study addresses an appropriate and clearly focused question	WC	
Description of the methodology used is included	WC	
The literature search was sufficiently rigorous to identify all the relevant studies	WC	
Study quality was addressed and taken into account?	WC	
There were enough similarities between the studies to justify combining them.	Adequately Covered	
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		
SECTION 3: Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.		
This publication is more related to clinical guideline than a specific systematic review. Similar to other SR's no significant difference in CVD or all-cause mortality. Like other SR's ASA reduced risk of MI in men but not women and stroke in women but not men. ASA increases risk of haemorrhage in men but not women. No overall effect on mortality found. The overall benefit in the reduction of CVD events with aspirin use depends on baseline CVD risk and risk for gastrointestinal bleeding.		

* Assessment of whether the criteria has been met should be made according to one of the following descriptors
Well covered
Adequately addressed
Poorly addressed

Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
Not applicable.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Antiplatelets		Question number: Q18	
Characteristics of study			
Checklist completed by: Kelvin Hill			
Study citation	Yerman T, Gan WQ, Sin DD. The influence of gender on the effects of aspirin in preventing myocardial infarction. BMC Med 2007; 5:29.		
Study design	Systematic review	N (total)	23 trials (n=113 494)
Search strategy	We supplemented the electronic search by probing the reference lists of retrieved articles and previous reviews on this topic, and by a search of the Antithrombotic Trialists' Collaboration website [3] and EMBASE. We also contacted primary authors where necessary for clarification of data.		
Selection criteria	We limited the search to randomized controlled trials conducted in human subjects and published in English language, using aspirin and MI-specific search terms. Excluded trials that: (1) had a follow-up period of less than 3 months; (2) co-administered aspirin with another agent; (3) prescribed aspirin for clinical indications other than for primary or secondary cardiovascular prevention (e.g. pain, headache, or arthritic symptoms); (4) did not have a placebo arm; (5) had a paucity of MI events (fewer than 10) during follow-up; or (6) had unacceptable methodological quality score (Jadad score of less than 3)		
Intervention	Aspirin		
Comparison	Placebo (no treatment)		
Outcomes	fatal and non-fatal MI separately as well as combined		
Results	Overall, compared with placebo, aspirin reduced the risk of non-fatal MI (RR = 0.72, 95% confidence interval (CI) 0.64–0.81, p < 0.001) but not of fatal MI (RR = 0.88, 95% CI 0.75–1.03, p = 0.120). A total of 27% of the variation in the non-fatal MI results could be accounted for by considering the gender mix of the trials (p = 0.017). Trials that recruited predominantly men demonstrated the largest risk reduction in non-fatal MI (RR = 0.62, 95% CI 0.54–0.71), while trials that contained predominately women failed to demonstrate a significant risk reduction in non-fatal MI (RR = 0.87, 95% CI 0.71–1.06).		
Quality of study			
Quality criteria (from SIGN)		*Met?	Comments
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused		WC	

question		
Description of the methodology used is included	Adequate	
The literature search was sufficiently rigorous to identify all the relevant studies	Adequate	Only really one database used
Study quality was addressed and taken into account?	Adequate	Jadad score completed
There were enough similarities between the studies to justify combining them.	Poorly address	Included both primary and secondary prevention trials but did not report separately.
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
	+	+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
	-	- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?	Mixed populations	
SECTION 3: Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.		
Aspirin reduces non-fatal MI but this is mainly due to effects in men rather than women indicating a possible gender difference.		

* Assessment of whether the criteria has been met should be made according to one of the following descriptors
Well covered
Adequately addressed
Poorly addressed
Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
Not applicable.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS	
Guideline topic: Antiplatelets	Question number: Q18
Characteristics of study	
Checklist completed by: Kelvin Hill	

Study citation	Zhang C, Sun A, Zhang P, Wu C, Zhang S, Fu M, Wang K, Zou Y, Ge J. Aspirin for primary prevention of cardiovascular events in patients with diabetes: A meta-analysis. Diabetes Res Clin Pract. 2010 Feb;87(2):211-8. Epub 2009 Oct 23.		
Study design	Systematic review	N (total)	7 trials included 11,618 individuals
Search strategy	MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials without language restriction between 1950 and June 2009. The bibliographies of retrieved articles and previous meta-analysis were searched for other relevant studies.		
Selection criteria	prospective randomized controlled trials; participants with diabetes mellitus; assignment of participants to aspirin therapy or control group for primary prevention of cardiovascular events; follow-up duration at least 12 months; any of the data about major cardiovascular events (a composite of cardiovascular mortality, nonfatal MI or nonfatal stroke), MI, stroke, all-cause mortality, cardiovascular mortality or major bleeding.		
Intervention	Aspirin		
Comparison	Placebo (no treatment)		
Outcomes	any of the data about major cardiovascular events (a composite of cardiovascular mortality, nonfatal MI or nonfatal stroke), MI, stroke, all-cause mortality, cardiovascular mortality or major bleeding.		
Results	Aspirin therapy was not associated with a statistically significant reduction in major cardiovascular events (relative risk [RR] 0.92, 95% confidence interval [CI] 0.83–1.02, p = 0.11). Aspirin use also did not significantly reduce all-cause mortality (0.95, 95% CI 0.85–1.06; p = 0.33), cardiovascular mortality (0.95, 95% CI 0.71–1.27; p = 0.71), stroke (0.83, 95% CI 0.63–1.10; p = 0.20), or MI (0.85, 95% CI 0.65–1.11; p = 0.24). There was no significant increased risk of major bleeding in aspirin group (2.46, 95% CI 0.70–8.61; p = 0.16). Meta-regression suggested that aspirin agent could reduce the risk of stroke in women and MI in men.		
Quality of study			
Quality criteria (from SIGN)		*Met?	Comments
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		WC	
Description of the methodology used is included		WC	
The literature search was sufficiently rigorous to identify all the relevant studies		WC	
Study quality was addressed and taken into account?		Poorly addressed	
There were enough similarities between the studies to justify combining them.		Adequately Covered	
SECTION 2: Overall assessment of the study			
How well was the study done to minimise bias?			++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the

Determine the methodological quality of the study according to this ranking, based on responses above.		conclusions of the study or review are thought very unlikely to alter.
	+	+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?	No analysis of study quality was included.	
SECTION 3: Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.		
Similar to other SR's no significant difference in effect were found with aspirin with those with diabetes. Like other SR's ASA reduced risk of MI in men but not women and stroke in women but not men. No overall effect on mortality found.		

* Assessment of whether the criteria has been met should be made according to one of the following descriptors
Well covered
Adequately addressed
Poorly addressed
Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
Not applicable.

FORM framework Question 18

Key question(s): 18. Does antiplatelet therapy compared to control reduce CVD events and all cause mortality?

1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*

No trials using absolute risk approach to guide treatment decisions. All evidence taking relative risk approach.
Mulitiple high quality systematic reviews for relative risk approach (level I) including in those with diabetes

- ATT 2009
- Berger 2006
- Wolf 2009
- Zhang 2010
- De Berardis 2009
- Calvin 2009

A	**One or more level I studies with a low risk of bias or several level II studies with a low risk of bias RELATIVE RISK APPROACH**
B	**One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias**
C	**One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias**
D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**

2. Consistency *(if only one study was available, rank this component as 'not applicable')*

Most papers confirm that aspirin may lead to a small risk reduction in CVD events although this is not statistically significant. Benefit of aspirin due to reduction in MI in men. Aspirin reduces stroke in women not MI. Overall increase in major bleeding rates.

A	**All studies consistent**
B	**Most studies consistent and inconsistency can be explained**
C	**Some inconsistency, reflecting genuine uncertainty around question**
D	**Evidence is inconsistent**

3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could*

While individual impact is small the evidence applies to a large patient population, and hence is associated with substantial potential benefits, but also increases possible harms.

A	**Very large**
B	**Substantial**
C	**Moderate**
D	**Slight/Restricted**

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*

Large amount of data related to diverse populations, international trials including Australian data.

A	**Evidence directly generalisable to target population RELATIVE RISK APPROACH**
B	**Evidence directly generalisable to target population with some caveats**
C	**Evidence not directly generalisable to the target population but could be sensibly applied**
D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*

Highly applicable.

A	**Evidence directly applicable to Australian healthcare context**
B	**Evidence applicable to Australian healthcare context with few caveats**
C	**Evidence probably applicable to Australian healthcare context with some caveats**
D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Different effects in men and women found consistently. In men ASA reduces risk of MI but not stroke (but increases risk of haemorrhagic stroke). In women ASA reduces risk of stroke but not MI and no difference in haemorrhage. Smokers derived less benefit than non-smokers.
Only ATT estimated 5 year risk of MI (tool/process unclear). No trend noted for higher risk but numbers small. Modelling (excluding effect of age or sex) suggests absolute benefit of aspirin double the absolute risks. However if patients take a statin the benefit/risk would be neutral. An older modeling study (Sanmuganathan et al 2001) included in SIGN guideline reported benefit for those >15% over 10 years.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1.Evidence base	A	
2.Consistency	A	
3.Clinical impact	B	
4. Generalisability	A	
5. Applicability	A	

Evidence statement

Currently all evidence is based on studies of relative risk and hence unknown effect using an absolute risk approach. Aspirin does not affect mortality (all-cause or CV related) but does have a small benefit to reduce non fatal vascular events (primarily due to reduced MI in men). The overall benefit in the reduction of CVD events with aspirin use depends on baseline CVD risk and risk for gastrointestinal bleeding. The benefit of aspirin in people with diabetes is smaller (and non significant).

Indicate any dissenting opinions

RECOMMENDATION	**GRADE OF RECOMMENDATION**	B

Aspirin is not routinely recommended for primary prevention of CVD.

FORM framework Question 19

Key question(s): 19. What is the evidence for one antiplatelet therapy or dose or any combination of therapy/doses being more effective than any other antiplatelet therapy/dose or combination for the reduction of CVD events and all cause mortality?		
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Dose Previous systematic review (ATT 2002): Indirect evidence from the ATT collaboration suggests that the risk reductions achieved with low doses (75–162 mg/day) are as large as those obtained with higher doses (500–1,500 mg/day) and larger than those in the few trials that have used doses below 75 mg/day. Most trials in last 15 years have used 75-150mg doses. **Agent/s** Only one RCT (CHARISMA) compared dual antiplatelet therapy (ASA + Clopidogrel) – approx 2000 of the 15,000 participants were free of existing CVD and reported separately. Dual treatment in the primary prevention cohort, had non significant increase in CV death (P = 0.07). Multivariate analysis of the primary prevention group showed a trend towards excess CV death (P = 0.054; HR 1.72; CI 0.99–2.97) with dual-antiplatelet therapy (aspirin plus clopidogrel). Other independent predictors of CV death included increasing age, hypertension, atrial fibrillation, and a history of heart failure.	A	**One or more level I studies with a low risk of bias or several level II studies with a low risk of bias**
	B	**One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias**
	C	**One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias**
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Consistent for effect of low dose aspirin. Only one RCT for dual therapy so not applicable.	A	**All studies consistent**
	B	**Most studies consistent and inconsistency can be explained**
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could*		
Potential significant increase in CVD mortality with dual therapy. Higher doses of aspirin known to increase bleeding complications	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Australian populations included in trials	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to**

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

nil

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	
2. Consistency	B	
3. Clinical impact	A	
4. Generalisability	A	
5. Applicability	A	

Evidence statement

Aspirin monotherapy at low doses shown to be clearest evidence if any antiplatelet therapy used.

Indicate any dissenting opinions

RECOMMENDATION	**GRADE OF RECOMMENDATION**	
No recommendation formed.		

Subgroup evidence for antiplatelet questions:

a. Those deemed clinically high risk as outlined in the assessment guidelines (those with SBP >180 or DBP>110mmHg, diabetes >60yrs, diabetes with microalbuminuria, CKD [see levels below], familial hypercholesterolaemia, cholesterol >7.5mmol/L)

ATT 2009 found consistent effect irrespective of age (> or < 65, BP level >160SBP or >90DBP, diabetes, cholesterol >6mmol/L)

b. Those with atrial fibrillation

Several Cochrane reviews identified for prevention of stroke in those with AF without pre-existing TIA or Stroke. NOTE: unclear from these reviews if study populations included other CVD's.

- Aguilar 2005 (3 trials, N=1965). Aspirin (75-125mg daily or 125mg every second day) consistent, but modest reductions in stroke and other ischemic events that were of marginal statistical significance. The combination of stroke, myocardial infarction or vascular death was significantly reduced (OR 0.71, 95% CI 0.51 to 0.97). No statistically significant reduction in vascular death 0.82 [0.54, 1.25]. No increase in intracranial hemorrhage or major extracranial hemorrhage was observed.
- Aguilar 2005 (5 trials, N= 2313). Robust systematic review of RCTs which found clear benefits of warfarin for preventing stroke (OR 0.39, 95% CI 0.26 to 0.59), all cause mortality (OR 0.69, 95% CI 0.50 to 0.94) and combined endpoint of all stroke, myocardial infarction or vascular death (OR 0.56, 95% CI 0.42 to 0.76) -but not vascular death alone, compared to placebo.
- Aguilar 2007 (8 trials, N= 9598 patients). Robust systematic review of RCTs which found clear benefits (~30%) of warfarin over APT for preventing stroke and all cause mortality and combined endpoints (but not vascular death alone, all cause mortality or MI alone). OAC doubled heamorhage rates but was relatively infrequent (41 v 20).

Subsequent RCTs of note:

- Mant 2007. Warfarin very effective and safe in elderly population (>75 years) compared to aspirin but unclear CVD comorbidities.
- ACTIVE A investigators 2009. Good quality study demonstrating benefits of ASA (75-100mg) +Clopidogrel (75mg) for AF versus ASA (75-100mg alone) where warfarin is not considered appropriate. Major vascular events were reduced with dual therapy (RR 0.89; 95% CI 0.81 to 0.98; P = 0.01) mostly due to reduction in stroke. Benefits were partially offset by increase major bleeding 2% v 1.3% (RR 1.57; 95% CI, 1.29 to 1.92; P<0.001). The authors indirectly compared ASA+C to warfarin and noted that effect was smaller but bleeding was also less (but this is not direct comparision). Impossible to determine population in this trial with pre-existing CVD (probably high) therefore results should be considered with caution (authors have been emailed to confirm) especially given the results of the primary prevention cohort in the CHARISMA study.
- Connolly 2009. Warfarin versus two different (blinded) doses of dabigatran (110mg and 150mg). Both doses of dabigatran were shown to be statistically non-inferior to warfarin. There appeared to be statistically significant benefits from both doses of dabigatran for outcomes such as haemorrhagic stroke, life threatening major bleeding, minor bleeding and intra-cranial bleeding. But there was a statistically significant excess of MI in the 150mg dabigatran dose compared to warfarin, with the lower dabigatran dose also with a excess (non-significant). In addition there was a non-significant excess of

pulomonary embolism in the dabigatran groups. There was a statistically significant excess of gastrointestinal bleeds in the 150mg dabigatran dose, with a non-significant excess in the 110mg dose, compared to warfarin. Impossible to determine population in this trial with pre-existing CVD (probably high) therefore results should be considered with caution. Also currently not licenced in Australia for AF and cost benefit analysis unknown.

c. High, medium and low absolute risk of CVD

Not reported. ATT however calculated 5 year risk of CHD.

d. Abnormal BP and normal BP

No difference found in ATT as above.

e. Hypercholesterol and normal cholesterol

No difference found in ATT as above

f. Diabetes and no diabetes

4 systematic reviews and one guideline report consistent findings –mostly non significant reduction in serious vascular risk. No difference in mortality:

- ATT 2009 (6 trials ~4000 with diabetes out of 95,000): RR 0.88, 95%CI 0.67-1.15 v RR 0.87, 95%CI 0.79-0.96 no previous diabetes
- Calvin 2009 (8 trials): MI RR 0.86 (95% CI 0.67–1.11) using seven trials. For ischemic stroke, RR 0.62 (95% CI 0.31–1.24) using only the results of two trials.
- De Berardis 2009 (6 studies ~10,000): Major cardiovascular events (five studies, 9584 participants; RR 0.90, 95% CI 0.81 to 1.00), cardiovascular mortality (four studies, n=8557, RR 0.94; 0.72 to 1.23), or all cause mortality (four studies, n=8557; 0.93, 0.82 to 1.05). For MI (six studies n=10117, RR 0.86 (95% CI 0.61–1.21). For stroke (five studies n=9584, RR 0.83 (95% CI 0.60 –1.14). Aspirin significantly reduced the risk of MI in men (0.57, 0.34 to 0.94) but not in women (1.08, 0.71 to 1.65; P for interaction=0.056). No effect for preventing stroke for either men or women. Any bleeding (3 studies n=7281, RR 2.50 (0.76 to 8.21) & GI bleeding (3 studies n= 4846, RR 2.11 (0.64 to 6.95).
- Zhang 2010 (7 studies ~11,600 participants): Major cardiovascular events (RR 0.92, 95% CI 0.83–1.02, p = 0.11). All-cause mortality (0.95, 95% CI 0.85–1.06; p = 0.33), cardiovascular mortality (0.95, 95% CI 0.71–1.27; p = 0.71), stroke (0.83, 95% CI 0.63–1.10; p = 0.20), or MI (0.85, 95% CI 0.65–1.11; p = 0.24). There was no significant increased risk of major bleeding in aspirin group (2.46, 95% CI 0.70–8.61; p = 0.16). Meta-regression suggested that aspirin agent could reduce the risk of stroke in women and MI in men.
- Pignone 2010 (guideline -9 studies): CHD events (nonfatal and fatal MI) RR 0.91, 95% CI 0.79 –1.05. Stroke (RR 0.85, 95% CI 0.66 –1.11)

Some of the authors argue reduction small but maybe significant if greater numbers (and hence narrower CIs). This does not take into consideration other interventions. Note: most trials used 100mg doses.

g. Chronic kidney disease and no chronic kidney disease (break down into GFR <45 ml/min, GFR 45-60 ml/min and GFR >60 ml/min)

Not reported.

Additional studies

Selak V, Elley CR, Wells S, Rodgers A, Sharpe N. Aspirin for primary prevention: yes or no? J Prim Health Care. 2010 Jun;2(2):92-9.

This useful modeling study of the benefits and harm of aspirin for primary prevention of CVD was undertaken in New Zealand, using outcomes data from three recent, high quality SRs; ATT (2009), Brugts (2009) and Law (2009). Several points were raised by the EWG regarding this study:

- Classification of events and classification of what fits in with bleeding i.e. concern regarding a comment 'inter-cranial bleeding is an event and that aspirin may prevent'. Aspirin may cause the event rather than prevent.
- Concern was raised about a presumption of reduction in vascular events will be the same in different risk categories. This may be incorrect for different cohorts (rather than inferred from ATT 2009).
- Individual patient data not used for bleeding complications.
- Why was such an important study not published in an international journal?

References of considered studies for Q18 and 19:

Active Investigators, Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M. Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation. N Engl J Med. 2009;360(20):2066-78. **Unclear those without pre-existing CVD.**

Aguilar MI, Hart R, Pearce LA. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD006186.

Aguilar MI, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD001927.

Aguilar M, Hart R. Antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD001925.

Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, Meade T, Patrono C, Roncaglioni MC, Zanchetti A. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009 May 30;373(9678):1849-60.

Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. JAMA. 2006; 295:306-13.

Calvin AD. Aggarwal NR. Murad MH. Shi Q. Elamin MB. Geske JB. Fernandez-Balsells MM. Albuquerque FN. Lampropulos JF. Erwin PJ. Smith SA. Montori VM. Aspirin for the primary prevention of cardiovascular events: a systematic review and meta-analysis comparing patients with and without diabetes. Diabetes Care. 32(12):2300-6, 2009 Dec.

Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;361(12):1139-51. Epub 2009 Aug 30. **Unclear those without pre-existing CVD.**

De Berardis G, Sacco M, Strippoli GF, Pellegrini F, Graziano G, Tognoni G, Nicolucci A. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials.BMJ. 2009 Nov 6;339:b4531. Erratum in: BMJ. 2010;340:c374.

Fowkes FG, Price JF, Stewart MC, Butcher I, Leng GC, Pell AC, Sandercock PA, Fox KA, Lowe GD, Murray GD; Aspirin for Asymptomatic Atherosclerosis Trialists. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. JAMA. 2010 Mar 3;303(9):841-8.

Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, Murray E; BAFTA investigators; Midland Research Practices Network (MidReC). Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet. 2007 Aug 11;370(9586):493-503. **Unclear those without pre-existing CVD.**

Pignone et al 2010. Aspirin for primary prevention of cardiovascular events in people with diabetes. American Diabetes Association statement. Diabetes Care. 2010 June;33(6):1395-1402.

Squizzato A, Keller T, Middeldorp S. Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular disease. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD005158. DOI: 10.1002/14651858.CD005158.pub2. **Only one trial with non CVD –CHARISMA which is reported separately. Hence this review was not appraised.**

Wang T.H. Bhatt D.L. Fox K.A.A. Steinhubl S.R. Brennan D.M. Hacke W. Mak K.-H. Pearson T.A. Boden W.E. Steg P.G. Flather M.D. Montalescot G. Topol E.J. An analysis of mortality rates with dual-antiplatelet therapy in the primary prevention population of the CHARISMA trial. European Heart Journal. 28(18):2200-2207.

Wolff T, Miller T, Ko S. Aspirin for the primary prevention of cardiovascular events: an update of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2009 Mar 17;150(6):405-10.

Yerman T, Gan WQ, Sin DD. The influence of gender on the effects of aspirin in preventing myocardial infarction. BMC Med 2007; 5:29.

Zhang C, Sun A, Zhang P, Wu C, Zhang S, Fu M, Wang K, Zou Y, Ge J. Aspirin for primary prevention of cardiovascular events in patients with diabetes: A meta-analysis. Diabetes Res Clin Pract. 2010 Feb;87(2):211-8. Epub 2009 Oct 23.

8. Weight reduction (Q20)

Search results

Sources	Dates	Total hits	Retrieval list	Final inclusions
Databases Medline; Embase ; Cinahl; PsychINFO Cochrane Library, including CENTRAL Cochrane Controlled Trial Register (CCTR) **Other sources:** pearling; expert working group.	**2002-2010**	**321**	**61**	**4** Avenell 2004 Hession 2009 Shaw 2006 Witham 2010
Search terms:	weight loss; weight reduction; reducing weight; Bariatric surgery; antiobesity medications; behavioural therapy			

Literature identified

Question 20. Does reducing weight reduce CVD events and all cause mortality? Report evidence for secondary outcomes	
References	**Comments / quality**
AVENELL, A., BROOM, J., BROWN, T. J., POOBALAN, A., AUCOTT, L., STEARNS, S. C., SMITH, W. C., JUNG, R. T., CAMPBELL, M. K. & GRANT, A. M. (2004) *Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement.* Health Technol Assess, 8**,** iii-iv, 1-182.	High quality SR. Unclear mix of primary or secondary CVD
HESSION, M., ROLLAND, C., KULKARNI, U., WISE, A. & BROOM, J. (2009) *Systematic review of randomized controlled trials of low-carbohydrate vs. low-fat/low-calorie diets in the management of obesity and its comorbidities*. Obes Rev, 10, 36-50.	High quality SR. Unclear mix of primary or secondary CVD . Limited data on CV endpoints.

SHAW, K., GENNAT, H., O'ROURKE, P. & DEL MAR, C. (2006) *Exercise for overweight or obesity.* Cochrane Database Syst Rev, CD003817.	High quality SR. Unclear mix of primary or secondary CVD . Confirms benefits of exercise for risk factor control irrespective of weight loss.
Witham, M., Avenell, A. *Interventions to achieve long-term weight loss in obese older people. A systematic review and meta-analysis*. Age and Ageing; 2010; 39; 176-184.	High quality SR. Unclear mix of primary or secondary CVD .

Evidence details

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Obesity, diet and nutrition		**Question number: q20**	
Characteristics of study			
Checklist completed by: Jonathan Ucinek			
Study citation	AVENELL, A., BROOM, J., BROWN, T. J., POOBALAN, A., AUCOTT, L., STEARNS, S. C., SMITH, W. C., JUNG, R. T., CAMPBELL, M. K. & GRANT, A. M. (2004) Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement. *Health Technol Assess,* 8**,** iii-iv, 1-182.		
Study design	**Systematic review**	**N (total)**	84 RCTs used in study
Search strategy	A review protocol (for full details see Appendix 1 of paper) was formulated using the structure recommended by the Cochrane Collaboration.		
Selection criteria	RCTs with at least one year follow-up		
Intervention	Interventions took the form of drugs, diets, exercise, behaviour therapy, surgery and complementary therapies specifically aimed to reduce weight or prevent weight gain.		
Comparison	• Placebo • Placebo +weight loss drug • Behaviour modification • Exercise with no additional support		
Outcomes	Weight loss, or prevention of weight gain Risk factor modification Improved clinical outcome		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			

Study addresses an appropriate and clearly focused question	WC	1. To review systematically obesity treatments in adults to identify therapies that impact by achieving weight reduction, risk factor modification or improved clinical outcomes. 2. Based on a systematic review of epidemiological data, to model the impact of moderate weight reduction on reducing the burden of obesity-associated disease. 3. To review systematically health economic evaluations of obesity treatments and assess costs to the NHS of these treatments. 4. To integrate the findings from the above objectives.
Description of the methodology used is included	WC	
The literature search was sufficiently rigorous to identify all the relevant studies	WC	
Study quality was addressed and taken into account?	WC	
There were enough similarities between the studies to justify combining them.		
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		
This systematic review looks at a variety of interventions for weight loss and its effects on CVD related outcomes. This SR probably has enough information to be able to contribute towards answering question 20. A summary of results can be found below: • Orlistat was associated with a weight change of –3.26 kg [95% confidence interval (CI) –4.15 to –2.37 kg] after 2 years, and beneficial changes in risk factors. • Sibutramine was associated with a weight change of –3.40 kg (95% CI –4.45 to –2.35 kg) after 18 months for people on a weight		

maintenance diet and beneficial changes in risk factors apart from diastolic blood pressure.

- Metformin was associated with decreased mortality and myocardial infarction-related mortality in the UK Prospective Diabetes Study after 10 years.
- Low-fat diets (which included 600 kcal/day deficit diets) were associated with the prevention of type 2 diabetes, and improved control of hypertension. These diets were associated with a weight loss after 12 months of –5.31 kg (95% CI –5.86 to –4.77 kg) and improvements in risk factors, with weight loss continuing for 3 years. Insufficient evidence was available to assess putative benefits of low-calorie or very low-calorie diets.
- Studies combining low-fat diets and exercise, with or without behaviour therapy, suggested improved control of hypertension and type 2 diabetes.
- The addition of an exercise programme to diet was associated with improved weight loss and risk factors for at least 1 year.
- The addition of a behaviour therapy programme to diet was also associated with improved weight loss for at least 1 year. It was unclear whether both exercise and behaviour therapy together further enhanced the effect of diet.
- Family therapy was associated with improved weight loss for up to 2 years compared with individual therapy.
- However, there was insufficient evidence to conclude that individual therapy was more beneficial than group therapy.
- Women with obesity-related illnesses, who had intentional weight loss, irrespective of the amount of weight lost, had an associated reduced risk of death, CVD death, cancer and diabetes related death.
- Weight loss appeared more beneficial if achieved within 1 year.
- Men with general illness who lost weight intentionally appeared to have a reduced risk of diabetes related death, but there was no demonstrable effect on CVD mortality, and cancer mortality appeared increased.
- Long-term weight loss was associated with reduced risk of developing type 2 diabetes and improved glucose tolerance in men and women, especially after surgery for obesity.
- A weight loss of 10 kg was associated with a fall in total cholesterol of 0.25 mmol/l and a fall in diastolic blood pressure of 3.6 mmHg.
- A weight loss of 10% was associated with a fall in systolic blood pressure of 6.1 mmHg.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS

Guideline topic: obesity diet and nutrition			**Question number: Q20**
Characteristics of study			
Checklist completed by: Jonathan Ucinek			
Study citation	HESSION, M., ROLLAND, C., KULKARNI, U., WISE, A. & BROOM, J. (2009) Systematic review of randomized controlled trials of low-carbohydrate vs. low-fat/low-calorie diets in the management of obesity and its comorbidities. *Obes Rev,* 10**,** 36-50.		
Study design	**Systematic review**	**N (total)**	13 studies(1222 volunteers)
Search strategy	This systematic review was restricted to RCTs where the full study report was available. Thirteen electronic databases were searched including		

	• MEDLINE, • Commonwealth Agricultural Bureau (CAB) abstracts and • the Cochrane Central Register of Controlled Trials. The search strategy incorporated • weight loss, • cardiovascular disease and • obesity-related terms and text terms, specific to each database. Seven obesity and nutrition journals were hand-searched including the *International Journal of Obesity and Obesity Research*. Reference lists of included studies were searched and authors contacted for further details of their trials.
Selection criteria	RCTs were included if they assessed the weight-loss effects of LC/HP diets against LF/HC diets. Only RCTs from January 2000 to March 2007 were evaluated, as this review is intended to assess the current literature in this field and update the National Health Service R&D Health Technology Assessment systematic review of diet and lifestyle on weight loss and cardiovascular risk published by Avenell *et al.* (8). Only studies conducted in an adult population were included, as defined by minimum age greater than 18 years. RCTs where the participants had a mean or median body mass index (BMI) of ≥28 kg m-2 were included. RCTs evaluated in this review had to be of at least 6-month duration, including the period of active intervention and follow-up.
Intervention	• HP 'ketogenic' diet, where the carbohydrate content was less than 40 g d-1, irrespective of calorie content. • LC diets (carbohydrate ≤ 60 g d-1). • 'Healthy eating' advice. • LF (30% or less daily energy from dietary fat) – 600 kcal deficit diet.
Comparison	Low Fat/High Carbohydrate (LF/HC)
Outcomes	Weight loss or prevention of weight gain Serum lipids, including total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triacylglycerols. Systolic and diastolic blood pressure. Glycemic control Attrition rates

Quality of study		
Quality criteria (from SIGN)	***Met?**	**Comments**
SECTION 1: Internal validity		
Study addresses an appropriate and clearly focused question	WC	This systematic review focuses on randomized controlled trials (RCTs) of LC/HP diets compared with LF/high carbohydrate (HC) conventional diets.
Description of the methodology used is included	WC	
The literature search was sufficiently rigorous to identify all the relevant studies	WC	
Study quality was addressed and taken into account?	AC	
There were enough similarities between the studies to		

justify combining them.		
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		
There were significant differences between the groups for weight, high-density lipoprotein cholesterol, triacylglycerols and systolic blood pressure, favouring the low-carbohydrate diet. There was a higher attrition rate in the low-fat compared with the low-carbohydrate groups suggesting a patient preference for a low-carbohydrate/high-protein approach as opposed to the Public Health preference of a low-fat/high-carbohydrate diet. Evidence from this systematic review demonstrates that low-carbohydrate/high-protein diets are more effective at 6 months and are as effective, if not more, as low-fat diets in reducing weight and cardiovascular disease risk factors up to 1 year (lipids and SBP only)		

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Obesity, diet and nutrition			**Question number:**
Characteristics of study			
Checklist completed by: Jonathan Ucinek			
Study citation	SHAW, K., GENNAT, H., O'ROURKE, P. & DEL MAR, C. (2006) Exercise for overweight or obesity. *Cochrane Database Syst Rev*, CD003817.		
Study design	**Systematic review**	**N (total)**	43 studies included 3476 participants
Search strategy	Use the following sources for the identification of trials: • *The Cochrane Library;* • MEDLINE (until 2005); • SPORT Discus (until 2005); • EMBASE (until 2005). Also searched databases of ongoing trials: Current Controlled Trials (www.controlled-trials.com - with links to other databases of ongoing trials). The reference lists of review articles and of all included studies were searched in order to find other potentially eligible studies. Potential missing, unpublished		

	or ongoing studies were planned to be sought by contacting experts in the field. This was not necessary. Publications in all languages were sought.
Selection criteria	All randomised controlled clinical trials of exercise in people with overweight or obesity, with a duration of at least three months and loss to follow-up of less than 15%, were considered for inclusion. Studies were included if they were randomised controlled trials that examined body weight change using one or more physical activity intervention in adults with overweight or obesity at baseline and loss to follow-up of participants of less than 15%.
Intervention	The studies included had an exercise prescription. Exercise is defined as any form of physical activity performed on a repeated basis for a defined period of time (exercise training). Exercise prescriptions include specific recommendations for the type, intensity, frequency and duration of any physical activity with a specific objective (e.g. increase fitness, lose weight) (Bouchard 1994). Studies stating that they simply recommended increasing physical activity were not included within the analyses unless it was possible to quantify the exercise stimulus by some means. Studies that combined exercise and medication associated with weight loss as an intervention were excluded.
Comparison	• Exercise versus No treatment; • High versus low intensity exercise; • High versus low intensity exercise with dietary change; • Exercise versus diet; • Exercise and diet versus diet alone
Outcomes	**Primary outcomes** • weight or another indicator of body mass (e.g. body mass index, waist measurement, waist-to-hip ratio); • morbidity and mortality; • well-being and quality of life. **Secondary outcomes** • serum lipids; • serum glucose; • systolic and diastolic blood pressure; • adverse effects. We planned on examining the following effect modifiers if there were sufficient data: sex, age, adherence to treatment, initial weight and co-morbidities

Quality of study

Quality criteria (from SIGN)	***Met?**	**Comments**
SECTION 1: Internal validity		
Study addresses an appropriate and clearly focused question	WC	To assess exercise as a means of achieving weight loss in people with overweight or obesity, using randomised controlled clinical trials.
Description of the methodology used is included	WC	
The literature search was sufficiently rigorous to identify all the relevant studies	WC	
Study quality was addressed and taken into account?	WC	
There were enough similarities between the studies to justify combining them.		
SECTION 2: Overall assessment of the study		

How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		

SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**

When compared with no treatment, exercise resulted in small weight losses across studies.
Exercise combined with diet resulted in a greater weight reduction than diet alone (WMD - 1.0 kg; 95% confidence interval (CI) -1.3 to -0.7).
Increasing exercise intensity increased the magnitude of weight loss (WMD -1.5 kg; 95% CI -2.3 to -0.7).

There were significant differences in other outcome measures such as serum lipids, blood pressure and fasting plasma glucose.
Exercise as a sole weight loss intervention resulted in significant reductions in diastolic blood pressure (WMD -2 mmHg; 95% CI -4 to -1), triglycerides (WMD - 0.2 mmol/L; 95% CI -0.3 to -0.1) and fasting glucose (WMD - 0.2 mmol/L; 95% CI -0.3 to -0.1).
Higher intensity exercise resulted in greater reduction in fasting serum glucose than lower intensity exercise (WMD - 0.3 mmol/L; 95% CI -0.5 to -0.2).
No data were identified on adverse events, quality of life, morbidity, costs or on mortality.

The results of this review support the use of exercise as a weight loss intervention, particularly when combined with dietary change.

This systematic review provides evidence that Exercise is associated with improved cardiovascular disease risk factors even if no weight is lost, however it is unable to provide evidence that exercise decreases cardiovascular disease endpoints due to the lack of long term follow up in studies. Therefore any benefit on CVD endpoints can only be assumed to be a follow on based upon improvements in other markers.

However, the effect of exercise on disease endpoints such as myocardial infarction, cerebrovascular accident and type 2 diabetes could not be demonstrated.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS

Guideline topic: Obesity		**Question number: Q. 20 and Q22.**	
Characteristics of study			
Checklist completed by: Carly			
Study citation	Witham, M., Avenell, A. Interventions to achieve long-term weight loss in obese older people. A systematic review and meta-analysis . *Age and Ageing; 2010; 39; 176-184.*		
Study design	**Systematic review**	**N (total)**	9
Search strategy	Searched electronic databases including Medline, CINAHL, PsycINFO, Cochrane database and EMBASE + handsearched obesity and geriatrics journals.		

Selection criteria	Included: RCTs with follow-up data for 1 year Mean age >60 years, and mean baseline BMI was >30kg/m^2 Excluded: studies in which weight loss was a coincidental change produced by another type of intervention.
Intervention	Weight loss interventions
Comparison	Placebo or no intervention for control group.
Outcomes	Meta-analysis results: **Weight**: • At 12 months, weight change between intervention & control group was -3.0kg (95% CI -5.1 to -0.9, P=0.005) • Post hoc grouping – physical activity advice with dietary advice provided greater weight loss. **Lipids:** • **Total cholesterol (data available for 4 studies):** Overall weighted mean difference in intervention & control groups at 12 months was -0.36mmol/l (95% CI -0.75 to 0.04, P=0.008). • **LDL, HDL and triglycerides (data from 2 studies)**: Difference in LDL was -0.04mmol/l (95% CI -0.25 to 0.18, P=0.74) ; HDL 0.04mmol/l (95% CI -0.04 to 0.12, P=0.37) and triglycerides was 0.44mmol/l (95% CI -0.55 to 1.43, P=0.39) **Blood Pressure:** • Data from TONE study: weight loss group had reduction of 4.0/1.1 mmHg in BP, whilst control had reduction of 0.8/0.8mmHg (P<0.001). Antihypertensives could be successfully stopped in 93% of weight loss group and 87% of control **Mortality, morbidity and hospitalization:** • Data from TONE study: hazard ratio for primary end point (recurrence of hypertension or cardiovascular events) was 0.65 (95% CI 0.50 to 0.85) for weight loss compared with controls

Quality of study		
Quality criteria (from SIGN)	***Met?**	**Comments**
SECTION 1: Internal validity		
Study addresses an appropriate and clearly focused question	Y	Well covered
Description of the methodology used is included	Y	Well covered
The literature search was sufficiently rigorous to identify all the relevant studies	Y	Well covered
Study quality was addressed and taken into account?	Y	Well covered
There were enough similarities between the studies to justify combining them.	Y	Well covered
SECTION 2: Overall assessment of the study		

How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or – what is the likely direction in which bias might affect the study results?		
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		
• Some reference to physical activity intervention, but primary focus on weigh loss interventions. • Well addressed review of weight loss and health consequences, but limited in only dealing with elderly participants. • Demonstrated that weight loss/physical activity have some effect on weight loss, and cardiovascular events, but limited impact on lipoprotein profiles.		

FORM framework Question 20

Key question(s): Q 20 Does reducing weight reduce CVD events and all cause mortality? Report evidence for secondary outcomes:

1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*

Four high quality SR:

- Shaw 2006 - Exercise
- Avenell 2004 – multiple strategies
- Hession 2009 - low-carbohydrate/high-protein diets
- Witham 2010 – multiple strategies specific to elderly population

A	**One or more level I studies with a low risk of bias or several level II studies with a low risk of bias**
B	**One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias**
C	**One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias**
D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**

2. Consistency *(if only one study was available, rank this component as 'not applicable')*

The SRs are consistent in that reductions in lipids and BP can be achieved with weight loss. There is clinical heterogeneity across methodologies and questions though.

A	**All studies consistent**
B	**Most studies consistent and inconsistency can be explained**
C	**Some inconsistency, reflecting genuine uncertainty around question**
D	**Evidence is inconsistent**
NA	**Not applicable (one study only)**

3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*

The reductions in lipids and SBP need to be considered by EWG to determine clinical impact as they may be questionable. Also limited data on CV endpoints – most rely on a rationale that improving risk factors improves endpoints.

A	**Very large**
B	**Substantial**
C	**Moderate**
D	**Slight/Restricted**

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*

Note some populations studied were limited to elderly or particular BMI.

A	**Evidence directly generalisable to target population**
B	**Evidence directly generalisable to target population with some caveats**
C	**Evidence not directly generalisable to the target population but could be sensibly applied**
D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*

Dietary questions strongly influenced by cultural factors that need to be considered

A	**Evidence directly applicable to Australian healthcare context**
B	**Evidence applicable to Australian healthcare context with few caveats**
C	**Evidence probably applicable to Australian healthcare context with some caveats**
D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The evidence that investigates CVD endpoints is not strong (ie there are not sufficient studies). Predominantly use the secondary outcomes (lipids and BP). For example Curioni 2006 perfomed a Cochrane Review to investigate the effect of weight reduction on stroke incidence and found no trials.

EVIDENCE STATEMENT MATRIX

Component	Rating	Description
1.Evidence base	A	High quality SRs
2.Consistency	B	Clinical heterogeneity in primary trials
3.Clinical impact	C	Somewhat open to question given use of secondary outcomes with little data on CVD endpoints
4. Generalisability	B	One SR only considered overweight elderly.
5. Applicability	B	As some interventions involve diet and behavioural change cultural influences must be considered

Evidence statement

There is evidence to support the promotion of weight reducing interventions to favourably influence CVD risk factors such as lipid and blood pressure levels. There is limited evidence that directly links weight loss with a reduction in CVD events.

RECOMMENDATION	**GRADE OF RECOMMENDATION**	B

Weight loss should be recommended for people who are overweight or obese.

UNRESOLVED ISSUES

If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up

IMPLEMENTATION OF RECOMMENDATION	
Will this recommendation result in changes in usual care?	**NO**
Are there any resource implications associated with implementing this recommendation?	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**NO**

9. Dietary advice (Q21)

Search results

Sources	Dates	Total hits	Retrieval list	Final inclusions
Databases Medline; Embase ; Cinahl; PsychINFO Cochrane Library, including CENTRAL Cochrane Controlled Trial Register (CCTR) **Other sources:** pearling; expert working group.	**2002-2010**	**1626**	**32+16**	**18** Bouzan 2005 Brunner 2007 Castro 2005 Dauchet 2005 Dauchet 2006 Dickinson 2006 Elwood 2008 Flores- Mateo 2006 Harland 2008 He 2004 He 2006 He 2007 Hooper 2004 Hooper 2006 Kelly 2004 Kelly 2007 Sofi 2008 Wang 2006
Search terms:	Diet$;Intervention; Advice; Lifestyle; Sodium chloride/salt; Saturated fats; Antioxidants; Omega-3 fatty acids; Soy protein; Glycaemic index or load; Vegetables; Phytosterols, sterols, stanols; Nuts; Low carbohydrate; Low fat; High protein; Weight loss/ energy restriction; Fibre pectin; soluble fibre; Trans fats			

Literature identified

Question 21. Is there evidence that following dietary advice reduces CVD events and all cause mortality? Report evidence for outcomes: Blood pressure; Lipid parameters; Diabetes	
References	**Comments / quality**
Bouzan C, Cohen JT, Connor WE, Kris-Etherton PM, Gray GM, Konig A, Lawrence RS, Savitz DA and Teutsch SM: *A quantitative analysis of fish consumption and stroke risk*. Am J Prev Med. 29: 347-52, 2005	
Brunner, E. J., Rees, K., Ward, K., Burke, M. & Thorogood, M. (2007) *Dietary advice for reducing cardiovascular risk*. Cochrane Database Syst Rev, CD002128.	High quality SR. Surrogate outcomes.
Castro I, Barroso L, and Sinnecker P : *Functional foods for coronary heart disease risk reduction: a meta-analysis using a multivariate approach1–3*. American Journal of Clinical Nutrition, Vol. 82, No. 1, 32-40, July 2005.	
Dauchet L, Amouyel P, Dallongeville J. *Fruit and vegetable consumption and risk of stroke: a meta-analysis of cohort studies*. Neurology. 2005 Oct 25;65(8):1193-7.	Good quality SR. Prospective cohort studies.
Dauchet L, Amouyel P, Hercberg S, Dallongeville J. *Fruit and vegetable consumption and risk of coronary heart disease: a meta-analysis of cohort studies*. J Nutr. 2006 Oct;136(10):2588-93.	Good quality SR. Prospective cohort studies.
Dickinson HO, Mason JM, Nicolson DJ, Campbell F, Beyer FR, Cook JV, Williams B, Ford GA. Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials. J Hypertens. 2006 Feb;24(2):215-33.	High quality SR. Not restricted to primary prevention. Surrogate outcomes.
Elwood PC, Givens DI, Beswick AD, Fehily AM, Pickering JE, Gallacher J. *The survival advantage of milk and dairy consumption: An overview of evidence from cohort studies of vascular diseases, diabetes and cancer*. J Am Coll Nutr. 2008; 27 (6): 723S-734S.	Low quality SR. Cohort and case controlled studies.
Flores-Mateo, G., Navas-Acien, A., Pastor-Barriuso, R. & Guallar, E. (2006) *Selenium and coronary heart disease: a meta-analysis*. Am J Clin Nutr, 84, 762-73.	Good quality SR.
Harland J et al 2008. *Systematic review, meta-analysis and regression of randomised controlled trials reporting an association between an intake of circa 25 g soya protein per day and blood cholesterol.* Artherosclerosis, Volume 200, Issue	

1, Pages 13-27, September 2008.	
He FJ, Nowson CA, MacGregor GA. *Fruit and vegetable consumption and stroke: meta-analysis of cohort studies*. Lancet. 2006 Jan 28;367(9507):320-6.	Good quality SR. Prospective cohort studies.
He FJ, Nowson CA, Lucas M, MacGregor GA. *Increased consumption of fruit and vegetables is related to a reduced risk of coronary heart disease: meta-analysis of cohort studies*. J Hum Hypertens. 2007 Sep;21(9):717-28.	Good quality SR. Prospective cohort studies.
He K, Song Y,Daviglus M, Liu K, Van Horn L, Dyer A, Greenland P: *Accumulated Evidence on Fish Consumption and Coronary Heart Disease Mortality. A Meta-Analysis of Cohort Studies*. The American Journal of Clinical Nutrition, Circulation 2004;109:2705–11.	Good quality SR. Prospective cohort studies.
Hooper L, Summerbell CD, Higgins JP, Thompson RL, Clements G, Capps N*, et al.* Reduced or modified dietary fat for preventing cardiovascular disease. *Cochrane Database Syst Rev*. 2001: CD002137.	High quality SR included in SIGN.
Hooper, L, Thompson, R, Harrison R, Summerbell C, Ness A, Moore H, Worthington H, Durrington P, Higgins J, Capps N, Riemersma R, Ebrahim S, Smith G : *Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review* :BMJ, doi:10.1136/bmj.38755.366331.2F (published 24 March 2006)	High quality SR. Based on Cochrane review by same authors in 2004 included in SIGN.
Hooper L, Bartlett C, Davey Smith G, Ebrahim S. *Advice to reduce dietary salt for prevention of cardiovascular disease*. Cochrane Database of Systematic Reviews 2004, Issue 1. Art. No.: CD003656. DOI: 10.1002/14651858.CD003656.pub2	High quality SR. Included in SIGN
Kelly, S., Frost, G., Whittaker, V. & Summerbell, C. (2004) *Low glycaemic index diets for coronary heart disease*. Cochrane Database Syst Rev, CD004467.	High quality SR. Included trials with people with preexisting CHD.
Kelly, S. A., Summerbell, C. D., Brynes, A., Whittaker, V. & Frost, G. (2007) *Wholegrain cereals for coronary heart disease.* Cochrane Database Syst Rev, CD005051.	High quality SR. No CVD endpoints noted in included studies
Sofi, F., Cesari, F., Abbate, R., Gensini, G. F. & Casini, A. (2008) *Adherence to Mediterranean diet and health status: meta-analysis*. BMJ, 337, a1344.	Good quality SR. CVD endpoints
Wang, C., Harris, W. S., Chung, M., Lichtenstein, A. H., Balk, E. M., Kupelnick, B., Jordan, H. S. & Lau, J. (2006) : n-*3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review*. Am J Clin Nutr*,* 84, 5-17.	High quality SR based mostly on cohort studies.

Evidence details

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Diet		**Question number: 21**	
Characteristics of study			
Checklist completed by:			
Study citation	BRUNNER, E. J., REES, K., WARD, K., BURKE, M. & THOROGOOD, M. (2007) Dietary advice for reducing cardiovascular risk. *Cochrane Database Syst Rev*, CD002128.		
Study design	**Systematic review**	**N (total)**	Thirty-eight trials; 17,871 participants/clusters were randomised. Twenty-six of the 38 included trials were conducted in the USA
Search strategy	Cochrane Central Register of Controlled Trials, DARE and HTA databases on The Cochrane Library (Issue 4 2006), MEDLINE (1966 to December 2000, 2004 to November 2006) and EMBASE (1985 to December 2000, 2005 to November 2006). Additional searches were done on CAB Health (1972 to December 1999), CVRCT registry (2000), CCT (2000) and SIGLE (1980 to 2000). Dissertation abstracts and reference lists of articles were checked and researchers were contacted		
Selection criteria	Randomised studies with no more than 20% loss to follow-up, lasting at least 3 months involving healthy adults comparing dietary advice with no advice or minimal advice. Trials involving children, trials to reduce weight or those involving supplementation were excluded. Multiple interventions, such as those involving advice on physical activity, are excluded. Trials of weight reducing diets are excluded.		
Intervention	Dietary interventions involve verbal or written advice: to decrease consumption of one or more of fat, saturated fatty acids, cholesterol, salt, and/or increase consumption of one or more of fruit, vegetables, polyunsaturated fatty acids, monounsaturated fatty acids, fish, fibre, and potassium.		
Comparison	The control group received no or minimal dietary advice		
Outcomes	Primary Outcome Measures 1. Cardiovascular risk factors: resting blood pressure, blood lipids and lipoproteins (cholesterol), and blood or red cell folate and/or homocysteine. 2. Bio-markers of dietary intake: urinary sodium, urinary potassium and blood diet-derived antioxidants such as B-carotene. Secondary outcomes Self-reported measures of dietary intake, including fat, fat fractions, dietary fibre, fish, fruit and vegetables, vitamin C (ascorbic acid), vitamin E (tocopherols), carotenoids, flavonoids, and folic acid.		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		Y	To assess the effects of providing dietary advice to achieve sustained dietary changes or improved cardiovascular risk profile among healthy adults

Description of the methodology used is included	Y	
The literature search was sufficiently rigorous to identify all the relevant studies	Y	
Study quality was addressed and taken into account?	Y	
There were enough similarities between the studies to justify combining them.	Y	
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		
Dietary advice appears to be effective in bringing about modest beneficial changes in diet and cardiovascular risk factors over approximately 10 months but longer term effects are not known. Trials not long enough to provide data on CVD events and mortality. Dietary advice reduced total serum cholesterol by 0.16 mmol/L (95% CI 0.06 to 0.25) and LDL cholesterol by 0.18 mmol/L (95% CI 0.1 to 0.27) after 3-24 months. Mean HDL cholesterol levels and triglyceride levels were unchanged. Dietary advice reduced blood pressure by 2.07 mmHg systolic (95% CI 0.95 to 3.19) and 1.15 mmHg diastolic (95% CI 0.48 to 1.85) and 24-hour urinary sodium excretion by 44.2 mmol (95% CI 33.6 to 54.7) after 3-36 months. Three trials reported plasma antioxidants where small increases were seen in lutein and Beta-cryptoxanthin, but there was heterogeneity in the trial effects. Self-reported dietary intake may be subject to reporting bias, and there was significant heterogeneity in all the following analyses. Compared to no advice, dietary advice increased fruit and vegetable intake by 1.25 servings/day (95% CI 0.7 to 1.81). Dietary fibre intake increased with advice by 5.99 g/day (95% CI 1.12 to 10.86), while total dietary fat as a percentage of total energy intake fell by 4.49 % (95% CI 2.31 to 6.66) with dietary advice and saturated fat intake fell by 2.36 % (95% CI 1.32 to 3.39)		

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS

Guideline topic: Nutrition		**Question number:21**	
Characteristics of study			
Checklist completed by: Kelvin Hill			
Study citation	Dickinson HO, Mason JM, Nicolson DJ, Campbell F, Beyer FR, Cook JV, Williams B, Ford GA. Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials. J Hypertens. 2006 Feb;24(2):215-33.		
Study design	**Systematic review**	**N (total)**	105 trials randomizing 6805 participants
Search strategy	Cochrane methodology 1998-2003, used existing guidelines, reviews, meta analysis prior to 1998. English papers only.		

Selection criteria	randomized, controlled trials with at least 8 weeks' follow-up, comparing lifestyle with control interventions, enrolling adults with blood pressure at least 140/85 mmHg. Studies excluded if: Studies of pregnant women, Studies of patients with secondary hypertension, or renal disease. Studies in which participants received antihypertensive medication that varied during the course of the study.		
Intervention	lifestyle intervention (eg. diet, exercise, supplements, relaxation etc)		
Comparison	placebo, sham therapy, usual care, or no treatment		
Outcomes	Primary outcome measures were systolic and diastolic blood pressure. Authors state: "We analysed blood pressure because most of the trials included were small and short term, and so reported blood pressure rather than major events (death, myocardial infarction, stroke)."		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		WC	Adequately covered
Description of the methodology used is included		WC	
The literature search was sufficiently rigorous to identify all the relevant studies			
Study quality was addressed and taken into account?		WC	
There were enough similarities between the studies to justify combining them.		WC	
SECTION 2: Overall assessment of the study			
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
			+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
			- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?			
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**			

This large, comprehensive review provides useful evidence for the reduction in BP for specific lifestyle interventions. However it does not include outcomes of interest to current guidelines (mortality, CVD outcomes). The review concluded: "Robust statistically significant effects were found for improved diet, aerobic exercise, alcohol and sodium restriction, and fish oil supplements: mean reductions in systolic blood pressure of 5.0 mmHg [95% confidence interval (CI): 3.1–7.0], 4.6 mmHg (95% CI: 2.0–7.1), 3.8 mmHg (95% CI: 1.4–6.1), 3.6 mmHg (95% CI: 2.5– 4.6) and 2.3 mmHg (95% CI: 0.2–4.3), respectively, with corresponding reductions in diastolic blood pressure. Relaxation significantly reduced blood pressure only when compared with non-intervention controls. We found no robust evidence of any important effect on blood pressure of potassium, magnesium or calcium supplements. "

* Assessment of whether the criteria has been met should be made according to one of the following descriptors

Well covered
Adequately addressed
Poorly addressed
Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
Not applicable.

Template for Intervention Study – Systematic Review		
Completed by: Kelvin Hill		
REFERENCE Dauchet L, Amouyel P, Hercberg S, Dallongeville J. *Fruit and vegetable consumption and risk of coronary heart disease: a meta-analysis of cohort studies*. J Nutr. 2006 Oct;136(10):2588-93.		
SOURCE OF FUNDING		
SUMMARY		
Inclusion criteria	Types of studies	Prospective cohort studies were selected if they reported relative risks (RRs) and 95% CI for coronary heart disease or mortality and if they presented a quantitative assessment of fruit and vegetable intake. 9 studies included.
	Participants	91,379 men, 129,701 women, and 5,007 CHD events.
	Interventions	Fruit and vegetable intake
	Primary outcome	1) fatal and nonfatal myocardial infarction (MI), 2) ischemic heart disease mortality or coronary death, and 3) coronary heart disease incidence.
	Additional outcomes	
Search		Medline and EMBASE) from 1970 to January 2006. References from the extracted papers, reviews, and previous meta-analysis were also consulted to complete the data bank
Methods of review	Method of applying inclusion criteria	2 reviewers extracted data
	Assessment of methodological quality	Not reported/undertaken
Comparisons		Little or no intake in fruit and vegetables
Main results		The risk of CHD was decreased by 4% [RR (95% CI): 0.96 (0.93–0.99), P =0.0027] for each additional portion per day of fruit and vegetable intake and by 7% [0.93 (0.89–0.96), P < 0.0001] for fruit intake. The association between vegetable intake and CHD risk was heterogeneous (P = 0.0043), more marked for cardiovascular mortality [0.74 (0.75–0.84), P < 0.0001] than for fatal and nonfatal myocardial infarction [0.95 (0.92–0.99), P = 0.0058]. Visual inspection of the funnel plot suggested a publication bias, although not statistically significant.

QUALITY CHECK			
Process	**Questions**	**Answer**	**Comment**
Search:	**Are**:		
	two or more databases named and used	Y	
	reference lists of selected articles searched	Y	
	experts and trialists contacted	N	
	any journals searched by hand	N	
	databases searched from their inception	N	1970 so close to inception
	all languages accepted	N	English only
Selection:	**Is there a clear definition of**:		
	the population being studied	Y	
	the interventions being investigated	Y	
	the principal outcomes being studied	Y	
	the study designs included (and excluded)	Y	
Validity:	**Does the review process**:		
	assess (measure, quantify) the quality of studies identified	N	
	blind reviewers to study origin (authors, journal etc)	N	
	abstract data into a structured database	N	
	use two independent people to abstract data and assess study quality	N	
	measure heterogeneity and bias of studies included	Y	Funnel plot
Data:	**For each study are the details (or their absence) noted of**:		
	participants included in study (number and type)	Y	
	interventions studied	Y	
	outcome	Y	
Analysis:	**Does the review process**:		
	undertake meta-analysis or state why not done	Y	
	investigate agreement between independent assessors	Y	
	give confidence intervals for outcomes reported	Y	

CLINICAL IMPLICATIONS	
Benefits	Reduced CHD with F&V
Harms	None reported
Comments / quality	Moderate quality SR. No review of included study methodology.

REASON FOR EXCLUSION (Poor quality +not clinically relevant / interesting or if relevant for preamble)
Include –although risk of bias

RELEVANCE TO AN AUSTRALIAN CONTEXT
Yes

OVERALL CONCLUSION
Data from several large prospective cohort studies found increased fruit and veges reduces risk of CHD.

Template for Intervention Study – Systematic Review		
Completed by: Kelvin Hill		
REFERENCE Elwood PC, Givens DI, Beswick AD, Fehily AM, Pickering JE, Gallacher J. *The survival advantage of milk and dairy consumption: An overview of evidence from cohort studies of vascular diseases, diabetes and cancer*. J Am Coll Nutr. 2008; 27 (6): 723S-734S.		
SOURCE OF FUNDING Stated no funding received.		
SUMMARY		
Inclusion criteria	Types of studies	Prospective cohort studies and case controlled studies. 15 studies related to stroke and/or CHD. 4 studies related to diabetes.
	Participants	General population
	Interventions	milk and dairy consumption
	Primary outcome	Vascular disease (MI, stroke, metabolic syndrome) and diabetes
	Additional outcomes	cancer
Search		Cochrane systematic review methods [6] the computerised database MEDLINE was searched up to June 2008
Methods of review	Method of applying inclusion criteria	Not reported. But state Cochrane review methodology.
	Assessment of methodological quality	Not reported
Comparisons		Little or no milk or dairy consumption
Main results		From meta-analysis of 15 studies the relative risk of stroke and/or heart disease in subjects with high milk or dairy consumption was 0.84 (95% CI 0.76, 0.93) and 0.79 (0.75, 0.82) respectively, relative to the risk in those with low consumption. Four studies reported incident diabetes as an outcome, and the relative risk in the subjects with the highest intake of milk or diary foods was 0.92 (0.86, 0.97).

QUALITY CHECK

Process	**Questions**	**Answer**	**Comment**
Search:	**Are**:		
	two or more databases named and used	N	Medline only
	reference lists of selected articles searched	Y	
	experts and trialists contacted	N	
	any journals searched by hand	N	
	databases searched from their inception	N	Not stated
	all languages accepted	N	Not stated
Selection:	**Is there a clear definition of**:		
	the population being studied	Y	
	the interventions being investigated	Y	
	the principal outcomes being studied	Y	
	the study designs included (and excluded)	Y	
Validity:	**Does the review process**:		
	assess (measure, quantify) the quality of studies identified	N	
	blind reviewers to study origin (authors, journal etc)	N	
	abstract data into a structured database	N	Not stated “Cochrane review

			methodology"?
	use two independent people to abstract data and assess study quality	N	Not stated
	measure heterogeneity and bias of studies included	N	
Data:	**For each study are the details (or their absence) noted of**:		
	participants included in study (number and type)	Y	
	interventions studied	Y	
	outcome	Y	
Analysis:	**Does the review process**:		
	undertake meta-analysis or state why not done	Y	
	investigate agreement between independent assessors	Y	
	give confidence intervals for outcomes reported	Y	

CLINICAL IMPLICATIONS	
Benefits	Reduced CVD events.
Harms	Not reported
Comments / quality	Low quality SR with risk of bias. Not enough data to differentiate between full cream and low fat milk/dairy.

REASON FOR EXCLUSION (Poor quality +not clinically relevant / interesting or if relevant for preamble)
Include –although risk of bias

RELEVANCE TO AN AUSTRALIAN CONTEXT
Yes

OVERALL CONCLUSION
Some evidence for link between dairy but based on poor methodology/reporting and hence risk of bias. No differentiation between full cream and low fat milk by authors (they 'refrained' from undertaking separate analysis even though some studies specifically included different types).

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: diet and nutrition			**Question number: 21**
Characteristics of study			
Checklist completed by: Jonathan Ucinek			
Study citation	FLORES-MATEO, G., NAVAS-ACIEN, A., PASTOR-BARRIUSO, R. & GUALLAR, E. (2006) Selenium and coronary heart disease: a meta-analysis. *Am J Clin Nutr,* 84**,** 762-73.		
Study design	**Systematic review**	**N (total)**	Trials (n=6) for question 2
Search strategy	The MEDLINE and the Cochrane Library databases were searched for studies conducted from 1966 through 2005. Relative risks were pooled by using an inverse-variance weighted random effects model.		
Selection criteria	RCTs investigating effect of selenium supplements on CVD prevention (second question of review) Humans.		
Intervention	(first question – not relevant to Guidelines: observational studies that assessed the association of selenium concentrations in blood or toenails with clinical coronary heart disease outcomes and **Second question: selenium supplements, either alone or in combination with other vitamins or minerals**		

Comparison	Placebo or control		
Outcomes	The a priori selected endpoint was coronary heart disease, which was defined as any combination of fatal or nonfatal coronary heart disease and myocardial infarction. Studies reporting only total cardiovascular endpoints were also included, because coronary heart disease is the major contributor to cardiovascular disease in many populations		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		WC	
Description of the methodology used is included		AC	
The literature search was sufficiently rigorous to identify all the relevant studies		AC	
Study quality was addressed and taken into account?		AC	
There were enough similarities between the studies to justify combining them.		AC	
SECTION 2: Overall assessment of the study			
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
			+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
			- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?			
SECTION 3: Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.			
Few randomized trials have addressed the cardiovascular efficacy of selenium supplementation, and their findings are still inconclusive. Evidence from large ongoing trials is needed to establish low selenium concentrations as a cardiovascular disease risk factor. Currently, selenium supplements should not be recommended for cardiovascular disease prevention. **Randomized trials, on the other hand, are still inconclusive*** with respect to the effect of selenium supplementation. The ongoing Selenium and Vitamin E Cancer Prevention Trial, a placebo controlled trial that is testing the effects of 200 _g selenium/d in 32 400 men in the United States and Canada (78), will provide more definitive evidence. The results of this trial are scheduled to appear in 2013. Until then, the observational evidence that low selenium concentrations are a cardiovascular risk factor should be treated as suggestive but not definitive. Furthermore, the public should be warned against the use of selenium supplements for cardiovascular disease prevention. The benefits of selenium supplementation are uncertain, and their indiscriminate use carries a risk of toxicity. *In these trials, participants taking supplements containing selenium had a non significant 11% reduction in coronary events, but the trials were small and selenium was given in combination with other vitamins or minerals in all but 2 trials. Overall, the evidence is still inadequate to establish a protective role of selenium in coronary heart disease.			

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Nutrition		**Question number:21**	
Characteristics of study			
Checklist completed by: Kelvin Hill			
Study citation	He K, Song Y,Daviglus M, Liu K, Van Horn L, Dyer A, Greenland P: *Accumulated Evidence on Fish Consumption and Coronary Heart Disease Mortality. A Meta-Analysis of Cohort Studies*. The American Journal of Clinical Nutrition, Circulation 2004;109:2705–11.		
Study design	**Systematic review (cohort studies)**	**N (total)**	11 eligible studies and 13 cohorts, including 222 364 individuals with an average 11.8 years of follow-up
Search strategy	MEDLINE and EMBASE (1966 to September 2003). Search terms included "fish," "seafood," "omega-3 fatty acids," "n-3 fatty acids," "cardiovascular disease," "fatal coronary heart disease," and "fatal myocardial infarction" (MI). The search was restricted to studies using prospective cohort study design and published in Englishlanguage journals. We also used information of bibliographies from retrieved articles and recent reviews.		
Selection criteria	Studies were included if they provided a relative risk (RR) and corresponding 95% CI for CHD mortality in relation to fish consumption and the frequency of fish intake.		
Intervention	Fish consumption		
Comparison	Limited or no fish consumption		
Outcomes	CHD mortality		
Quality of study			
Quality criteria (from SIGN)	***Met?**	**Comments**	
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question	WC	Adequately covered	
Description of the methodology used is included	WC		
The literature search was sufficiently rigorous to identify all the relevant studies	AC	Adequately covered	
Study quality was addressed and taken into account?	WC		
There were enough similarities between the studies to justify combining them.	WC		
SECTION 2: Overall assessment of the study			
How well was the study done to minimise bias? Determine the methodological quality of the study	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.	
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not	

according to this ranking, based on responses above.		adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		

SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**

Limited to prospective cohort studies. Overall compared with those who never consumed fish or ate fish less than once per month, individuals with a higher intake of fish had lower CHD mortality. The pooled multivariate RRs for CHD mortality were 0.89 (95% CI, 0.79 to 1.01) for fish intake 1 to 3 times per month, 0.85 (95% CI, 0.76 to 0.96) for once per week, 0.77 (95% CI, 0.66 to 0.89) for 2 to 4 times per week, and 0.62 (95% CI, 0.46 to 0.82) for 5 or more times per week. Each 20-g/d increase in fish intake was related to a 7% lower risk of CHD mortality (*P* for trend 0.03).

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic:			**Question number: 21**
Characteristics of study			
Checklist completed by: Jonathan Ucinek			
Study citation	KELLY, S., FROST, G., WHITTAKER, V. & SUMMERBELL, C. (2004) Low glycaemic index diets for coronary heart disease. *Cochrane Database Syst Rev*, CD004467.		
Study design	**Systematic review**	**N (total)**	**Twenty-one** RCTs, with 713 participants randomised
Search strategy	CENTRAL on *The Cochrane Library* (Issue 2, 2006), MEDLINE (1966 to July 2006), EMBASE (1980 to July 2006) and CINAHL (1982 to July 2006). Checked references and contacted experts in the field. No language restrictions were applied.		
Selection criteria	RCTs that assessed the effects of low GI diets, over a minimum of 4 weeks, on CHD and risk factors for CHD. Participants included were adults with at least one major risk factor for CHD e.g. abnormal lipids, diabetes or being overweight or who had previously been diagnosed with CHD		
Intervention	low GI diets The intervention had to be advice on diet or carbohydrate foods, or a prescribed diet when the glycaemic index of the diet or carbohydrate foods were reported or compared and the effect on risk factors for CHD or CHD events or mortality were reported. Studies needed to have a minimum of 4 weeks intervention period. Comparisons had to be between diets with similar overall carbohydrate and fat levels and similar levels of energy and macronutrients. Studies did not need to specifically aim to compare the effect of glycaemic index of the diet but if the glycaemic indices were reported and the diets had similar carbohydrate, fat and energy levels, they were included. Studies which compared the effect of lower GI diets or foods with any higher GI diets or foods were included. Metabolic ward studies, conducted on-inpatients, were not included as the participants are not free-living. Studies were not included if they were multiple component interventions which included factors other than glycaemic index of the diet , unless the effect of glycaemic index of diet could be separated out from the other		

	interventions		
Comparison	Other diets		
Outcomes	**Primary outcomes** 1. Total CHD mortality; 2. Combined CHD events and morbidity (to include fatal and non fatal myocardial infarction, angina, unplanned coronary artery bypass graft or percutaneous transluminal coronary angioplasty); 3. Changes in the severity of major risk factors for CHD including lipids (HDL, LDL cholesterol levels, triglycerides and total cholesterol), measures of diabetic control (including changes in medication, glycosylated haemoglobin, glucose tolerance and control), overweight, blood pressure, insulin resistance, insulin sensitivity, hyperinsulinaemia, hyperglycaemia		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		WC	
Description of the methodology used is included		WC	
The literature search was sufficiently rigorous to identify all the relevant studies		WC	
Study quality was addressed and taken into account?		WC	
There were enough similarities between the studies to justify combining them.		WC	
SECTION 2: Overall assessment of the study			
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
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If coded as +, or - what is the likely direction in which bias might affect the study results?			
SECTION 3: Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.			
Review of RCTs, well documented, found that low GI diets did not have a significant effect on measures of BP, Cholesterol, triglycerides. No studies reported on effect of low GI on CHD events or mortality. **LDL cholesterol** Fourteen studies reported LDL cholesterol as an outcome. There is borderline evidence of a reduction in LDL cholesterol on low GI diets compared to high GI diets when data from both parallel and crossover studies at all endpoint intervals were pooled, and a sensitivity analysis carried out (-0.16mmol/L, 95%CI -0.32 to 0.00, P=0.05).However, there is no evidence of an effect from any of the other comparisons examined.			

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS				
Guideline topic: diet and nutrition			**Question number: 21**	
Characteristics of study				
Checklist completed by: Jonathan Ucinek				
Study citation	KELLY, S. A., SUMMERBELL, C. D., BRYNES, A., WHITTAKER, V. & FROST, G. (2007) Wholegrain cereals for coronary heart disease. *Cochrane Database Syst Rev*, CD005051.			
Study design	**Systematic review**	**N (total)**	10 studies (11 papers)	
Search strategy	We searched CENTRAL (Issue 4, 2005), MEDLINE (1966 to 2005), EMBASE (1980 to 2005), CINAHL (1982 to 2005), ProQuest Digital Dissertations (2004 to 2005). No language restrictions were applied			
Selection criteria	Randomised controlled trials that assessed the effects of wholegrain foods or diets containing whole grains, over a minimum of 4 weeks, on CHD and risk factors. Participants included were adults with existing CHD or who had at least one risk factor for CHD, such as abnormal lipids, raised blood pressure or being overweight. Studies had to have a minimum of four weeks intervention period (or follow-up period following dietary advice).			
Intervention	individual wholegrain foods, or diets high in wholegrain foods. For the purpose of this review the term wholegrain includes foods based on milled wholegrains, such as wholemeal or oatmeal, where the components of the endosperm, bran and germ have not been removed.			
Comparison	other diets or foods with lower levels or no wholegrains. Comparisons were between diets with similar overall carbohydrate, fat, protein and energy levels			
Outcomes	**Primary outcomes** (1) Total CHD mortality. (2) Combined CHD events and morbidity (including fatal and non fatal myocardial infarction, angina, unplanned coronary artery bypass graft or percutaneous transluminal coronary angioplasty). (3) Changes in major risk factors for CHD including overweight, lipids (HDL and LDL cholesterol levels, triglycerides and total cholesterol), blood pressure, measures of diabetic control including changes in medication, glycosylated haemoglobin, glucose tolerance and control), insulin resistance, insulin sensitivity, clotting factors, hyperinsulinaemia, hyperglycaemia.			
Quality of study				
Quality criteria (from SIGN)		***Met?**	**Comments**	
SECTION 1: Internal validity				
Study addresses an appropriate and clearly focused question		WC		
Description of the methodology used is included		WC		
The literature search was sufficiently rigorous to identify all the relevant studies		WC		
Study quality was addressed and taken into account?		WC		
There were enough similarities between the studies to justify combining them.		AC		
SECTION 2: Overall assessment of the study				
How well was the study done to minimise bias? Determine the		++	++ All or most of the criteria have been fulfilled. Where they have not been	

methodological quality of the study according to this ranking, based on responses above.		fulfilled the conclusions of the study or review are thought very unlikely to alter.
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SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**

No studies were found that reported the effect of wholegrain foods or diets on CHD mortality or CHD events and morbidity. All ten included studies report the effect of wholegrain foods or diets on major risk factors for CHD.
In eight of the included studies, the wholegrain component was oats. **Seven of the eight studies reported lower total and low density lipoproteins (LDL) cholesterol with oatmeal foods than control food**s. When the studies were **combined in a meta-analysis lower total cholesterol (-0.20 mmol/L, 95% confidence interval (CI) -0.31 to -0.10, P = 0.0001) and LDL cholesterol (0.18 mmol/L, 95% CI -0.28 to -0.09, P < 0.0001) were found with oatmeal foods**. However, there is a **lack of studies** on other wholegrains or wholegrain diets. Included studies were of low quality and often funded by wholegrain food companies so results should be viewed cautiously.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS

Guideline topic:		**Question number:**	
Characteristics of study			
Checklist completed by: Jonathan Ucinek			
Study citation	SOFI, F., CESARI, F., ABBATE, R., GENSINI, G. F. & CASINI, A. (2008) Adherence to Mediterranean diet and health status: meta-analysis. *BMJ,* 337**,** a1344.		
Study design	**Systematic review**	**N (total)**	12 studies
Search strategy	PubMed, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials databases up to 30 June 2008, using a search strategy that included both truncated free text and exploded MeSH terms. MeSH headings included “Mediterranean”, “diet”, “dietary pattern”, “disease”, “health”, “cardiovascular disease”, “cerebrovascular disease”, “coronary heart disease”, “degenerative diseases”, “cancer”, “neoplasm”, “prospective”, “follow- up”, or “cohort”, and their variants. The search strategy had no language restrictions.		
Selection criteria	studies that prospectively evaluated the association of an a priori score used for assessing adherence to a Mediterranean diet and adverse clinical outcomes. Excluded the studies if they had a cross sectional or case-control design, if they analysed adherence to a non-specific dietary pattern or to a recommended dietary guideline and not to a Mediterranean diet, if they evaluated a cohort of patients with a previous clinical event (that is, secondary prevention), if they did not adjust for potential confounders, and if they did not report an adequate statistical analysis.		
Intervention	Mediterranean diet		

Comparison	Non med diet		
Outcomes	Cardiovascular outcomes from the included studies included: Overall mortality, CHD mortality; CVD mortality, CVD deaths		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		y	The aim of this study was to do a systematic review with meta-analysis of all the available prospective cohort studies that have assessed the association between adherence to a Mediterranean diet and adverse outcomes, in order to establish the role of adherence to a Mediterranean diet in primary prevention
Description of the methodology used is included		y	
The literature search was sufficiently rigorous to identify all the relevant studies		y	
Study quality was addressed and taken into account?		y	
There were enough similarities between the studies to justify combining them.		y	
SECTION 2: Overall assessment of the study			
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
			+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
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Greater adherence to a Mediterranean diet is associated with a significant improvement in health status, as seen by a significant reduction in overall mortality (9%), mortality from cardiovascular diseases (9%), incidence of or mortality from cancer (6%), and incidence of Parkinson's disease and Alzheimer's disease (13%). These results seem to be clinically relevant for public health, in particular for encouraging a Mediterranean-like dietary pattern for primary prevention of major chronic diseases.			

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS	
Guideline topic: diet and nutrition	**Question number: 21**
Characteristics of study	
Checklist completed by: Jonathan Ucinek	

Study citation	WANG, C., HARRIS, W. S., CHUNG, M., LICHTENSTEIN, A. H., BALK, E. M., KUPELNICK, B., JORDAN, H. S. & LAU, J. (2006) n-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. *Am J Clin Nutr,* 84**,** 5-17.		
Study design	**Systematic review**	**N (total)**	**Primary Prevention studies:(n=1; RCT, n=25; cohort, n=7; case controlled)** reported outcomes in study populations with no history of CVD
Search strategy	1966 to July 2005 in 6 databases: MEDLINE, PreMEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Biological Abstracts, and Commonwealth Agricultural Bureau of Health. Consulted domain experts and examined references of retrieved articles to identify additional studies. Search terms for n-3 FAs included the specific FAs, fish and other marine oils, and the specific plant oils flaxseed, linseed, rapeseed, canola, soy, walnut, mustard seed, butternut, and pumpkin seed.		
Selection criteria	English-language studies that reported original data on the effect of any type of n-3 FA intake in human adults on all-cause mortality and the following clinical CVD outcomes: cardiac death, sudden death, myocardial infarction (MI), and stroke. Both primary-prevention (general population without a history of CVD) and secondary-prevention (patients with a history of CVD) studies were included. Because of distinct differences in the population, we separately analyzed the results of studies that evaluated the effect of fish oils in patients with implantable cardioverter defibrillators (ICDs). We accepted RCTs and prospective cohort studies that followed patients for _1 y and case-control studies that reported intakes of n-3 FAs or fish. Supplementation with >6 g n-3 FAs/d (12–18 large capsules) was not considered to be a practical daily dose; thus, these studies were excluded. Also excluded were case-control and cohort studies based on n-3 FA biomarkers that did not include estimates of dietary intakes. For the purpose of reviewing adverse events and drug interactions, we reviewed prospective human trials analyzed for either CVD clinical outcomes or risk factors. We included studies of any duration or dosage. We also reviewed prospective and retrospective studies that evaluated potential interactions between n-3 FAs and commonly used drugs.		
Intervention	**n-3Fatty acid dosage intake** **n-3 Fatty Acid diet** 1. Indo Mediterranean diet (ALA:1.8 g/d) *2.* Cretan Mediterranean diet (ALA: 1.9 g/d)*4* 3. ALA: 6.3 g/d 4. EPA_DHA: 1.07 g/d 5. EPA_DHA: 0.86 g/d		
Comparison	**n-3Fatty acid dosage intake** 1. Usual care 2. Corn oil:3.4 g/d 3. Equivalent dose of mixed fatty acids (nonmarine n-3) 4. Sunflower seed oil: 3 g/d 5. Olive oil 6. Non-oil placebo 7. Non-oil placebo **n-3 Fatty Acid diet**		
Outcomes	All-cause mortality, Cardiac death, Sudden death, MI, Stroke		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**

SECTION 1: Internal validity		
Study addresses an appropriate and clearly focused question	WC	
Description of the methodology used is included	WC	
The literature search was sufficiently rigorous to identify all the relevant studies	WC	
Study quality was addressed and taken into account?	WC	
There were enough similarities between the studies to justify combining them.	AC	
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
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If coded as +, or - what is the likely direction in which bias might affect the study results?		
SECTION 3: Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.		

Note: Results seem to be varied, with different studies reporting both significant and non-significant effects of treatment on the outcome measures listed below.

Meta analysis of RCTs.

Evidence suggests that increased consumption of n-3 FAs from fish or fish-oil supplements, but not of ALA, reduces the rates of all-cause mortality, cardiac and sudden death, and possibly stroke. Evidence of the benefits of fish oil is stronger in secondary- than in primary-prevention settings. However, no benefits of FA supplementation were seen in patients with an ICD, and adverse effects appear to be minor.

Cardiac Death

- The Multiple Risk Factor Intervention Trial (MRFIT), which followed 12 866 middle-aged men at high risk of CHD for 10.5 y, found no association between ALA intake and risk of cardiac death, whereas the highest quintile **of EPA_DHA intake was associated with a 40% lower risk**
- Eight cohort studies showed some protective benefit, and 4 showed none
- The Cardiovascular Health Study by Mozaffarian (60), which followed 3910 older subjects for 9.3 y, found that a **statistically significant lower risk of total ischemic heart disease associated specifically with higher intakes of oily fish** (ie, tuna and other non fried fish). Of note, in this study, trends for increased cardiac events were observed with increasing consumption of fried fish or fish sandwiches.

Sudden Death

- The Physicians' Health Study followed 20 551 men for 11 y and reported an ~50%lower relative risk even in participants who ate fish only once a month (>0.3 g/mo n_3 FA) (41).
- Siscovick et al (48) reported a significant decrease in sudden death with increasing fish intake and fish-oil consumption.
- Chicago Western Electric Study, followed 1822 men for 30 y and provided data on fish consumption and also found an association between higher fish

consumption and lower rates of sudden death (64).

Myocardial infarction

- higher EPA-DHA intakes were associated with a lower risk of nonfatal MI, ie, a 31% lower risk in the highest compared with the lowest quintile of intake, this was in contrast to the Physicians' Health Study nor the Zutphen Elderly Study (which followed 667 Dutch elderly men free of coronary artery disease for 10 y) reported reductions in the risk of MI with increasing intakes of EPA_DHA or fish
- Four of the 9 cohort studies and 1 case-control study showed a statistically significant reduction in CHD, whereas 3 cohort studies and 1 case-control study found no such reduction in risk.

Note that studies report both an effect and no effect of fish oil intake on MI and CHD.

Stroke

- the Health Professionals Follow-Up Study which followed 43 671 men free of CVD for 12 y, reported a significant reduction in ischemic strokes at all fish-oil intakes above the lowest quintile
- The Nurses' Health Study found a non significant trend of decreased strokes with increasing fish-oil intake
- Three large cohort studies showed a statistically significant reduction in stroke, particularly ischemic stroke.
- The Health Professionals Follow-Up Study reported a significant reduction in ischemic strokes with any level of fish consumption
- The Hiroshima/ Nagasaki Life Span Study, which followed 30 827 male and female survivors of the atomic bomb in Japan, found that those in the highest tertile of fish consumption had a lower risk of death from stroke than did those in the lowest tertile
- In the Cardiovascular Health Study by Mozaffarian et al increased consumption of tuna or other non fried fish was associated with a decrease in total stroke and ischemic stroke. In contrast, increased consumption of fried fish and fish sandwiches was associated with an increased risk of stroke.
- There was no association with hemorrhagic stroke in either of the latter 2 studies.
- Three cohort studies and 1 case-control study found a non significant trend of decreased strokes with increasing fish consumption.
- An additional 5 cohort studies provided no evidence to support the hypothesis that fish consumption reduces the risk of stroke.

FORM framework Question 21

Key question(s): Q 21. Is there evidence that following dietary advice reduces CVD events and all cause mortality? Report evidence for outcomes: Blood pressure; Lipid parameters; Diabetes

1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*

18 systematic reviews (many covered by SIGN guidelines)– variable quality – mostly relying on cohort studies:

- Dauchet 2005 – **Fruit and vegetable** consumption reduces the risk of stroke (by 11% for each additional portion per day of fruit; 5% for F and V; by 3% for vegetables).
- Dauchet 2006 – **Fruit and vegetables** reduce the risk of CHD (by 7% for each additional portion of fruit per day, 4% for f and v).
- He 2006 – **Fruit and vegetables** have significant protective effect on both ischaemic and haemorrhagic stroke (recommend 5 serves per day)
- He 2007 - **Fruit and vegetables** have significant protective effect on CHD (3-5 serves pd – 17% effect)
- Elwood 2008 – **Dairy** is protective for CVD: RR of stroke and/or heart disease in subjects with high milk/dairy consumption was 0.84 (95% CI 0.76, 0.93) and 0.79 (0.75, 0.82) respectively,

A
B
C
D

relative to risk in those with low consumption; RR for incident diabetes was 0.92 (0.86, 0.97).

- Wang 2006 - Evidence suggests increased consumption of **n3 Fatty Acids** from fish or fish-oil supplements (but not of α-linolenic acid) reduces rates of all-cause mortality, cardiac and sudden death, and possibly stroke. Evidence for the benefits of fish oil is stronger in secondary than in primary-prevention settings.
- Bouzan 2005- any **fish** consumption confers substantial RR reduction for stroke compared to no fish consumption; additional consumption confers incremental benefits.
- He 2004 – mortality from CHD may be reduced by eating **fish** once per week or more.
- Whelton 2004 – **fish** consumption is associated with significantly lower risk of fatal and total CHD.
- Hooper 2004 – not clear that dietary or supplemental **omega 3 fats** alter total deaths or CVD events in any population (general, high risk or already with CVD).
- Kelly 2006 – no evidence that **wholegrain diets** have an effect on CHD outcomes; there is evidence that those diets (studies mostly of **oatmeal)** have a reducing effect on total and low density lipoproteins (LDL).
- Sofi 2008 - Greater adherence to a **Mediterranean diet** is associated with a significant improvement in health status, as seen by a significant reduction in overall mortality (9%), mortality from cardiovascular diseases (9%).
- Brunner 2007 - **Dietary advice** reduced total serum cholesterol by 0.16 mmol/L (95% CI 0.06, 0.25) and LDL cholesterol by 0.18 mmol/L (95% CI 0.1, 0.27) after 3-24 months. Mean HDL cholesterol levels and triglyceride levels unchanged. Reduced SBP by 2.07 mmHg (95% CI 0.95 to 3.19) and DBP 1.15 mmHg (95% CI 0.48 to 1.85). No data on CVD events/mortality. (Advice highly varied - around F and V, fibre increase and fat reduction)
- Castro 2005 – principal components analysis – **phytosterols and soluble fibres** have hypocholesterolemic effect; **n-3 fatty acids** lower triglycerol and increased total/LDL/HDL cholesterol.
- Harland 2008 – inclusion of **soya protein** (ca 25g) for adults with normal or mild hypercholesterolemia reduces total and LDL cholesterol (ca 6% reduction)
- Hooper 2004 (salts) – **salt reduction** in diets may lower blood pressure but by small amounts (<1mmHg SBP, less for DBP after one year), however reductions may be higher in people with higher BP.
- Flores-Mateo 2006 – insufficient evidence to recommend **selenium supplements** for CVD prevention
- Kelly 2004 – no evidence that **low GI diets** have any effect on CHD outcomes and only weak evidence for minor effects on some CHD risk factors (LDL)

2. Consistency *(if only one study was available, rank this component as 'not applicable')*

There is consistent evidence that following dietary advice can have a protective effect against CVD events and mortality. The nature of the advice varies in consistency however. The evidence is consistent for fruit and vegetables and for fish. More uncertainty around other food groups/substances may reflect differing definitions, preparation or consumption levels (eg wholegrains, or supplements)	A	**All studies consistent**
	B	**Most studies consistent and inconsistency can be explained**
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
	NA	**Not applicable (one study only)**

3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*

Appears to be substantial effects in some major food groups.	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Most studies conducted in developed countries – where investigated foods are common.	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Foods recommended are readily available in Australia to most populations – need to consider if some socio-demographic groups do have easy access to fresh fruit and vegetables or fresh fish?	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

As for the other "public health" questions – the level of evidence has been downgraded because of the reliance on cohort studies in the meta-analyses. The WG may like to consider this further given the difficulty in running long term RCTs for diet – for example there will not be long term RCTS for fruit and vegetables with a meaningful control group. The extant body of literature for fruit and vegetables is large and consistent and has been for years so this may mitigate against the lower grade?

Also as noted diet is subject to cultural, ethnic and socio-demographic factors: there is some evidence (for example) that there is an association between education levels and levels of dairy consumption. So any recommendations formulated need to bear this in mind. Suggest keeping recommendations very general and refer to sister NHMRC publications for dietary guidance for healthy eating. *EWG agreed to be consistent with current guidelines and hence while recognizing evidence basis have agreed on a practice point linking to current national guidelines.*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account

Component	Rating	Description
1.Evidence base	B/C	Note reliance on cohort studies for meta-analyses
2.Consistency	B	Overall answer to question is consistently YES. The inconsistency is more about the heterogeneity of the dietary approaches/food groups.
3.Clinical impact	B	This needs confirmation by the expert working group
4. Generalisability	B	Diet as for other lifestyle factors is very culture specific – the data is relevant for "western"/developed countries but not necessarily for minority groups within
5. Applicability	B	As above – there is apparently some evidence that socio-demographics influence access to certain food groups

Evidence statement

Inclusion of key food groups in the diet is an important aspect of primary prevention of CVD.

RECOMMENDATION	**GRADE OF RECOMMENDATION**	
What recommendation(s) does the guideline development group draw from this evidence? Use action		
All adults should be supported to follow the current *Australian Dietary Guideline.* (Practice point)		

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up*	
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	**NO**
Are there any resource implications associated with implementing this recommendation?	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**NO**

10.Physical activity (Q22-23)

Search results

Sources	Dates	Total hits	Retrieval list	Final inclusions
Databases Medline; Embase ; Cinahl; PsychINFO Cochrane Library, including CENTRAL Cochrane Controlled Trial Register (CCTR) **Other sources:** pearling; expert working group.	**2002-2010**	**1211**	**103+2**	**17** Aldana 2005 Barker 2008 Carroll 2004 Coghill 2008 Hamer 2008 Löllgen 2009 Makrides 2008 Nocon 2008 Orozco 2008 Pazoki 2007 Pedersen 2009 Racette 2009 Shaw 2006 Shirmoa 2010 Thomas 2006 Tudor-Locke 2004 Woodcock 2010
Search terms:	exercise; sports; physical education and training; exertion; physical$ adj2 Fit; physical$ adj2 fitness; physical adj2 train$; physical adj2 activit$; train$ adj2 strength$; train$ adj2 aerobic$; aerobic$ adj2 exercise$; exercise$ adj2 train$; *Added FITNESS adj (Train$ or program$);* Resistance training			

Literature identified

Question 22. Is there evidence that physical activity reduces CVD events and all cause mortality?

Question 23. What is the evidence for physical activity type and dose or any combination of type/doses being more effective than any other physical activity type and dose

or combination for the reduction of CVD events and all cause mortality? Report evidence for secondary outcomes: Blood pressure; Lipid parameters	
References	**Comments /Quality**
ALDANA, S. G., GREENLAW, R. L., DIEHL, H. A., SALBERG, A., MERRILL, R. M. & OHMINE, S. (2005) The effects of a worksite chronic disease prevention program. J Occup Environ Med, 47, 558-64.	Fair quality RCT. Workplace program in USA.
BAKER, G., GRAY, S. R., WRIGHT, A., FITZSIMONS, C., NIMMO, M., LOWRY, R. & MUTRIE, N. (2008) The effect of a pedometer-based community walking intervention "Walking for Wellbeing in the West" on physical activity levels and health outcomes: a 12-week randomized controlled trial. Int J Behav Nutr Phys Act, 5, 44.	Fair quality RCT. Scotland. Very small sample.
Carroll & Dudfield (2004) What is the relationship between exercise and metabolic abnormalities? A review of the metabolic syndrome. Sports Medicine. 34(6)(pp 371-418).	Good quality SR. Surrogate outcomes
COGHILL, N. & COOPER, A. R. (2008) The effect of a home-based walking program on risk factors for coronary heart disease in hypercholesterolaemic men. A randomized controlled trial. Prev Med, 46, 545-51.	Good quality RCT. Small sample size. Lipid marker outcomes.
M Hamer and Y Chida. Walking and primary prevention: a meta-analysis of prospective cohort studies. Br J Sports Med 2008;42:238–243. doi:10.1136/bjsm.2007.039974	Good quality SR. Prospective cohort studies.
H. Löllgen, A. Böckenhoff, G. Knapp. Physical Activity and All-cause Mortality: An Updated Meta-analysis with Different Intensity Categories. Int J Sports Med 2009; 30: 213– 224.	Good quality SR. Prospective cohort studies.
Makrides, L; Dagenais, G.R.; Chockalingam, A; LeLorier, J; Kishchuk, N; Richard, J; Stewart, J; Chin, C; Alloul, K; Veinot, P. Clinical Governance. Volume 13, Number 2, 2008 , pp. 95-105(11)	Fair quality RCT. Large drop out due to workplace downsizing.
Nocon M, Hiemann T, Müller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. Eur J Cardiovasc Prev Rehabil. 2008 Jun;15(3):239-46.	Fair quality RCT. Prospective cohort studies.
Orozco LJ, Buchleitner AM, Gimenez-Perez G, Roqué i Figuls M, Richter B, Mauricio D. Exercise or exercise and diet for preventing type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No.: CD003054. DOI: 10.1002/14651858.CD003054.pub3	Good quality SR. People at risk of diabetes. Surrogate outcomes
PAZOKI, R., NABIPOUR, I., SEYEDNEZAMI, N. & IMAMI, S. R. (2007) Effects of a community-based healthy heart program on increasing healthy women's physical activity: a randomized controlled trial guided by Community-based	Fair quality RCT. Community setting for women in Iran.

Participatory Research (CBPR). *BMC Public Health,* 7**,** 216.	
PEDERSEN, M. T., BLANGSTED, A. K., ANDERSEN, L. L., JORGENSEN, M. B., HANSEN, E. A. & SJOGAARD, G. (2009) The effect of worksite physical activity intervention on physical capacity, health, and productivity: a 1-year randomized controlled trial. J Occup Environ Med, 51, 759-70.	Fair quality RCT. Workplace intervention. Danish study.
RACETTE, S. B., DEUSINGER, S. S., INMAN, C. L., BURLIS, T. L., HIGHSTEIN, G. R., BUSKIRK, T. D., STEGER-MAY, K. & PETERSON, L. R. (2009) Worksite Opportunities for Wellness (WOW): effects on cardiovascular disease risk factors after 1 year. Prev Med, 49, 108-14.	Good quality RCT. Workplace intervention in USA.
SHAW, K., GENNAT, H., O'ROURKE, P. & DEL MAR, C. (2006) *Exercise for overweight or obesity.* Cochrane Database Syst Rev, CD003817.	Good quality SR. Unclear mix of primary or secondary CVD . Confirms benefits of exercise for risk factor control irrespective of weight loss.
Shiroma EJ; Lee IM. Physical Activity and Cardiovascular Health. Lessons Learned From Epidemiological Studies Across Age, Gender, and Race/Ethnicity. Circulation. 2010;122:743-752	Fair quality SR. More narrative review based on previous systematic review for a guideline.
Thomas DE, Elliott EJ, Naughton GA. Exercise for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2006; 3: CD002968.	Good quality SR. Small number of people (377) with diabetes. Surrogate outcomes.
TUDOR-LOCKE, C., BELL, R. C., MYERS, A. M., HARRIS, S. B., ECCLESTONE, N. A., LAUZON, N. & RODGER, N. W. (2004) Controlled outcome evaluation of the First Step Program: a daily physical activity intervention for individuals with type II diabetes. Int J Obes Relat Metab Disord, 28, 113-9.	Fair quality RCT. Small sample. Based Canada.
Woodcock et al. Non-vigorous physical activity and all-cause mortality: systematic review and meta-analysis of cohort studies. International Journal of Epidemiology 2010;1–18	Good quality SR. Clear evidence from prospective cohort studies in heathy/general populations.

Evidence details

KEY QUESTION(S)	
22	
COMPLETED BY:	
Jonathan Ucinek	
REFERENCE(S)	

ALDANA, S. G., GREENLAW, R. L., DIEHL, H. A., SALBERG, A., MERRILL, R. M. & OHMINE, S. (2005) The effects of a worksite chronic disease prevention program. J Occup Environ Med, 47, 558-64.	
SOURCE OF FUNDING	
Not described	
METHOD	
Patient Eligibility Criteria	
Study design	Randomized clinical trial of an intensive lifestyle intervention. Nutrition and physical activity behaviour and several chronic disease risk factors were assessed at baseline, 6 weeks, and 6 months.
Setting	Employees of community
Intervention(s)	live version of the Coronary Health Improvement Project (CHIP).3 Participants met for 4 weeks—four times each week for 2 hours each session—where they received instruction. The curriculum included topics: modern medicine and health myths, atherosclerosis, coronary risk factors, obesity, dietary fibre, dietary fat, diabetes, hypertension, cholesterol, exercise, osteoporosis, cancer, lifestyle and health, the optimal diet, behavioural change, and self-worth.
Primary outcome measure	Variables included cognitive and behavioural measurements and physiological outcomes related to chronic disease (incl lipids and BP).
Additional outcome measures	Demographic data were collected at baseline. Attendance at each of the classes was tracked and averaged.
Sample Size	145 randomized participants, 8 were lost to follow-up
Main results	Numbers analysed:137
	Study duration: 4 week intervention, 6/12 follow-up
	Patients characteristics and group comparability: equal
	Effect size – primary outcome: BP ns; intervention lower cholesterol
	Effect size – additional outcomes:

QUALITY CHECK		
Patient selection	YES/NO	Comment
Were the eligibility criteria specified?	Y	
Was a method of randomisation performed?	Y	
Was the treatment allocation concealed?	N	
Were the groups similar at baseline regarding the most important prognostic indicators?	N	
Interventions		
Were the index and control interventions explicitly described?	N	
Was the care provider blinded for the intervention?	N	
Were co-interventions avoided or comparable?	N	

Was the compliance acceptable in all groups?	Y	Short term yes, long term to be determined.
Was the patient blinded to the intervention?	N	
Outcome measurement		
Was the outcome assessor blinded to the interventions?	N	
Were the outcome measures relevant?	Y	
Were adverse effects described?	N	
Was the withdrawal/drop-out rate described and acceptable?	Y	
Was a short-term follow-up measurement performed?	Y	
Was a long-term follow-up measurement performed?	N	
Was the timing of the outcome assessment in both groups comparable?	Y	
Statistics		
Was the sample size for each group described?	Y	
Did the analysis include an intention-to-treat analysis?	Y	
Were point estimates and measures or variability presented for the primary outcome measures?		

CLINICAL IMPLICATIONS	
Benefits	Improved diet and PA levels, improved some CVD risk factors
Harms	Nil reported
Comments	
REASON FOR EXCLUSION	
RELEVANCE TO AN AUSTRALIAN CONTEXT	
Swedish American Health Workers (company in the US) similar to health worker cohort in Australia	
OVERALL CONCLUSIONS	
Employees who participated in this intensive lifestyle change program improved their health knowledge, adopted and maintained healthy eating and physical activity behaviours, and experienced favourable improvements in many chronic disease risk factors. SAHS was able to improve the health of many of its employees by encouraging them to participate in this lifestyle change program. Participants in the control group were allowed to participate in the CHIP program after completing the 6-month follow-up period.	

KEY QUESTION(S)	
23	
COMPLETED BY:	
Jonathan Ucinek	
REFERENCE(S)	
BAKER, G., GRAY, S. R., WRIGHT, A., FITZSIMONS, C., NIMMO, M., LOWRY, R. & MUTRIE, N. (2008) The	

effect of a pedometer-based community walking intervention "Walking for Wellbeing in the West" on physical activity levels and health outcomes: a 12-week randomized controlled trial. *Int J Behav Nutr Phys Act,* 5**,** 44.	
SOURCE OF FUNDING	
METHOD	
Patient Eligibility Criteria	
Study design	RCT
Setting	Recruitment was targeted at data zones within 1.5 km of the university campus that were ranked within the top 15% of the Scottish Index of Multiple Deprivation (SIMD) (i.e. the most deprived zones).
Intervention(s)	Participants assigned to the intervention group received a physical activity consultation and then followed a 12- week pedometer-based walking program.
Primary outcome measure	steps/day measured by the Omron HJ-109E Step-O-Meter
Additional outcome measures	body mass index (BMI) was calculated as height(m)/weight(kg)2; height;Waist-to-hip ratio, Percentage body fat , Blood pressure, Fasting blood samples, Total cholesterol and high-density lipoprotein (HDL) cholesterol (direct method), from the plasma.
Sample Size	The intervention group (*n* = 39) consisted of 31 females and eight males and the control group (*n* = 40) consisted of 32 females and eight males.
Main results	
	Study duration:12wks
	Patients characteristics and group comparability: equal
	Effect size – primary outcome: increased walking
	Effect size – additional outcomes: no effect

QUALITY CHECK [3]		
Patient selection	**YES/NO**	**Comment**
Were the eligibility criteria specified?	Y	
Was a method of randomisation performed?	Y	
Was the treatment allocation concealed?	N	
Were the groups similar at baseline regarding the most important prognostic indicators?	Y	
Interventions		
Were the index and control interventions explicitly described?	Y	
Was the care provider blinded for the intervention?	N	
Were co-interventions avoided or comparable?	NA	Not supplied
Was the compliance acceptable in all groups?	NA	Not supplied
Was the patient blinded to the intervention?	N	
Outcome measurement		
Was the outcome assessor blinded to the interventions?	N	
Were the outcome measures relevant?	Y	
Were adverse effects described?		

Was the withdrawal/drop-out rate described and acceptable?	Y	
Was a short-term follow-up measurement performed?		
Was a long-term follow-up measurement performed?	Y	
Was the timing of the outcome assessment in both groups comparable?	Y	
Statistics		
Was the sample size for each group described?	Y	
Did the analysis include an intention-to-treat analysis?	Y	
Were point estimates and measures or variability presented for the primary outcome measures?		

CLINICAL IMPLICATIONS	
Benefits	The major finding of this study was that a graduated pedometer-based walking program, in conjunction with a physical activity consultation increased walking in low-active adults over a period of 12 weeks. The control group, included to account for the intrinsic motivation of volunteer participants [63], displayed no significant change in steps/day over time. The conservative intention to treat analysis (baseline carried forward for missing values) produced a mean change in the intervention group of 3,175 steps/day, an increase of 47% above baseline values, a favorable increase compared with other pedometer-based randomized controlled trials However there was no significant effect of walking on health outcomes- possibly due to the intensity of walking not being sufficient enough to provide health changing effects.
Harms	
Comments	Mislead people into thinking that walking the recommended number of steps/day is sufficient enough to impact on health outcomes- people won't necessarily be thinking about walking intensity which would be the greater benefit, furthermore by conducting this walking exercise may lead them to believe they are burning enough energy to eat more leading to further negative health outcomes
REASON FOR EXCLUSION	
RELEVANCE TO AN AUSTRALIAN CONTEXT	
OVERALL CONCLUSIONS	
The major finding of this study was that a graduated pedometer-based walking program, in conjunction with a physical activity consultation increased walking in low-active adults over a period of 12 weeks. The control group, included to account for the intrinsic motivation of volunteer participants [63], displayed no significant change in steps/day over time. The conservative intention to treat analysis (baseline carried forward for missing values) produced a mean change in the intervention group of 3,175 steps/day, an increase of 47% above baseline values, a favorable increase compared with other pedometer-based randomized controlled trials	

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS	
Guideline topic: Exercise and CVD risk factors	**Question number: 22/23**
Characteristics of study	

Checklist completed by: Susan Hillier			
Study citation	*Sean Carroll* and *Mike Dudfield*, What is the Relationship Between Exercise and Metabolic Abnormalities? A Review of the Metabolic Syndrome. Sports Med 2004; 34 (6): 371-418		
Study design	**Systematic review (within general review)**	**N (total) 1017**	15 RCT
Search strategy	English language literature search from 1987 to the end of 2002 conducted via MEDLINE (National Library of Medicine, Bethesda, Maryland, USA). Key words used alone or in various combinations for computer searches: physical activity, exercise, lipids and lipoproteins. Pearling and expert working group.		
Selection criteria	RCTs; no evidence of CVD or T2DM' overweight/obese; sedentary; follow-up 12-52 weeks; evidence of dyslipidaemia.		
Intervention	Physical activity interventions and/or Exercise training		
Comparison	Non-exercise group		
Outcomes	Risk factor modification		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		WC	
Description of the methodology used is included		WC	
The literature search was sufficiently rigorous to identify all the relevant studies		C	Only Medline
Study quality was addressed and taken into account?		WC	
There were enough similarities between the studies to justify combining them.		WC	
SECTION 2: Overall assessment of the study			
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
			+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
			- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.

If coded as +, or - what is the likely direction in which bias might affect the study results?	
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**	
Supervised, long-term, moderate to moderately vigorous intensity exercise training, in the absence of therapeutic weight loss, improves the dyslipidaemic profile by raising high density lipoprotein-cholesterol and lowering triglycerides in overweight and obese adults with characteristics of the metabolic syndrome.	

KEY QUESTION(S)	
Q22/23 – hypercholesterolemic men	
COMPLETED BY:	
Jonathan Ucinek	
REFERENCE(S)	
COGHILL, N. & COOPER, A. R. (2008) The effect of a home-based walking program on risk factors for coronary heart disease in hypercholesterolaemic men. A randomized controlled trial. Prev Med, 46, 545-51.	
SOURCE OF FUNDING	
METHOD	
Patient Eligibility Criteria	Participants were middle-aged (45–65 years) male non-smokers, with hypercholesterolaemia defined as TCN6.2mmol/l and/or a TC/HDLC ratio≥6 who were not receiving pharmacological treatment for hypercholesterolaemia or other conditions related to CHD, including both type 1 and 2 diabetes. Participants were sedentary (defined as no regular moderate or vigorous physical activity in excess of 30 min a day on at least five days a week over the last three months) and able to undertake a program of walking.
Study design	RCT
Setting	community
Intervention(s)	Intervention participants were requested to walk briskly for at least 30 min on at least five days out of every seven for a period of 12 weeks Control participants were requested to maintain their current activities of daily living.
Primary outcome measure	TC, HDL-C, LDL-C, TG, glucose and insulin were collected between 7.30 and 10 am,
Additional outcome measures	Blood pressure and resting heart rate
Sample Size	**67**
Main results	**Numbers analysed:67**
	Study duration:12 weeks
	Patients characteristics and group comparability: equal
	Effect size – primary outcome: TC/HDL-C was significantly lower in the intervention group at follow-up (−0.28, 95%CI: −0.52, −0.03, p=0.03).
	Effect size – additional outcomes:

QUALITY CHECK [3]		
Patient selection	**YES/NO**	**Comment**
Were the eligibility criteria specified?	Y	
Was a method of randomisation performed?	Y	
Was the treatment allocation concealed?	N	

Were the groups similar at baseline regarding the most important prognostic indicators?	Y	
Interventions		
Were the index and control interventions explicitly described?	Y	
Was the care provider blinded for the intervention?	Y	
Were co-interventions avoided or comparable?		
Was the compliance acceptable in all groups?	Y	
Was the patient blinded to the intervention?	N	
Outcome measurement		
Was the outcome assessor blinded to the interventions?	Y	
Were the outcome measures relevant?	Y	
Were adverse effects described?	N	
Was the withdrawal/drop-out rate described and acceptable?	Y	
Was a short-term follow-up measurement performed?	Y	
Was a long-term follow-up measurement performed?	N	
Was the timing of the outcome assessment in both groups comparable?	Y	
Statistics		
Was the sample size for each group described?	Y	
Did the analysis include an intention-to-treat analysis?	Y	
Were point estimates and measures or variability presented for the primary outcome measures?	Y	

CLINICAL IMPLICATIONS	
Benefits	Twelve weeks of moderate intensity walking was sufficient to improve TC/HDL-C in hypercholesterolaemic men, primarily through improvement in HDL-C. After controlling for baseline differences, TC/HDL-C was significantly lower in the intervention group at follow-up (−0.28, 95%CI: −0.52, −0.03, p=0.03). An increase in HDL-C (0.07 mmol/l: −0.01, 0.12, p=0.07) and reduction in TG (−0.30 mmol/l: −0.64, 0.03, p=0.07) in intervention participants were of borderline statistical significance. Weight significantly decreased in intervention participants (−1.40 kg: −2.43, −0.38, pb0.01). No other significant between group effects were found. Compliance to the walking program was 97.6%.
Harms	
Comments	
REASON FOR EXCLUSION	
RELEVANCE TO AN AUSTRALIAN CONTEXT	
Relevant to hypercholesterolemic sedentary men in western setting	
OVERALL CONCLUSIONS	
Walking as a physical activity can reduce lipid markers in men at moderate risk	

Template for Intervention Study – Systematic Review
Completed by: Leah Wright
REFERENCE M Hamer and Y Chida. Walking and primary prevention: a meta-analysis of prospective cohort studies. Br J Sports Med 2008;42:238–243. doi:10.1136/bjsm.2007.039974
SOURCE OF FUNDING

SUMMARY		
Inclusion criteria	Types of studies	18 Prospective epidemiological studies
	Participants	459 833 participants free from CVD at baseline with 19 249 cases at follow-up
	Interventions	Walking
	Primary outcome	All-cause mortality; non-fatal CVD
	Additional outcomes	
Search		Medline, Cochrane Database of Systematic Reviews, and Web of Science databases were searched to May 2007.
Methods of review	Method of applying inclusion criteria	Prospective epidemiological studies of walking and CVD and all-cause mortality.
	Assessment of methodological quality	Adhered to the guidelines for reporting metaanalysis of observational studies in epidemiology (MOOSE)
Comparisons		Walking and the risk of cardiovascular disease (CVD) and all-cause mortality in healthy men and women.
Main results		Meta-analysis of the pooled hazard ratio of CVD in the highest walking category compared with the lowest was 0.69, (95% CI 0.61 to 0.77, p,0.001), and 0.68 (0.59 to 0.78, p,0.001) for all-cause mortality. These effects were robust among men and women, although there was evidence of publication biases for the associations with CVD risk. Walking pace was a stronger independent predictor of overall risk compared with walking volume (48% versus 26% risk reductions, respectively). There was also evidence of a dose–response relationship across the highest, intermediate, and lowest

QUALITY CHECK			
Process	**Questions**	**Answer**	**Comment**
Search:	**Are**:		
	two or more databases named and used	Yes	
	reference lists of selected articles searched	No	Not stated
	experts and trialists contacted	No	Not stated
	any journals searched by hand	No	Not stated
	databases searched from their inception	Yes	
	all languages accepted	No	English only
Selection:	**Is there a clear definition of**:		
	the population being studied	Yes	
	the interventions being investigated	Yes	
	the principal outcomes being studied	Yes	
	the study designs included (and excluded)	Yes	
Validity:	**Does the review process**:		
	assess (measure, quantify) the quality of studies identified	Yes	
	blind reviewers to study origin (authors, journal etc)	No	
	abstract data into a structured database	Yes	
	use two independent people to abstract data and assess study quality	Yes	

	measure heterogeneity and bias of studies included	Yes	
Data:	**For each study are the details (or their absence) noted of**:		
	participants included in study (number and type)	Yes	
	interventions studied	Yes	
	outcome	Yes	
Analysis:	**Does the review process**:		
	undertake meta-analysis or state why not done	Yes	
	investigate agreement between independent assessors	Yes	
	give confidence intervals for outcomes reported	Yes	

CLINICAL IMPLICATIONS	
Benefits	Reduced mortality with greater activity
Harms	Non reported
Comments / quality	Good quality review
REASON FOR EXCLUSION (Poor quality +not clinically relevant / interesting or if relevant for preamble) include	
RELEVANCE TO AN AUSTRALIAN CONTEXT relevant	
OVERALL CONCLUSION The results suggest walking is inversely associated with clinical disease endpoints and largely support the current guidelines for physical activity. The mechanisms that mediate this relationship remain largely unknown and should be the focus of future research.	

Template for Intervention Study – Systematic Review		
Completed by: Leah Wright		
H. Löllgen, A. Böckenhoff, G. Knapp. Physical Activity and All-cause Mortality: An Updated Meta-analysis with Different Intensity Categories. Int J Sports Med 2009; 30: 213– 224.		
SOURCE OF FUNDING None stated		
SUMMARY		
Inclusion criteria	Types of studies	38 prospective cohort studies
	Participants	271,000 males and females ranging in age from 20 – 80 years
	Interventions	Regular physical activity on primary prevention – 3 or 4 different intensities
	Primary outcome	All-cause mortality
	Additional outcomes	
Search		Systematic literature search was performed in EMBASE, PUBMED, and MEDLINE data bases
Methods of review	Method of applying inclusion criteria	Prospective cohort studies on physical leisure activity were included with a study duration of at least four years.

	Assessment of methodological quality	Since multivariate-adjusted estimates exclude the eff ect of confounding variables, the main conclusions of the meta-analysis are drawn from pooling multivariate-adjusted relative risk estimates. As sensitivity analyses, we also present the results for pooling age-adjusted estimates.
Comparisons		Mildly, moderately, and highly active activity levels
Main results		There was a significant association of lower all-cause mortality for active individuals compared with sedentary persons. For studies with three activity categories (mildly, moderately, and highly active) and multivariateadjusted models, highly active men had a 22 % lower risk of all-cause mortality (RR = 0.78; 95 % CI: 0.72 to 0.84) compared to mildly active men. For women, the relative risk was 0.69 (95 % CI: 0.53 to 0.90). We observed similar results in moderately active persons compared to mildly active individuals (RR = 0.81 for men and RR = 0.76 for women). This association of activity to all-cause mortality was similar and significant in older subjects.

QUALITY CHECK

Process	**Questions**	**Answer**	**Comment**
Search:	**Are**:		
	two or more databases named and used	Yes	
	reference lists of selected articles searched	Yes	
	experts and trialists contacted	No	
	any journals searched by hand	No	
	databases searched from their inception	No	Update
	all languages accepted	No	English only
Selection:	**Is there a clear definition of**:		
	the population being studied	Yes	
	the interventions being investigated	Yes	
	the principal outcomes being studied	Yes	
	the study designs included (and excluded)	Yes	
Validity:	**Does the review process**:		
	assess (measure, quantify) the quality of studies identified	Yes	
	blind reviewers to study origin (authors, journal etc)	No	
	abstract data into a structured database	Yes	
	use two independent people to abstract data and assess study quality	Yes	
	measure heterogeneity and bias of studies included	Yes	
Data:	**For each study are the details (or their absence) noted of**:		
	participants included in study (number and type)	Yes	
	interventions studied	Yes	
	outcome	Yes	
Analysis:	**Does the review process**:		
	undertake meta-analysis or state why not done	Yes	
	investigate agreement between independent assessors	Yes	

	give confidence intervals for outcomes reported	Yes	

CLINICAL IMPLICATIONS	
Benefits	
Harms	
Comments / quality	
REASON FOR EXCLUSION (Poor quality +not clinically relevant / interesting or if relevant for preamble) include	
RELEVANCE TO AN AUSTRALIAN CONTEXT Relevant	
OVERALL CONCLUSION Regular physical activity over longer time is strongly associated with a reduction in all-cause mortality in active subjects compared to sedentary persons. There is a dose-response curve especially from sedentary subjects to those with mild and moderate exercise with only a minor additional reduction with further increase in activity level.	

KEY QUESTION(S)	
Q22/23	
COMPLETED BY:	
REFERENCE(S)	
Authors: Makrides, Lydia; Dagenais, Gilles R.; Chockalingam, Arun; LeLorier, Jacques; Kishchuk, Natalie; Richard, Josie; Stewart, John; Chin, Christine; Alloul, Karine; Veinot, Paula Source: Clinical Governance: An International Journal, Volume 13, Number 2, 2008 , pp. 95-105(11)	
SOURCE OF FUNDING	
METHOD	
Patient Eligibility Criteria	**Employees were included if they:** Were between 19 and 66 years old Had at least two modifiable coronary risk factors Lived within a 45-minute driving distance from Halifax Were able to take part in a 12-week program Could provide informed consent Could write and understand English **Employees were excluded if they had any of the following:** Unstable cardiovascular disease Any condition that contraindicated exercise testing

	A cardiac pacemaker Resting diastolic blood pressure .115 mmHg or resting systolic blood pressure .200 mmHg Myocardial infarction within the last six months prior to baseline Considerable emotional distress Pregnancy Uncontrolled metabolic or life-threatening disease
Study design	Intervention participants received a 12-week health promotion program involving exercise, education seminars, nutritional analysis and smoking cessation counselling.
Setting	Workplace environment
Intervention(s)	12 week health program
Primary outcome measure	Outcome measures included differences in coronary risk factors of control and intervention participants between baseline and three and six-month follow-up visits.
Additional outcome measures	
Sample Size	566
Main results	Numbers analysed:397
	Study duration:12 weeks
	Patients characteristics and group comparability: =
	Effect size – primary outcome: **Cholesterol (mmol/L)** (mean difference in change at 3months) -0.13 *; (95%)-0.27; (CI) -0.00 (mean difference in change at 6months) -0.12; (95%) -0.26; (CI) 0.03 (Significantly different from control *=p<0.05)
	Effect size – additional outcomes: no change in BP

QUALITY CHECK 3		
Patient selection	YES/NO	Comment
Were the eligibility criteria specified?	Y	
Was a method of randomisation performed?	Y	
Was the treatment allocation concealed?	NA	
Were the groups similar at baseline regarding the most important prognostic indicators?	Y	
Interventions		
Were the index and control interventions explicitly described?	Y	
Was the care provider blinded for the intervention?	NA	
Were co-interventions avoided or comparable?		
Was the compliance acceptable in all groups?	N	

Was the patient blinded to the intervention?	NA	
Outcome measurement		
Was the outcome assessor blinded to the interventions?	NA	
Were the outcome measures relevant?	Y	
Were adverse effects described?	N	
Was the withdrawal/drop-out rate described and acceptable?	N	Drop out rate affected by downsizing by two employers.
Was a short-term follow-up measurement performed?	Y	
Was a long-term follow-up measurement performed?	N	
Was the timing of the outcome assessment in both groups comparable?	Y	
Statistics		
Was the sample size for each group described?	Y	
Did the analysis include an intention-to-treat analysis?	Y	
Were point estimates and measures or variability presented for the primary outcome measures?	Y	

CLINICAL IMPLICATIONS	
Benefits	significant improvements in modifiable coronary risk factors after only a 12-week health promotion program for employee which resulted in reduced cardiac disease and stroke risk
Harms	
Comments	(Requisite sample size not attained) No significant difference in changes to measures of blood pressure
REASON FOR EXCLUSION	
(Requisite sample size not attained)	
RELEVANCE TO AN AUSTRALIAN CONTEXT	
Canadian worker cohort	
OVERALL CONCLUSIONS	
In conclusion, this project demonstrated significant improvements in modifiable coronary risk factors after only a 12-week health promotion program for employees, which resulted in reduced cardiac disease and stroke risk. Health promotion interventions for employees are feasible, and can help reduce modifiable coronary and stroke disease risk factors. However, further studies with larger sample size and longer periods of time for intervention and follow-up are needed for definitive results.	

Template for Intervention Study – Systematic Review
Completed by: Leah Wright
REFERENCE Nocon M, Hiemann T, Müller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. Eur J Cardiovasc Prev Rehabil. 2008 Jun;15(3):239-46.
SOURCE OF FUNDING

SUMMARY		
Inclusion criteria	Types of studies	33 prospective cohort studies
	Participants	883,372 without CVD
	Interventions	Physical activity
	Primary outcome	All-cause and CV mortality
	Additional outcomes	
Search		Medline
Methods of review	Method of applying inclusion criteria	Cohort studies that assessed the primary preventive impact of physical activity on all-cause and cardiovascular mortality
	Assessment of methodological quality	
Comparisons		Risk reductions on the basis of comparison between the least active and the most active population subgroups, with the least active population subgroup as the reference group.
Main results		A total of 33 studies with 883,372 participants were included. Follow-up ranged from 4 years to over 20 years. The majority of studies reported significant risk reductions for physically active participants. Concerning cardiovascular mortality, physical activity was associated with a risk reduction of 35% (95% confidence interval, 30-40%). All-cause mortality was reduced by 33% (95% confidence interval, 28-37%). Studies that used patient questionnaires to assess physical activity reported lower risk reductions than studies that used more objective measures of fitness.

QUALITY CHECK			
Process	**Questions**	**Answer**	**Comment**
Search:	**Are**:		
	two or more databases named and used	N	Medline only
	reference lists of selected articles searched	N	
	experts and trialists contacted	N	
	any journals searched by hand	N	
	databases searched from their inception	N	Not specified but included studies between 1992-2007
	all languages accepted	N	English and German only
Selection:	**Is there a clear definition of**:		
	the population being studied	Y	
	the interventions being investigated	Y	
	the principal outcomes being studied	Y	
	the study designs included (and excluded)	Y	
Validity:	**Does the review process**:		
	assess (measure, quantify) the quality of studies identified	N	
	blind reviewers to study origin (authors, journal etc)	N	
	abstract data into a structured database	N	Not reported
	use two independent people to abstract data and assess study quality	N	
	measure heterogeneity and bias of studies included	Y	

Data:	**For each study are the details (or their absence) noted of**:		
	participants included in study (number and type)	Y	
	interventions studied	Y	
	outcome	Y	
Analysis:	**Does the review process**:		
	undertake meta-analysis or state why not done	Y	
	investigate agreement between independent assessors	N	
	give confidence intervals for outcomes reported	Y	

CLINICAL IMPLICATIONS	
Benefits	Reduction in CVD and all –cause mortality
Harms	Not reported
Comments / quality	Fair quality SR. Cohort studies

REASON FOR EXCLUSION (Poor quality +not clinically relevant / interesting or if relevant for preamble)
Include

RELEVANCE TO AN AUSTRALIAN CONTEXT
yes

OVERALL CONCLUSION
Physical activity is associated with a marked decrease in cardiovascular and all-cause mortality in both men and women, even after adjusting for other relevant risk factors.

Template for Intervention Study – Systematic Review

Completed by: Kelvin Hill

REFERENCE Orozco LJ, Buchleitner AM, Gimenez-Perez G, Roqué i Figuls M, Richter B, Mauricio D. Exercise or exercise and diet for preventing type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No.: CD003054. DOI: 10.1002/14651858.CD003054.pub3

SOURCE OF FUNDING
Internal sources
• Corporacio Parc Taulí, Spain. • Hospital de la Santa Creu i Sant Pau, Spain. • Hopital Universitari Arnau de Vilanova, Spain. • Institut de Recerca Biomèdica de Lleida, Spain.
External sources
• Agència d'Avaluació de Tecnologia i Recerca Mèdiques, Departament de Salut de la Generalitat de Catalunya, Spain. The review was supported by Grant No. 075/23/06

SUMMARY

Inclusion criteria	Types of studies	8 trials that had an exercise plus diet (2241 participants) and a standard recommendation arm (2509 participants). Two studies had a diet only (167 participants) and exercise only arm (178 participants). Study duration ranged from one to six years. Studies were included if they were randomised controlled trials of exercise and diet interventions of at least six month duration and reported diabetes incidence in people at risk for type 2 diabetes
	Participants	People at risk of type 2 diabetes
	Interventions	effects of exercise or exercise and diet for preventing type 2 diabetes mellitus
	Primary outcome	development of type 2 diabetes mellitus (incidence); • diabetes and cardiovascular related morbidity

	Additional outcomes	Cholesterol, BP, QOL, cost, adverse events, development of impaired glucose tolerance, anthropometric measures
Search		The Cochrane Library, MEDLINE, EMBASE, CINAHL, LILACS, SocioFile, databases of ongoing trials and reference lists of relevant reviews
Methods of review	Method of applying inclusion criteria	As per Cochrane (Two authors independently assessed trial quality and extracted data).
	Assessment of methodological quality	As per cochrane
Comparisons		
Main results		Overall, exercise plus diet interventions reduced the risk of diabetes compared with standard recommendations (RR 0.63, 95% CI 0.49 to 0.79). This had also favourable effects on weight and body mass index reduction, waist-to-hip ratio and waist circumference. However, statistical heterogeneity was very high for these outcomes. Exercise and diet interventions had a very modest effect on blood lipids. However, this intervention improved systolic and diastolic blood pressure levels (weighted mean difference -4 mmHg, 95% CI -5 to -2 and -2 mmHg, 95% CI -3 to -1, respectively). No statistical significant effects on diabetes incidence were observed when comparing exercise only interventions either with standard recommendations or with diet only interventions. No study reported relevant data on diabetes and cardiovascular related morbidity, mortality and quality of life.

QUALITY CHECK

Process	**Questions**	**Answer**	**Comment**
Search:	**Are**:		
	two or more databases named and used	Y	
	reference lists of selected articles searched	Y	
	experts and trialists contacted	N	
	any journals searched by hand	N	
	databases searched from their inception	Y	
	all languages accepted	Y	
Selection:	**Is there a clear definition of**:		
	the population being studied	Y	
	the interventions being investigated	Y	
	the principal outcomes being studied	Y	
	the study designs included (and excluded)	Y	
Validity:	**Does the review process**:		
	assess (measure, quantify) the quality of studies identified	Y	
	blind reviewers to study origin (authors, journal etc)	N	
	abstract data into a structured database	Y	
	use two independent people to abstract data and assess study quality	Y	
	measure heterogeneity and bias of studies included	Y	
Data:	**For each study are the details (or their absence) noted of**:		

	participants included in study (number and type)	Y	
	interventions studied	Y	
	outcome	Y	
Analysis:	**Does the review process**:		
	undertake meta-analysis or state why not done	Y	
	investigate agreement between independent assessors	Y	
	give confidence intervals for outcomes reported	Y	

CLINICAL IMPLICATIONS	
Benefits	Prevention of diabetes, reduction in weight, reduction in BP
Harms	Little or no difference
Comments / quality	High quality SR. Surrogate outcomes.
REASON FOR EXCLUSION (Poor quality +not clinically relevant / interesting or if relevant for preamble) Include	
RELEVANCE TO AN AUSTRALIAN CONTEXT Yes	
OVERALL CONCLUSION Benefits of moderate to long term physical activity and diet for several important risk factors.	

KEY QUESTION(S)	
23	
COMPLETED BY:	
Jonathan Ucinek	
REFERENCE(S)	
PAZOKI, R., NABIPOUR, I., SEYEDNEZAMI, N. & IMAMI, S. R. (2007) Effects of a community-based healthy heart program on increasing healthy women's physical activity: a randomized controlled trial guided by Community-based Participatory Research (CBPR). *BMC Public Health,* 7**,** 216.	
SOURCE OF FUNDING	
Not described	
METHOD	
Patient Eligibility Criteria	a community-based and community-driven intervention, in which healthy women were randomly assigned to the intervention and age-matched control groups.
Study design	randomized controlled trial,
Setting	community-based participatory research (CBPR)
Intervention(s)	detailed program material and four easy-to-read booklets consisting material about cardiovascular diseases, risk factors of coronary artery disease, smoking and nutrition for healthy heart were given to them. A program for increasing physical activity (Exercise for Healthy Heart, EHH) was designed to teach women how to incorporate a daily routine of physical activity into their lives in creative and practical ways, based on Choose to Move(CTM) program; an American Heart Association Physical Activity Program for Women [11]. Participants are asked to begin with 10

	minutes per day of moderate-intensity physical activity; women are encouraged to do 30 minutes of physical activity daily. Each participant had a total of eight 1.5-hour face-to-face educational interview sessions with her trainer.
Primary outcome measure	7-Day physical activity recall questionnaire based on the BRFSS; USA/CDC, 2002) and the Countrywide Integrated Non-communicable Diseases Intervention(CINID) program questionnaire
Additional outcome measures	Blood pressure etc
Sample Size	**N=335**
Main results	**Numbers analysed:**
	Study duration: 8 wk
	Patients characteristics and group comparability: =
	Effect size – primary outcome: increased activity levles
	Effect size – additional outcomes: intervention group subjects exhibited a significantly greater decrease in systolic blood pressure (-10.0 mmHg) than the control group women (+2.0. mmHg).

QUALITY CHECK [3]

Patient selection	**YES/NO**	**Comment**
Were the eligibility criteria specified?	y	
Was a method of randomisation performed?	y	
Was the treatment allocation concealed?	n	
Were the groups similar at baseline regarding the most important prognostic indicators?	y	
Interventions		
Were the index and control interventions explicitly described?	N	
Was the care provider blinded for the intervention?	-	
Were co-interventions avoided or comparable?	-	
Was the compliance acceptable in all groups?	Not descr	
Was the patient blinded to the intervention?	Not applic	
Outcome measurement		
Was the outcome assessor blinded to the interventions?	Not descr	
Were the outcome measures relevant?		
Were adverse effects described?	Not descr	
Was the withdrawal/drop-out rate described and acceptable?	Not described	
Was a short-term follow-up measurement performed?	Y	
Was a long-term follow-up measurement performed?	N	
Was the timing of the outcome assessment in both groups comparable?	Y	
Statistics		
Was the sample size for each group described?	Y	
Did the analysis include an intention-to-treat analysis?	Not described	
Were point estimates and measures or variability presented for the primary outcome measures?		

CLINICAL IMPLICATIONS

Benefits	the intervention group subjects exhibited a significantly greater decrease in systolic blood pressure (-10.0 mmHg) than the control group women (+2.0 mmHg)
Harms	nil
Comments	no significant differences between the groups with regard to BMI, WHR, serum sugar and lipid levels, and diastolic blood pressure changes from baseline.

REASON FOR EXCLUSION	
RELEVANCE TO AN AUSTRALIAN CONTEXT	
Women, community setting in Iran	
OVERALL CONCLUSIONS	
Does report a finding of a decrease in Systolic BP in the intervention group, however not enough information is reported about methods, what the control group was.	

KEY QUESTION(S)	
23	
COMPLETED BY:	
Jonathan Ucinek	
REFERENCE(S)	
PEDERSEN, M. T., BLANGSTED, A. K., ANDERSEN, L. L., JORGENSEN, M. B., HANSEN, E. A. & SJOGAARD, G. (2009) The effect of worksite physical activity intervention on physical capacity, health, and productivity: a 1-year randomized controlled trial. J Occup Environ Med, 51, 759-70.	
SOURCE OF FUNDING	
METHOD	
Patient Eligibility Criteria	The participants were office workers recruited from a Danish public administration authority, from 12 offices in geographically different locations 21 Criteria for exclusion were hypertension or cardiovascular diseases, symptomatic disc prolapses or severe disorders of the spine, postoperative conditions in neck and shoulder region, history of severe trauma, and pregnancy.
Study design	cluster randomized controlled trial.
Setting	in the eastern part of Denmark.
Intervention(s)	The interventions were: 1) SRT (specific resistance training), n = 180; 2) APE (all-round physical Exercise), n = 187; and 3) REF (reference intervention), n = 182. Participants in all interventions were allotted 1 hr/wk during working hours for intervention activities.
Primary outcome measure	*systolic blood pressure, body fat percentage, pain, Muscle strength and maximal oxygen uptake*
Additional outcome measures	
Sample Size	549 participants
Main results	**Numbers analysed:**
	Study duration: 1 year
	Patients characteristics and group comparability: yes
	Effect size – primary outcome: *SRT and APE compared with REF showed significant reductions in systolic blood*

	pressure (_6 mm Hg), body fat percentage (_2.2 body fat%), as well as shoulder and back pain (_30% reduction in duration). Muscle strength (APE and SRT) and maximal oxygen uptake (APE) increased approximately 10%.
	Effect size – additional outcomes:

QUALITY CHECK [3]		
Patient selection	**YES/NO**	**Comment**
Were the eligibility criteria specified?	Y	
Was a method of randomisation performed?	Y	
Was the treatment allocation concealed?	NA	Exercise intervention can't conceal
Were the groups similar at baseline regarding the most important prognostic indicators?	Y	
Interventions		
Were the index and control interventions explicitly described?	Y	
Was the care provider blinded for the intervention?	Y	
Were co-interventions avoided or comparable?	NA	
Was the compliance acceptable in all groups?	N	Another limitation is the low compliance rate and high dropout, eg, only 2/3 of the study participants completed the questionnaires at follow-up, resulting in decreased statistical power.
Was the patient blinded to the intervention?	NA	
Outcome measurement		
Was the outcome assessor blinded to the interventions?	Y	
Were the outcome measures relevant?	Y	
Were adverse effects described?	N	
Was the withdrawal/drop-out rate described and acceptable?	N	
Was a short-term follow-up measurement performed?	Y	
Was a long-term follow-up measurement performed?	Y	
Was the timing of the outcome assessment in both groups comparable?	Y	
Statistics		
Was the sample size for each group described?	Y	
Did the analysis include an intention-to-treat analysis?	Y	
Were point estimates and measures or variability presented for the primary outcome measures?	Y	SD presented as error bars in graphs

CLINICAL IMPLICATIONS	
Benefits	SRT and APE resulted in clinically relevant reductions of musculoskeletal pain symptoms and systolic blood pressure at 1 year and body fat percentage at 6 months post intervention.
Harms	Nil reported
Comments	Reports evidence for secondary measures of CVD- systolic bp

REASON FOR EXCLUSION	

RELEVANCE TO AN AUSTRALIAN CONTEXT	
Danish – mixed worker cohort	

OVERALL CONCLUSIONS	

The main finding of the present study was that the worksite physical activity interventions resulted in clinically relevant effects on musculoskeletal pain as well as systolic blood pressure at 1 year, and body fat percentage at 6 months. These positive health related adaptations occurred despite relatively small changes in physical capacity. The first hypothesis—that questionnaire assessment could monitor worksite intervention with increased physical activity—was not confirmed The second hypothesis—that worksite physical activity interventions would have positive effects on physical capacity, self-rated general health, and self-rated productivity—was confirmed for some aspects of physical capacity, but not for self rated general health and productivity The third hypothesis—that SRT, in contrast to APE, reduces the duration of neck as well as shoulder and low back pain—was not confirmed, because not only SRT but also APE decreased duration of pain in the right shoulder in comparison with REF. The fourth hypothesis—that APE, in contrast with SRT, increases maximal oxygen uptake and reduces metabolic syndrome- and cardiovascular disease-related risk factors—was partly confirmed SRT and APE resulted in clinically relevant reductions of musculoskeletal pain symptoms and systolic blood pressure at 1 year and body fat percentage at 6 months post intervention. These positive health related adaptations occurred despite relatively small changes in physical capacity. The IPAQ questionnaire did not allow monitoring the physical activity introduced by the intervention. No significant changes in self rated productivity and general health were noted probably due to high levels at baseline. In the baseline cross-sectional analyses, participants being most intensively physically active had the highest physical capacity and the best self-rated general health.

KEY QUESTION(S)	
23	
COMPLETED BY:	
Jonathan Ucinek	
REFERENCE(S)	
RACETTE, S. B., DEUSINGER, S. S., INMAN, C. L., BURLIS, T. L., HIGHSTEIN, G. R., BUSKIRK, T. D., STEGER-MAY, K. & PETERSON, L. R. (2009) Worksite Opportunities for Wellness (WOW): effects on cardiovascular disease risk factors after 1 year. Prev Med, 49, 108-14.	
SOURCE OF FUNDING	

METHOD	
Patient Eligibility Criteria	Workers across 2 sites in Missouri US (large medical centres)
study design	randomized trial (by site)
Setting	workplace
Intervention(s)	Assessments + intervention versus assessment only
Primary outcome measure	Outcomes included BMI, body composition, blood pressure, fitness, lipids, and Framingham 10-year coronary heart disease risk.
Additional outcome measures	
Sample Size	151
Main results	Numbers analysed: 123
	Study duration: 1 yr
	Patients characteristics and group comparability: =

	Effect size – primary outcome: **Blood Pressure (mmHg):** Systolic - Intervention- 127 (19) bpm (Baseline); 121 (16) bpm(1Year) vs Control – 121 (15) bpm (Baseline); 116 (18) bpm (1Year) p<0.01 Diastolic - Intervention- 84 (11) bpm (Baseline); 77 (9) bpm(1Year) vs Control – 79 (10) bpm (Baseline); 75 (11) bpm (1Year) p<0.01
	Effect size – additional outcomes: **Lipids (mg/dL):** Total Cholesterol: Intervention- 200 (32) (Baseline); 192 (32) (1Year) vs Control – 199 (40) (Baseline); 195 (36) (1Year) p<0.01 HDL-cholesterol: Intervention- 56 (16) (Baseline); 62 (18) (1Year) vs Control – 54 (17) (Baseline); 61 (18) (1Year) p<0.01 LDL-cholesterol: Intervention- 121 (27) (Baseline); 106 (26) (1Year) vs Control – 121 (35) (Baseline); 109 (32) (1Year) p<0.01 Triglycerides: Intervention- 116 (62) (Baseline); 118 (60) (1Year) vs Control – 115 (59) (Baseline); 122 (63) (1Year) p<0.29 Total cholesterol: HDL ratio: Intervention- 3.9 (1.1) (Baseline); 3.3 (1.0) (1Year) vs Control – 3.9 (1.2) (Baseline); 3.4 (1.0) (1Year) p<0.01

QUALITY CHECK [3]		
Patient selection	YES/NO	Comment
Were the eligibility criteria specified?	Y	
Was a method of randomisation performed?	Y	
Was the treatment allocation concealed?	N	
Were the groups similar at baseline regarding the most important prognostic indicators?	Y	
Interventions		
Were the index and control interventions explicitly described?	Y	
Was the care provider blinded for the intervention?	N	
Were co-interventions avoided or comparable?		Not Described
Was the compliance acceptable in all groups?	Y	
Was the patient blinded to the intervention?	N	NA
Outcome measurement		
Was the outcome assessor blinded to the interventions?	N	Not Described
Were the outcome measures relevant?	Y	
Were adverse effects described?	Y	No adverse effects
Was the withdrawal/drop-out rate described and acceptable?	Y	
Was a short-term follow-up measurement performed?	Y	We
Was a long-term follow-up measurement performed?	Y	For 1 yr
Was the timing of the outcome assessment in both groups comparable?	Y	
Statistics		
Was the sample size for each group described?	Y	
Did the analysis include an intention-to-treat analysis?	N	
Were point estimates and measures or variability presented for the primary outcome measures?	Y	

CLINICAL IMPLICATIONS	
Benefits	A multi-faceted worksite intervention promoted favorable changes in cardiovascular disease risk factors, but many of the improvements were achieved with worksite health assessments and personalized health reports in the absence of an intervention
Harms	NA
Comments	

REASON FOR EXCLUSION	
RELEVANCE TO AN AUSTRALIAN CONTEXT	
Evidence for implementation of well being programs in work place having positive effect on BP and lipids	
OVERALL CONCLUSIONS	
A multi-faceted worksite intervention promoted favorable changes in cardiovascular disease risk factors, but many of the improvements were achieved with worksite health assessments and personalized health reports in the absence of an intervention	

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Obesity, diet and nutrition		**Question number:**	
Characteristics of study			
Checklist completed by: Jonathan Ucinek			
Study citation	SHAW, K., GENNAT, H., O'ROURKE, P. & DEL MAR, C. (2006) Exercise for overweight or obesity. *Cochrane Database Syst Rev*, CD003817.		
Study design	**Systematic review**	**N (total)**	43 studies included 3476 participants
Search strategy	Use the following sources for the identification of trials: • *The Cochrane Library;* • MEDLINE (until 2005); • SPORT Discus (until 2005); • EMBASE (until 2005). Also searched databases of ongoing trials: Current Controlled Trials (www.controlled-trials.com - with links to other databases of ongoing trials). The reference lists of review articles and of all included studies were searched in order to find other potentially eligible studies. Potential missing, unpublished or ongoing studies were planned to be sought by contacting experts in the field. This was not necessary. Publications in all languages were sought.		
Selection criteria	All randomised controlled clinical trials of exercise in people with overweight or obesity, with a duration of at least three months and loss to follow-up of less than 15%, were considered for inclusion. Studies were included if they were randomised controlled trials that examined body weight change using one or more physical activity intervention in adults with overweight or obesity at baseline and loss to follow-up of participants of less than 15%.		
Intervention	The studies included had an exercise prescription. Exercise is defined as any form of physical activity performed on a repeated basis for a defined period of time (exercise training). Exercise prescriptions include specific recommendations for the type, intensity, frequency and duration of any physical activity with a specific objective (e.g. increase fitness, lose weight) (Bouchard 1994). Studies stating that they simply recommended increasing physical activity were not included within the analyses unless it was possible to quantify the exercise stimulus by some means. Studies that combined exercise and medication associated with weight loss as an intervention were excluded.		
Comparison	Exercise versus No treatment; High versus low intensity exercise; High versus low intensity exercise with dietary change; Exercise versus diet; Exercise and diet versus diet alone		
Outcomes	**Primary outcomes** • weight or another indicator of body mass (e.g. body mass index, waist measurement, waist-to-hip ratio);		

	• morbidity and mortality; • well-being and quality of life. **Secondary outcomes** • serum lipids; • serum glucose; • systolic and diastolic blood pressure; • adverse effects. We planned on examining the following effect modifiers if there were sufficient data: sex, age, adherence to treatment, initial weight and co-morbidities

Quality of study		
Quality criteria (from SIGN)	***Met?**	**Comments**
SECTION 1: Internal validity		
Study addresses an appropriate and clearly focused question	WC	To assess exercise as a means of achieving weight loss in people with overweight or obesity, using randomised controlled clinical trials.
Description of the methodology used is included	WC	
The literature search was sufficiently rigorous to identify all the relevant studies	WC	
Study quality was addressed and taken into account?	WC	
There were enough similarities between the studies to justify combining them.		
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		

SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**

When compared with no treatment, exercise resulted in small weight losses across studies.
Exercise combined with diet resulted in a greater weight reduction than diet alone (WMD - 1.0 kg; 95% confidence interval (CI) -1.3 to -0.7).
Increasing exercise intensity increased the magnitude of weight loss (WMD -1.5 kg; 95% CI -2.3 to -0.7).

There were significant differences in other outcome measures such as serum lipids, blood pressure and fasting plasma glucose.
Exercise as a sole weight loss intervention resulted in significant reductions in diastolic blood pressure (WMD -2 mmHg; 95% CI -4 to -1), triglycerides (WMD - 0.2 mmol/L; 95% CI -0.3 to -0.1) and fasting glucose (WMD - 0.2 mmol/L; 95% CI -0.3 to -0.1).
Higher intensity exercise resulted in greater reduction in fasting serum glucose than lower intensity exercise (WMD - 0.3 mmol/L; 95% CI -0.5 to -0.2).
No data were identified on adverse events, quality of life, morbidity, costs or on mortality.

The results of this review support the use of exercise as a weight loss intervention, particularly when combined with dietary change.

This systematic review provides evidence that Exercise is associated with improved cardiovascular disease risk factors even if no weight is lost, however it is unable to provide evidence that exercise decreases cardiovascular disease endpoints due to the lack of long term follow up in studies. Therefore any benefit on CVD endpoints can only be assumed to be a follow on based upon improvements in other markers.

However, the effect of exercise on disease endpoints such as myocardial infarction, cerebrovascular accident and type 2 diabetes could not be demonstrated.

KEY QUESTION(S)		
23		
COMPLETED BY:		
Kelvin		
REFERENCE		
Shiroma EJ; Lee IM. Physical Activity and Cardiovascular Health. Lessons Learned From Epidemiological Studies Across Age, Gender, and Race/Ethnicity. Circulation. *2010;122:743-752*		
SOURCE OF FUNDING		
Not stated		
SUMMARY		
Inclusion criteria	Types of studies	Prospective cohort studies
	Participants	All including CVD
	Interventions	Physical activity
	Primary outcome	CHD and CVD
	Additional outcomes	
Search		Based on previous (2008) USA guidelines with extensive SR
Methods of review	Method of applying inclusion criteria	Not described
	Assessment of methodological quality	Not stated
Comparisons		Increased PA v lest active group
Main results		30 studies between 1995-2007 for CHD, 20 studies for CVD. Four additional studies after 2008. "most active men and women had median risk reductions of ~30% to 35% for developing CHD. The amount of physical activity currently recommended, at least 150 min/wk of moderate-intensity aerobic physical activity or 75 min/wk of vigorous-intensity aerobic physical activity, is clearly associated with reduced risk... With regard to CVD, a similar picture was observed in data from prospective cohort studies". Subsequent studies were also similar 20-50% reduction in events. "median or mean ages of subjects primarily in the range of 45 to 60 years. The median or mean ages of subjects at baseline exceeded 60 years in only 8 studies" (most 60-69yo). Subsequent trials confirm benefits irrespective of age.

	Greater mean risk reduction in women ~40% rather than men ~30% but this may be due to different intensities, studies etc. Rather than a gender difference.
QUALITY CHECK	

Process	**Questions**	**Answer**	**Comment**
Search:	**Are**:		
	two or more databases named and used	Unsure	
	reference lists of selected articles searched	Unsure	
	experts and trialists contacted	Unsure	
	any journals searched by hand	unsure	
	databases searched from their inception	No	2008 searched subsequent to 1995 –previous guidelines
	all languages accepted	unsure	
Selection:	**Is there a clear definition of**:		
	the population being studied	All	
	the interventions being investigated	Yes	
	the principal outcomes being studied	Yes	
	the study designs included (and excluded)	Yes	Only prospective cohorts as RCTs not available
Validity:	**Does the review process**:		
	assess (measure, quantify) the quality of studies identified	No	
	blind reviewers to study origin (authors, journal etc)	No	
	abstract data into a structured database	No	
	use two independent people to abstract data and assess study quality	No	
	measure heterogeneity and bias of studies included	Unsure	
Data:	**For each study are the details (or their absence) noted of**:		
	participants included in study (number and type)	No	
	interventions studied	No	
	outcome	no	
Analysis:	**Does the review process**:		
	undertake meta-analysis or state why not done	No	
	investigate agreement between independent assessors	No	
	give confidence intervals for outcomes reported	some	

CLINICAL IMPLICATIONS	
Benefits	Significant, consistent benefit of PA comparing increased levels to lowest levels in the order of 30-40% risk reduction for CHD and CVD.
Harms	Not disucssed
Comments (ischeamic v heamorraghic, quality issues etc.)	Narrative review based on previous systematic review for a guideline.
REASON FOR EXCLUSION (Poor quality +not clinically relevant /	

interesting or if relevant for preamble)
RELEVANCE TO AN AUSTRALIAN CONTEXT (Urban and rural / non urban settings)
yes
OVERALL CONCLUSION
Describes clear benefits of PA for CVD reduction. Unclear if the studies described include primary/secondary prevention.

Template for Intervention Study – Systematic Review		
Completed by: Kelvin Hill		
REFERENCE Thomas DE, Elliott EJ, Naughton GA. Exercise for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2006; 3: CD002968.		
SOURCE OF FUNDING		
SUMMARY		
Inclusion criteria	Types of studies	14 RCTs (n=377). All randomised controlled trials comparing any type of well-documented aerobic, fitness or progressive resistance training exercise with no exercise in people with type 2 diabetes mellitus.
	Participants	People with type 2 diabetes
	Interventions	Physical activity
	Primary outcome	Glycaemic control, body mass, fat, adverse events
	Additional outcomes	Cholesterol, insulin sensitivity,
Search		Trials were identified through the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and manual searches of bibliographies. Date of last search was March 3, 2005. Study authors were contacted for additional information.
Methods of review	Method of applying inclusion criteria	Two authors independently selected trials, assessed trial quality and extracted data.
	Assessment of methodological quality	As per normal Cochrane review
Comparisons		Control
Main results		Trials ranged from eight weeks to twelve months duration. Compared with the control, the exercise intervention significantly improved glycaemic control as indicated by a decrease in glycated haemoglobin levels of 0.6% (-0.6 % HbA(1c), 95% confidence interval (CI) -0.9 to -0.3; P < 0.05). This result is both statistically and clinically significant. There was no significant difference between groups in whole body mass, probably due to an increase in fat free mass (muscle) with exercise, as reported in one trial (6.3 kg, 95% CI 0.0 to 12.6). There was a reduction in visceral adipose tissue with exercise (-45.5 cm(2), 95% CI -63.8 to -27.3), and subcutaneous adipose tissue also decreased. No study reported adverse effects in the exercise group or diabetic complications. The exercise intervention significantly increased insulin response (131 AUC, 95% CI 20 to 242) (one trial), and decreased plasma triglycerides (-0.25 mmol/L, 95% CI -0.48 to -0.02). No significant difference was found between groups in quality of life (one trial), plasma cholesterol or blood pressure.
QUALITY CHECK		

Process	Questions	Answer	Comment
Search:	**Are**:		
	two or more databases named and used	Y	
	reference lists of selected articles searched	Y	
	experts and trialists contacted	Y	
	any journals searched by hand	N	
	databases searched from their inception	Y	
	all languages accepted	Y	
Selection:	**Is there a clear definition of**:		
	the population being studied	Y	
	the interventions being investigated	Y	
	the principal outcomes being studied	Y	
	the study designs included (and excluded)	Y	
Validity:	**Does the review process**:		
	assess (measure, quantify) the quality of studies identified	Y	
	blind reviewers to study origin (authors, journal etc)	N	
	abstract data into a structured database	Y	
	use two independent people to abstract data and assess study quality	Y	
	measure heterogeneity and bias of studies included	Y	
Data:	**For each study are the details (or their absence) noted of**:		
	participants included in study (number and type)	Y	
	interventions studied	Y	
	outcome	Y	
Analysis:	**Does the review process**:		
	undertake meta-analysis or state why not done	Y	
	investigate agreement between independent assessors	Y	
	give confidence intervals for outcomes reported	Y	

CLINICAL IMPLICATIONS	
Benefits	Improved glyceamic control
Harms	Non found/reported
Comments / quality	High quality SR. Small trials with surrogate outcomes.

REASON FOR EXCLUSION (Poor quality +not clinically relevant / interesting or if relevant for preamble)
Include

RELEVANCE TO AN AUSTRALIAN CONTEXT
Yes

OVERALL CONCLUSION
Physical activity is associated with improved glyceamic control. No adverse events found. No difference for cholesterol and BP measures although studies were often short.

KEY QUESTION(S)	
23 (T2D subgroup)	
COMPLETED BY:	
Jonathan ucinek	
REFERENCE(S)	
TUDOR-LOCKE, C., BELL, R. C., MYERS, A. M., HARRIS, S. B., ECCLESTONE, N. A., LAUZON, N. & RODGER, N. W. (2004) Controlled outcome evaluation of the First Step Program: a daily physical activity intervention for individuals with type II diabetes. Int J Obes Relat Metab Disord, 28, 113-9.	
SOURCE OF FUNDING	
METHOD	
Patient Eligibility Criteria	(1) aged 40–60 y; (2) minimum 3 months post diagnosis of type II diabetes; (3) treated by diet alone or by oral hypoglycaemic medications (not insulin); (4) no PA limitations or documented heart conditions; (5) not currently in an exercise program; and (6) <8800 steps/day
Study design	RCT
Setting	Community setting - Participants were recruited from a diabetes education centre (the Lawson Diabetes Centre in London, Ontario)
Intervention(s)	Physical activity intervention: The First Step Program (FSP) (pedometers and goal setting)
Primary outcome measure	daily PA assessed by pedometer (steps/day).
Additional outcome measures	anthropometric measures (weight, BMI, waist girth, hip girth); indicators of cardiovascular health (resting heart rate and blood pressure); glycemic control (fasting glucose, insulin, HbA1c, glucose concentration 120 min post glucose load); plasma lipid status (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides).
Sample Size	**60**
Main results	**Numbers analysed:47**
	Study duration: 24 weeks (12 week intervention)
	Patients characteristics and group comparability: =
	Effect size – primary outcome: Relative to the CONTROL group, FSP participants increased their PA 43000 steps/day (approximately 30 min/day) during the intervention (P<0.0001).
	Effect size – additional outcomes: no significant differences

QUALITY CHECK [3]		
Patient selection	**YES/NO**	**Comment**
Were the eligibility criteria specified?	Y	
Was a method of randomisation performed?	Y	Not described
Was the treatment allocation concealed?	N	
Were the groups similar at baseline regarding the most important prognostic indicators?	N	Not described
Interventions		
Were the index and control interventions explicitly described?	Y	
Was the care provider blinded for the intervention?	N	
Were co-interventions avoided or comparable?	N	
Was the compliance acceptable in all groups?	Y	
Was the patient blinded to the intervention?	N	
Outcome measurement		
Was the outcome assessor blinded to the interventions?	N	
Were the outcome measures relevant?		
Were adverse effects described?	N	

Was the withdrawal/drop-out rate described and acceptable?	Y	
Was a short-term follow-up measurement performed?	Y	
Was a long-term follow-up measurement performed?		
Was the timing of the outcome assessment in both groups comparable?	Y	
Statistics		
Was the sample size for each group described?	Y	
Did the analysis include an intention-to-treat analysis?	N	
Were point estimates and measures or variability presented for the primary outcome measures?	Y	

CLINICAL IMPLICATIONS	
Benefits	Relative to the CONTROL group, FSP participants increased their PA 43000 steps/day (approximately 30 min/day) during the intervention (P<0.0001). Waist and hip girth decreased (approximately 2–3 cm), **but did not differ significantly** between groups. No significant changes for other variables
Harms	Nil reported
Comments	

REASON FOR EXCLUSION
RELEVANCE TO AN AUSTRALIAN CONTEXT
North American cohort of T2D recent diagnoses
OVERALL CONCLUSIONS
Relative to the CONTROL group, FSP participants increased their PA 43000 steps/day (approximately 30 min/day) during the intervention (P<0.0001). Waist and hip girth decreased (approximately 2–3 cm), but did not differ significantly between groups. **Significant changes did not emerge for any of the other variables.**

KEY QUESTION(S)
23
COMPLETED BY:
Kelvin
REFERENCE
Woodcock et al. Non-vigorous physical activity and all-cause mortality: systematic review and meta-analysis of cohort studies. International Journal of Epidemiology 2010;1–18
SOURCE OF FUNDING
Not stated
SUMMARY

Inclusion criteria	Types of studies	Inclusion criteria were: (i) prospective cohort study in a healthy/general population with more than 10 000 people at baseline; (ii) measure of light or moderate physical activity (either in terms of duration, frequency, distance or a combination); and (iii) association with all-cause mortality. We excluded studies that only measured work-related activity. We only included studies of physical activity and not physical fitness. We included only those studies that compared more than two exposure levels.
	Participants	All including CVD
	Interventions	Physical activity

	Primary outcome	All-cause mortality
	Additional outcomes	
Search		We searched Medline, Embase, Cochrane (DARE), Web of Science and Global Health (in July 2008 and then an update in June 2009) for cohort studies. No time-period restrictions were included. Key words used in Medline included, 'physical activity', 'bicycling', 'walking', 'exercise', 'active travel', 'active commuting', 'active transport', in combination with 'mortality', 'life expectancy' and 'death' (see 'Online Appendix: Search strategy' available as Supplementary data at IJE online). MeSH headings included, 'Exercise', 'Exercise Therapy', 'Physical Fitness' and 'Exertion'. We searched the reference lists of included studies and other systematic reviews. We also contacted authors of all studies with over 10 000 participants identified as on February 2009 for unpublished studies.. No language restrictions were employed.
Methods of review	Method of applying inclusion criteria	assessed by two independent reviewers and any disagreements were resolved by discussion and mutual agreement
	Assessment of methodological quality	Newcastle Ottawa Scale.
Comparisons		Increased PA v lest active group
Main results		22 studies that met inclusion criteria, containing 977 925 (334 738 men and 643 187 women) people. There was considerable variation between the studies. Authors found that 2.5 h/week (equivalent to 30 min daily of moderate intensity activity on 5 days a week) compared with no activity was associated with a reduction in mortality risk of 19% [95% confidence interval (CI) 15–24], while 7 h/week of moderate activity compared with no activity reduced the mortality risk by 24% (95% CI 19–29). There was a smaller effect in studies that looked at walking alone.
QUALITY CHECK		

Process	**Questions**	**Answer**	**Comment**
Search:	**Are**:		
	two or more databases named and used	yes	
	reference lists of selected articles searched	yes	
	experts and trialists contacted	yes	
	any journals searched by hand	unsure	
	databases searched from their inception	yes	
	all languages accepted	yes	
Selection:	**Is there a clear definition of**:		
	the population being studied	All	
	the interventions being investigated	Yes	
	the principal outcomes being studied	Yes	
	the study designs included (and excluded)	Yes	Only prospective cohorts as RCTs not available
Validity:	**Does the review process**:		
	assess (measure, quantify) the quality of studies identified	yes	
	blind reviewers to study origin (authors, journal etc)	unsure	
	abstract data into a structured database	yes	
	use two independent people to abstract data and assess study quality	yes	
	measure heterogeneity and bias of studies included	yes	
Data:	**For each study are the details (or their absence) noted of**:		
	participants included in study (number and type)	yes	

	interventions studied	yes	
	outcome	yes	
Analysis:	**Does the review process**:		
	undertake meta-analysis or state why not done	yes	
	investigate agreement between independent assessors	yes	
	give confidence intervals for outcomes reported	yes	

CLINICAL IMPLICATIONS	
Benefits	3.5 hours/week of moderate activity resulted in 19% reduction in all cause mortality. 1hour per day (7hrs/wk) produced 24% reduction.
Harms	Not disucssed
Comments (ischeamic v heamorraghic, quality issues etc.)	
REASON FOR EXCLUSION (Poor quality +not clinically relevant / interesting or if relevant for preamble)	
Overall good quality systematic review of highest available literature (prospective cohort studies).	
RELEVANCE TO AN AUSTRALIAN CONTEXT (Urban and rural / non urban settings)	
yes	
OVERALL CONCLUSION	
Describes clear benefits of PA for reducing all cause mortality. Unclear if the studies described include primary/secondary prevention.	

Subgroup evidence:

a. Those deemed clinically high risk as outlined in the assessment guidelines (those with SBP >180 or DBP>110mmHg, diabetes >60yrs, diabetes with microalbuminuria, CKD [see levels below], familial hypercholesterolaemia, cholesterol >7.5mmol/L)

b. Those with atrial fibrillation

No specific literature identified

c. High, medium and low absolute risk of CVD

No specific literature identified

d. Abnormal BP and normal BP

No specific literature identified

e. Hypercholesterol and normal cholesterol

Coghill 2008 (RCT) reported twelve weeks of moderate intensity walking was sufficient to improve TC/HDL-C in hypercholesterolaemic men, primarily through improvement in HDL-C.

f. Diabetes and no diabetes

Tudor-Locke 2004 (RCT) reported a PA intervention program (pedometer and goal setting) increased PA (steps/day) compared to control but found no other changes in risk factors for people with T2D.

Thomas 2006 (Cochrane SR) reported that exercise significantly improves glycaemic control and reduces visceral adipose tissue and plasma triglycerides, but not plasma cholesterol, in people with type 2 diabetes, even without weight loss.

g. Chronic kidney disease and no chronic kidney disease (break down into GFR <45 ml/min, GFR 45-60 ml/min and GFR >60 ml/min)

N

FORM framework Question 22 & 23

Key question(s) –considered together due to overlap: Q 22. Is there evidence that physical activity reduces CVD events and all cause mortality?

Q 23. What is the evidence for physical activity type and dose or any combination of type/doses being more effective than any other physical activity type and dose or combination for the reduction of CVD events and all cause mortality? Report evidence for secondary outcomes: Blood pressure; Lipid parameters

1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*

Q22: Two systematic reviews (one high quality [Woodcock 2010], one fair quality [Shiroma 2010] both including >20 cohort studies) found that physical activity reduces CVD events and all cause mortality. Q23: Non-vigorous activity found to reduce mortality (Woodcock 2010) as does more vigorous activity (Shiroma 2010). Additional evidence for favourable effects on secondary outcomes of blood pressure and lipid parameters: 3 high quality systematic reviews: • Carroll 2004 • Shaw 2006 • Orozco 2008. 7 fair to good quality RCTs: Aldana 2005, Barker 2008, Makrides 2008, Pal 2009, Pazoki 2007, Pedersen 2009, Racette 2009. Various interventions and settings.	A	**One or more level I studies with a low risk of bias or several level II studies with a low risk of bias**
	B	**One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias**
	C	**One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias**
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**

2. Consistency *(if only one study was available, rank this component as 'not applicable')*

Q22. Almost all studies consistent. Q 23: The studies report a combination of reduction in risk factors – lipid or blood pressure or sometimes both. The inconsistency is probably explained by the heterogeneity of PA interventions. There is no one intervention that presents as more effective than the other.	A	**All studies consistent**
	B	**Most studies consistent and inconsistency can be explained**
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
	NA	**Not applicable (one study only)**

3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*

Q22: 20-30% reductions in mortality and CVD events based on prospective cohort studies. (substantial impact) with 3.5hours/week of moderate activity or less with high intensity Q23:The changes in risk factors appear moderate – the expert working group may need to consider this further. (Moderate impact)	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*

Most RCTs are workbased targeting middle age. Cohort studies covers all ages.	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**

	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*

	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Evidence for link between exercise and CVD is based on cohort studies. Intervention (RCT) studies demonstrate effects for CVD risk factors but not for CVD events.

EVIDENCE STATEMENT MATRIX

Component	Rating	Description
1.Evidence base	B	
2.Consistency	B	
3.Clinical impact	C	
4. Generalisability	B	
5. Applicability	A	

Evidence statement

Strong observation evidence to support physical activity being associated with a reduction in CVD events and all cause mortality.

There is good evidence to support the promotion of increased physical activity to reduce risk factors including blood pressure and lipid parameters. It is not clear which method to promote physical activity is best, nor to what level physical activity should be increased – this strongly suggests that methods to increase PA, and target levels, will be variable depending on the target population. Moderate activity found to reduce CVD in cohort studies at approximate levels of 30mins on all days of the week. More intense exercise can achieve reduced risk in slighty shorter times.

RECOMMENDATION	**GRADE OF RECOMMENDATION**	Grade B

All adults should be advised to participate in at least 30 minutes of moderate activity on most, or preferably every day of the week.

UNRESOLVED ISSUES	
IMPLEMENTATION OF RECOMMENDATION	
Will this recommendation result in changes in usual care?	**NO**
Are there any resource implications associated with implementing this recommendation?	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**NO**

11.Alcohol consumption (Q24)

Search results

Sources	Dates	Total hits	Retrieval list	Final inclusions
Databases Medline; Embase ; Cinahl; PsychINFO Cochrane Library, including CENTRAL Cochrane Controlled Trial Register (CCTR) **Other sources:** pearling; expert working group.	**2002-2010**	**139**	**76**	**13** Bagnardi 2008 Burger 2004 Conen 2008 Corrao 2004 Di Castelnuovo 2006 Djousse 2009 Howard 2004 Johson 2008 Koppes 2006 Malinski 2004 Sierksma 2004a Sierksma 2004b Taylor 2006
Search terms:	Alcohol Drinking; Alcohol drinking quantity; Alcohol drinking pattern ALCOHOLIC BEVERAGES; BEER; WINE; alcohol; spirits			

Literature identified

Question 24. What is the evidence that the patterns and levels of alcohol consumption alter CVD events and all cause mortality? Report evidence for secondary outcomes: Blood pressure; Lipid parameters	
References	**Comments / quality**
Bagnardi V, Zatonski W, Scotti L, La Vecchia C and Corrago G. *Does drinking pattern modify the effect of alcohol on the risk of coronary heart disease? Evidence from a met-analysis*. J Epidemiol Community Health 2008 62:615-9	Moderate quality SR. Low number of studies leads to significant risk of bias.
Burger M, Bronstrup A and Pietrzik K. *Derivation of tolerable upper alcohol intake levels in Germany: a systematic review of risks and benefits of moderate alcohol consumption.* Prev Med 2004 39: 111-127	Moderate quality SR. German focus. CHD outcomes rather than CVD
CONEN, D., TEDROW, U. B., COOK, N. R., MOORTHY, M. V., BURING, J. E. & ALBERT, C. M. (2008) Alcohol consumption and risk of incident atrial fibrillation in women. JAMA, 300, 2489-96.	Fair quality RCT. Part of Women's Health study
Corrao G, Bagnardi V, Zambon A, La Vecchia C: *A metaanalysis of alcohol consumption and the risk of 15 diseases*. Prev	High quality SR.

Med 2004, 38:613–619.	
DI CASTELNUOVO, A., COSTANZO, S., BAGNARDI, V., DONATI, M. B., IACOVIELLO, L. & DE GAETANO, G. (2006) *Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies*. Arch Intern Med, 166, 2437-45.	Good quality SR.
DJOUSSE, L., LEE, I. M., BURING, J. E. & GAZIANO, J. M. (2009) *Alcohol consumption and risk of cardiovascular disease and death in women: potential mediating mechanisms*. Circulation, 120, 237-44.	Fair quality RCT. Part of Women's Health study
Johson et al (2008) Improvement of physical health and quality of life of alcohol-dependent individuals with topiramate treatment: US multisite randomized controlled trial. *Archives of Internal Medicine. 168(11); 1188-1199*	Good quality RCT.
Sierksma et al (2004) Effect of moderate alcohol consumption on plasma dehydroepiandrosterone sulfate, testosterone, and estradiol levels in middle-aged men and postmenopausal women: A diet-controlled intervention study. *Alcoholism: Clinical and Experimental Research. 28(5)(pp 780-785),*	Moderate quality RCT. No CVD outcomes
Sierksma et al (2004) Effect of Moderate Alcohol Consumption on Parameters of Reverse Cholesterol Transport in Postmenopausal Women. *Alcoholism: Clinical and Experimental Research. 28(4); 662-666*	Fair quality RCT. Secondary outcomes only
TAYLOR, B. & REHM, J. (2006) When risk factors combine: the interaction between alcohol and smoking for aerodigestive cancer, coronary heart disease, and traffic and fire injury. Addict Behav, 31, 1522-35.	Moderate quality SR. One trial only related to CHD with inconclusive results. Combined alcohol and smoking.
References - Diabetes	
Howard et al (2004) *Effect of Alcohol Consumption on Diabetes Mellitus: A Systematic Review.* Annals of Internal Medicine. 140(3)(pp 211-219+I72	Good quality SR. Outcome measures focused on diabetes rather than CVD
Koppes et al (2006) *Meta-analysis of the relationship between alcohol consumption and coronary heart disease and mortality in type 2 diabetic patients* Diabetologia. 49(4)(pp 648-652), 2006	

Evidence details

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Alcohol		**Question number: 24**	
Characteristics of study			
Checklist completed by:			
Study citation	BAGNARDI, V., ZATONSKI, W., SCOTTI, L., LA VECCHIA, C. & CORRAO, G. (2008) Does drinking pattern modify the effect of alcohol on the risk of coronary heart disease? Evidence from a meta-analysis. J Epidemiol Community Health, 62, 615-9.		
Study design	**Meta analysis of observational studies**	**N (total)**	Six (4 cohort and 2 case–control)
Search strategy	Medline search from 1966 up to and including 2006, supplemented by attention to all references in the articles recovered through Medline and in several relevant reviews and meta-analyses published on this subject.		

Selection criteria	First, the study had to be published as an original article. This implied that only cohort and case–control studies were included and that abstracts, letters, editorials, reviews and meta-analyses were not eligible. Second, the study reported sufficient data to perform statistical analyses. Hence the reported findings (i) had to be expressed as relative risk (RR, odds ratio or hazard ratio), considering either different combinations of quantity and frequency of alcohol intake (eg, grams of alcohol per day, stratified according to number of days of consumption) or directly defining the drinking pattern (eg, binge drinking, heavy irregular drinking or heavy regular drinking) as exposure categories; (ii) had to report precision of RR (expressed as variance, standard error or confidence interval), or the absolute number of cases and noncases for each exposure category; (iii) considered abstainers as reference category, or at least reported data allowing to recalculate RRs with respect to abstainers. Moreover, studies reporting intake only during the day preceding the onset of coronary heart events were excluded. In fact, although a high current consumption might be considered as a proxy of binge drinking, we did not consider this definition to be satisfactory.
Intervention	alcohol consumption
Comparison	
Outcomes	effect modifier of alcohol intake on the risk of coronary heart disease (CHD).

Quality of study

Quality criteria (from SIGN)	***Met?**	**Comments**
SECTION 1: Internal validity		
Study addresses an appropriate and clearly focused question	Y	
Description of the methodology used is included	Y	
The literature search was sufficiently rigorous to identify all the relevant studies	Y	
Study quality was addressed and taken into account?	N	Not described
There were enough similarities between the studies to justify combining them.	N	
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
	+	+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?	Reporting bias	

SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**

This meta-analysis suggests that binge and heavy irregular drinking modify the favourable effect of alcohol intake on the CHD risk. However, this conclusion should be taken with caution because of the small number of studies considered.

This meta-analysis, including most published information on alcohol drinking pattern and CHD, offers evidence that drinking pattern modifies the action of alcohol intake on the CHD risk. In particular, the well-established protective effect of alcohol on CHD risk is confirmed for regular drinkers, even with heavy amounts of alcohol intake. Conversely, compared with abstainers, binge and heavy irregular drinkers are at increased risk of CHD.
Compared with those who abstained from alcohol, regular heavy drinkers and heavy irregular or binge drinkers showed significantly different pooled relative risks for CHD of 0.75 (95% confidence interval 0.64 to 0.89) and 1.10 (1.03 to 1.17) respectively.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS

Guideline topic: alcohol			**Question number: 24**
Characteristics of study			
Checklist completed by: Jonathan Ucinek			
Study citation	BURGER, M., BRONSTRUP, A. & PIETRZIK, K. (2004) Derivation of tolerable upper alcohol intake levels in Germany: a systematic review of risks and benefits of moderate alcohol consumption. *Prev Med,* 39**,** 111-27.		
Study design	**Systematic review**	**N (total)**	18 studies have been included to evaluate the risk association of alcohol consumption for CHD
Search strategy	Studies published from 1988 to 1999. In cohort studies, publications from 1985 on have been included.		
Selection criteria	Studies on participants of African or Asian origin have been excluded because of ethnic differences in alcohol metabolism that may have affected alcohol risk assessment.		
Intervention	Alcohol		
Comparison	Level of intake		
Outcomes	Risk of CVD etc		

Quality of study		
Quality criteria (from SIGN)	***Met?**	**Comments**
SECTION 1: Internal validity		
Study addresses an appropriate and clearly focused question	Y	The objective of this study is to weigh the risks of moderate alcohol consumption against its benefits and, as a result, to derive tolerable upper alcohol intake levels (TUALs) for the German adult population
Description of the methodology used is included	Y	
The literature search was sufficiently rigorous to identify all the relevant studies	Y	
Study quality was addressed and taken into account?	Y	
There were enough similarities between the studies to justify combining them.	N	Moreover, results across studies have not been perfectly comparable because different reference groups of alcohol intake were used, among them nondrinkers, nondrinkers/occasional drinkers, and nondrinkers/light drinkers. Some studies did not explicitly focus on analysing the relation of moderate alcohol consumption and disease. Some studies also insufficiently allowed for potential confounding factors.

SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?	Lack of studies and study quality available in this area.	

SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**

alcohol consumption of less than 14 g/day to be associated with beneficial effects on CHD risk compared to nondrinking

Risk reduction was most pronounced for women drinking 14 –29 g alcohol/day and for men drinking 29 – 43 g alcohol/day, with a generally smaller benefit or no benefit at all for those drinking more

Some but not all studies suggested that alcohol intake up to 14 g/day is associated with a decreased risk of stroke. This level was observed for ischaemic stroke, whereas the risk of haemorrhagic stroke was positively associated with all levels of alcohol intake.

Most studies analysing the effect of alcohol on blood pressure reported linear blood pressure elevations at drinking levels above 20 g alcohol/day for women and 30 g alcohol/day for men. A blood-pressure-lowering effect, however, was demonstrated in intervention studies after reduction of alcohol intake.

Template[1] for Intervention [2] Study – Randomised Controlled Trial

KEY QUESTION(S)	
24	
COMPLETED BY:	
Jonathan ucinek	
REFERENCE(S)	
CONEN, D., TEDROW, U. B., COOK, N. R., MOORTHY, M. V., BURING, J. E. & ALBERT, C. M. (2008) Alcohol consumption and risk of incident atrial fibrillation in women. JAMA, 300, 2489-96.	
SOURCE OF FUNDING	
Funding/Support: Dr Conen was supported by grant PASMA 118586/1 from the Swiss National Science Foundation. The Women's Health Study was supported by grants HL-043851 and HL-080467 from the National Heart, Lung, and Blood Institute and CA-047988 from the National Cancer Institute. Role of the Sponsors: The funding organizations had no role in the design and conduct of the study; the collection, analysis,	

and interpretation of the data; or the preparation, review, or approval of the manuscript	
METHOD	
Patient Eligibility Criteria	
Study design	Participants were 34 715 initially healthy women participating in the Women's Health Study, a completed randomized controlled trial conducted in the United States. Participants were older than 45 years and free of atrial fibrillation at baseline and underwent prospective follow-up from 1993 to October 31, 2006. Alcohol consumption was assessed via questionnaires at baseline and at 48 months of follow-up and was grouped into 4 categories (0, _0 and _1, _1 and _2, and _2 drinks per day). Atrial fibrillation was self-reported on the yearly questionnaires and subsequently confirmed by electrocardiogram and medical record review.
Setting	Alcohol consumption in women
Intervention(s)	receive aspirin (100 mg) every other day, vitamin E (600 IU) every other day, both agents, or placebo
Primary outcome measure	Time to first episode of atrial fibrillation.
Additional outcome measures	
Sample Size	34 715
Main results	**Numbers analysed:** 34 715
	Study duration:
	Patients characteristics and group comparability:
	Effect size – primary outcome:
	Effect size – additional outcomes:

QUALITY CHECK [3]		
Patient selection	**YES/NO**	**Comment**
Were the eligibility criteria specified?	Y	
Was a method of randomisation performed?	Y	
Was the treatment allocation concealed?	N	Not described
Were the groups similar at baseline regarding the most important prognostic indicators?	Y	
Interventions		
Were the index and control interventions explicitly described?	Y	
Was the care provider blinded for the intervention?	N	Not described
Were co-interventions avoided or comparable?	N	Not described
Was the compliance acceptable in all groups?	N	Not described
Was the patient blinded to the intervention?	N	
Outcome measurement		
Was the outcome assessor blinded to the interventions?	N	Not described
Were the outcome measures relevant?	Y	
Were adverse effects described?	N	Not described
Was the withdrawal/drop-out rate described and acceptable?	N	Not described
Was a short-term follow-up measurement performed?	Y	

Was a long-term follow-up measurement performed?	Y	
Was the timing of the outcome assessment in both groups comparable?	Y	
Statistics		
Was the sample size for each group described?	Y	
Did the analysis include an intention-to-treat analysis?	N	Not described
Were point estimates and measures or variability presented for the primary outcome measures?	Y	

CLINICAL IMPLICATIONS	
Benefits	consumption of up to 2 alcoholic beverages per day was not associated with an increased risk of incident atrial fibrillation
Harms	Heavier consumption of 2 or more drinks per day, however, was associated with a small but statistically significant increased risk of atrial fibrillation
Comments	Relevant only to female population
REASON FOR EXCLUSION	
RELEVANCE TO AN AUSTRALIAN CONTEXT	
OVERALL CONCLUSIONS	
Among healthy middle-aged women, consumption of up to 2 alcoholic beverages per day was not associated with an increased risk of incident atrial fibrillation. Heavier consumption of 2 or more drinks per day, however, was associated with a small but statistically significant increased risk of atrial fibrillation	

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS

Guideline topic: alcohol		**Question number: Q. 24**	
Characteristics of study			
Checklist completed by: Carly Hayman			
Study citation	Corrao G, Bagnardi V, Zambon A, La Vecchia C: **A metaanalysis of alcohol consumption and the risk of 15 diseases.** *Prev Med* 2004, **38:**613–619.		
Study design	**Systematic review**	**N (total)**	156 studies N=116 702
Search strategy	MEDLINE, Current Contents, EMBASE CAB Abstracts, Core Biomedical Collections		
Selection criteria	Published between 1966 and 1998 Inclusion: Case-controlled or cohort study Findings expressed as odds ratio or relative risk considering at least three levels of alcohol consumption Reported the number of cases and noncases and the estimates of the odds ratios or RR for each level		
Intervention	alcohol		
Comparison	Varying levels		
Outcomes	Neoplastic conditions (e.g. cancer of oral cavity, esophagus, breast etc.)		

	Hypertension Coronary heart disease Ischemic stroke		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		Y	Well covered
Description of the methodology used is included		Y	Well covered
The literature search was sufficiently rigorous to identify all the relevant studies		Y	Well covered
Study quality was addressed and taken into account?		Y	Well covered – selected studies were of high quality.
There were enough similarities between the studies to justify combining them.		Y	Well covered
SECTION 2: Overall assessment of the study			
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
			+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
			- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or – what is the likely direction in which bias might affect the study results?			
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**			

Significant increased risk found at 100g/day of alcohol for coronary heart disease Significant protective action observed at 25-50 g/day for coronary heart disease The minimum RR function of coronary heart disease (RR=0.80) reached at 20g/day, a significant protective effect observed up to 72g/day while a significant increased risk was obtained starting from 89g/day (RR=1.05) Study found a J-shaped relation between alcohol consumption and coronary heart disease, where within a certain range alcohol has a protective effect, though beyond that it increases the risk for CVD. Significant increased risks were found only at 100 g/day for ischemic stroke, and at 50 g/day for hemorrhagic stroke.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS

Guideline topic: alcohol		**Question number: 24**	
Characteristics of study			
Checklist completed by: Jonathan ucinek			
Study citation	DI CASTELNUOVO, A., COSTANZO, S., BAGNARDI, V., DONATI, M. B., IACOVIELLO, L. & DE GAETANO, G. (2006) Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies. *Arch Intern Med,* 166**,** 2437-45.		
Study design	**Systematic review**	**N (total)**	Thirty-four studies on men and women, for a total of 1 015 835 subjects and 94 533 deaths
Search strategy	PubMed for articles available until December 2005, supplemented by references from the selected articles.		
Selection criteria	Studies were excluded if they considered only 1 category of risk (n=4) or did not report mortality separately for the sexes (n=5); if they considered mortality for specific causes (n=3) or if they comprised multiple reports (n=9) (the longer follow-up was considered); or if the reference category was not the one with the lowest alcohol intake (n=4) or if relative risks or numbers of cases and person-years were not available (n=14). A total of 34 reports were identified.		
Intervention	Alcohol intake vs no alcohol intake		
Comparison			
Outcomes	Mortality		
Quality of study			

Quality criteria (from SIGN)	***Met?**	**Comments**
SECTION 1: Internal validity		
Study addresses an appropriate and clearly focused question	Y	investigate the relationship between alcohol dosing and allcause mortality, separately in men andwomen.
Description of the methodology used is included	Y	
The literature search was sufficiently rigorous to identify all the relevant studies	Y	

Study quality was addressed and taken into account?	Y	
There were enough similarities between the studies to justify combining them.	Y	
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?	The results of any meta-analysis may be plagued by publication bias; nevertheless, we considered only follow- up studies on total mortality, and it is hard to hypothesize that high-quality studies would not have been published because they reported negative results. We believe therefore that publication bias—if any—might have only weakly altered our findings	
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		
Low levels of alcohol intake (1-2 drinks per day for women and 2-4 drinks per day for men) are inversely associated with total mortality in both men and women. Our findings, while confirming the hazards of excess drinking, indicate potential windows of alcohol intake that may confer a net beneficial effect of moderate drinking, at least in terms of survival. Higher doses of alcohol were associated with increased mortality.		

Template[1] for Intervention [2] Study – Randomised Controlled Trial

KEY QUESTION(S)	
24	
COMPLETED BY:	
Jonathan Ucinek	
REFERENCE(S)	
DJOUSSE, L., LEE, I. M., BURING, J. E. & GAZIANO, J. M. (2009) Alcohol consumption and risk of cardiovascular disease and death in women: potential mediating mechanisms. Circulation, 120, 237-44.	
SOURCE OF FUNDING	
The Women's Health Study is supported by grants CA-047988, HL-43851, and HL-080467 from the National Institutes of Health, Bethesda, MD	
METHOD	
Patient Eligibility Criteria	For the present analyses, we included only 28 345 women (71.1%) who provided a blood sample at baseline. We then excluded women with (1) missing data on biomarkers (n_738), (2) missing alcohol information (n_6), (3) pre randomization reports of CVD that occurred before baseline (n_7), and (4) missing data on potential

	confounders, including body mass index, exercise, smoking, energy intake, fruits and vegetables, systolic blood pressure, and hypertension (n_1195). Thus a total sample of 26 399 women was used for current analyses. Characteristics between subjects who provided blood samples and those who did not were comparable (data not shown).
Study design	**Analysis of data from an RCT**
Setting	Female health professionals aged 45 years and older
Intervention(s)	randomized to low-dose aspirin, vitamin E, or their corresponding placebos.
Primary outcome measure	Baseline levels of hemoglobin A1c, inflammatory markers, hemostatic factors, and lipids were measured
Additional outcome measures	
Sample Size	28 345
Main results	**Numbers analysed:** 26 399
	Study duration: follow up for mean of 12 years
	Patients characteristics and group comparability:
	Effect size – primary outcome:
	Effect size – additional outcomes:

QUALITY CHECK [3]

Patient selection	**YES/NO**	**Comment**
Were the eligibility criteria specified?	y	
Was a method of randomisation performed?	y	
Was the treatment allocation concealed?	n	Not described
Were the groups similar at baseline regarding the most important prognostic indicators?	y	
Interventions		
Were the index and control interventions explicitly described?	y	
Was the care provider blinded for the intervention?	n	Not described, (ref to original study)
Were co-interventions avoided or comparable?	n	Not described, (ref to original study
Was the compliance acceptable in all groups?	n	Not described, (ref to original study
Was the patient blinded to the intervention?	n	Not described, (ref to original study
Outcome measurement		
Was the outcome assessor blinded to the interventions?	n	Not described, (ref to original study
Were the outcome measures relevant?	Y	
Were adverse effects described?	n	Not described, (ref to original study
Was the withdrawal/drop-out rate described and acceptable?	n	Not described, (ref to original study
Was a short-term follow-up measurement performed?	n	Not described, (ref to original study
Was a long-term follow-up measurement performed?	y	Not described, states mean follow up of 12.2 years
Was the timing of the outcome assessment in both groups comparable?	n	Not described, (ref to original study
Statistics		
Was the sample size for each group described?	y	
Did the analysis include an intention-to-treat analysis?	n	
Were point estimates and measures or variability presented for the primary outcome measures?	y	

CLINICAL IMPLICATIONS

Benefits	There was a J-shaped relation between alcohol consumption and incident CVD and total and CVD deaths in a multivariable model. Compared with abstainers, alcohol intake of 5 to 14.9 g/d was associated with 26%, 35%,

	and 51% lower risk of CVD, total death, and CVD death, respectively, in a multivariable model. For CVD risk reduction, lipids made the largest contribution to the lower risk of CVD (28.7%), followed by hemoglobin A1c/diabetes (25.3%), inflammatory/hemostatic factors (5%), and blood pressure factors (4.6%). All these mediating factors together explained 86.3%, 18.7%, and 21.8% of the observed lower risk of CVD, total death, and CVD death, respectively.
Harms	
Comments	

REASON FOR EXCLUSION	
RELEVANCE TO AN AUSTRALIAN CONTEXT	
OVERALL CONCLUSIONS	

There was a J-shaped relation between alcohol consumption and incident CVD and total and CVD deaths in a multivariable model. Compared with abstainers, alcohol intake of 5 to 14.9 g/d was associated with 26%, 35%, and 51% lower risk of CVD, total death, and CVD death, respectively, in a multivariable model. For CVD risk reduction, lipids made the largest contribution to the lower risk of CVD (28.7%), followed by hemoglobin A1c/diabetes (25.3%), inflammatory/hemostatic factors (5%), and blood pressure factors (4.6%). All these mediating factors together explained 86.3%, 18.7%, and 21.8% of the observed lower risk of CVD, total death, and CVD death, respectively.

These data suggest that alcohol effects on lipids and insulin sensitivity may account for a large proportion of the lower risk of CVD/death observed with moderate drinking under the assumption that the alcohol-CVD association is causal.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS

Guideline topic:		**Question number:** Q. 24 – diabetes subgroup	
Characteristics of study			
Checklist completed by: Carly Hayman			
Study citation	Howard et al (2004) Effect of Alcohol Consumption on Diabetes Mellitus: A Systematic Review. *Annals of Internal Medicine. 140(3)(pp 211-219+I72*		
Study design	**Systematic review**	**N (total)**	Total of 32 studies
Search strategy	MEDLINE Published from 1966 to August 2003		
Selection criteria	Studies on persons 19 years or older who had not been administered or were not users of alcohol, Experimental, cohort or case-control study with relevant primary outcomes.		
Intervention	alcohol		
Comparison	n/a		
Outcomes	Diabetes incidence Glycemic control Incidence of diabetic complications		

Quality of study		
Quality criteria (from SIGN)	***Met?**	**Comments**
SECTION 1: Internal validity		
Study addresses an appropriate and clearly focused question	Y	Well covered
Description of the methodology used is included	Y	Well covered
The literature search was sufficiently rigorous to identify all the relevant studies	N	Only searched MEDLINE
Study quality was addressed and taken into account?	Y	All studies were rated as “good” or “fair”
There were enough similarities between the studies to justify combining them.	Yes	Adequately covered – different studies however examined either type 1, type 2 or both, and used different markers to diagnose diabetes.
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or – what is the likely direction in which bias might affect the study results?		
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		
Incidence of diabetes: 8 studies found u-shaped relationship between alcohol consumption and incidence of diabetes - moderate drinkers had lowest risk. Compared to nondrinkers, persons who consumed approximately one to 3 drinks had a 33% to 56% reduction in risk. 4 studies treated alcohol consumption as dichotomous – 2 found no association between alcohol and risk of diabetes, 1 found an increased risk for those who drank more than 2 to 3 times weekly, 1 found an increased risk for those with current use with a low BMI and a decreased risk for those with normal BMI Glycemic control 6 studies looked at type 1 or type 2 – only rated as “fair”: 2 studies found decrease in plasma glucose after alcohol, this difference was sign. for type 2 but not type 1 diabetes. The 3 other studies found small to moderate amount of alcohol had no acute effect on glycemic control.		

Diabetic Complications
4 studies assessed alcohol consumption and coronary heart disease. Two studies were “good” and two were “fair”. All studies found decreased risk for death due to coronary heart disease with alcohol use. Three of these studies demonstrated an inverse association between alcohol consumption and risk of coronary heart disease. Compared with nondrinkers, moderate drinkers had a 34% to 55% decrease in incidence of coronary heart disease, and 55 to 79% decrease in the rate of death from coronary heart disease.

Discussion of coronary heart disease for diabetic population
Does not discuss specific measures of blood pressure etc.
Some evidence that moderate alcohol consumption decreases risk of coronary heart disease.

Template[1] for Intervention [2] Study – Randomised Controlled Trial

KEY QUESTION(S)	
Question 24	
COMPLETED BY:	
Carly Hayman	
REFERENCE(S)	
Johson et al (2008) Improvement of physical health and quality of life of alcohol-dependent individuals with topiramate treatment: US multisite randomized controlled trial. *Archives of Internal Medicine. 168(11); 1188-1199*	
SOURCE OF FUNDING	
Ortho-McNeil Janseen Scientific Affairs LLC	
METHOD	
Patient Eligibility Criteria	Diagnosed as having alcohol dependence according to DSM-IV Subjects recruited across 17 sites in the USA Aged between 18 and 65 years, who drank 35+ drinks (men) and 28+ drinks (women) per week Subjects excluded who had current Axis I psychiatric disorder or had other substance dependence.
Study design	Double-blink random control trial
Setting	
Intervention(s)	**Topiramate**
Primary outcome measure	Clinical Global Impression Scale for improvement and severity, Obsessive Compulsive Drinking Scale, Liver enzymes
Additional outcome measures	Blood pressure, pulse, temp, BMI Plasma cholesterol
Sample Size	total N=371; topiramate group N=183; placebo group N=188
Main results	**Numbers analysed:** N=112 (of 183) for topiramate N =144 (of 188) for placebo group
	Study duration: 14 weeks with weekly assessments
	Patients characteristics and group comparability: Subjects in placebo and treatment group had

	similar baseline characteristics
	Effect size – primary outcome: Topiramate decreased liver function test values compared to placebo
	Effect size – additional outcomes: Topiramate lowered plasma cholesterol: mean difference 13.30 (CI 95% 5.09 to 21.44), effect size = 0.41 p=.002 Topiramate reduced BM: mean difference= 1.08 (CI 95% 0.81 to 1.34), effect size= 0.91 p<.00 Topiramate significantly lowered blood pressure: Systolic BP: mean difference = 9.70 (CI 95% 6.81 to 12.60) effect size =0.77 p<.001 Diastolic BP: mean difference = 6.74 (CI 95% 4.57 to 8.90) effect size = 0.73 p<.001

QUALITY CHECK [3]		
Patient selection	**YES/NO**	**Comment**
Were the eligibility criteria specified?	Yes	
Was a method of randomisation performed?	Yes	
Was the treatment allocation concealed?	Yes	
Were the groups similar at baseline regarding the most important prognostic indicators?	Yes	
Interventions		
Were the index and control interventions explicitly described?	Yes	
Was the care provider blinded for the intervention?	Yes	
Were co-interventions avoided or comparable?	N/A	
Was the compliance acceptable in all groups?	N/A	Not discussed
Was the patient blinded to the intervention?	Yes	
Outcome measurement		
Was the outcome assessor blinded to the interventions?	Yes	
Were the outcome measures relevant?	Yes	
Were adverse effects described?	Yes	
Was the withdrawal/drop-out rate described and acceptable?	No	Approx 40% drop out rate for treatment group and 25% dropout for control.
Was a short-term follow-up measurement performed?	Yes	
Was a long-term follow-up measurement performed?	No	
Was the timing of the outcome assessment in both groups comparable?	Yes	
Statistics		
Was the sample size for each group described?	Yes	
Did the analysis include an intention-to-treat analysis?	n/a	Not discussed
Were point estimates and measures or variability presented for the primary outcome measures?	yes	

CLINICAL IMPLICATIONS	
Benefits	Topiramate significantly reduced plasma cholesterol, BMI and blood pressure
Harms	Reported adverse events included headaches, fatigue, anorexia, nausea, difficulty in concentration which were more frequent in topiramate group.
Comments	

REASON FOR EXCLUSION

RELEVANCE TO AN AUSTRALIAN CONTEXT
Urban settings of USA, may be applicable to Australian population.

OVERALL CONCLUSIONS

Topiramate was more effective than placebo in improving self-reported drinking outcomes Treatment group demonstrated improvements in total cholesterol levels, hepatic function and hemodynamic cardiovascular status, as well as an improvement in BMI

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS			
Guideline topic: Alcohol		**Question number: Q. 24 (T2DM subgroup)**	
Characteristics of study			
Checklist completed by: Susan Hillier			
Study citation	L. L. J. Koppes. J. M. Dekker. H. F. J. Hendriks, L. M. Bouter. R. J. Heine. Meta-analysis of the relationship between alcohol consumption and coronary heart disease and mortality in type 2 diabetic patients. Diabetologia (2006) 49: 648–652		
Study design	**Systematic review**	**N (total) 12751**	Six prospective cohort
Search strategy	Pubmed to Sept 2005, pearling		
Selection criteria	Inclusion: • Nested case-controlled or observational cohort study • Populations with T2DM • Reported relationship between alcohol consumption and incidence of diabetic complications		
Intervention	alcohol		
Comparison	Varying levels (3)		
Outcomes	Pooled relative risk of mortality and CHD		
Quality of study			
Quality criteria (from SIGN)	***Met?**	**Comments**	
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question	Y		
Description of the methodology used is included	Y		
The literature search was sufficiently rigorous to identify all the relevant studies	?	Only Pubmed	
Study quality was addressed and taken into account?	Y		

There were enough similarities between the studies to justify combining them.	Y	
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.	++	++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or – what is the likely direction in which bias might affect the study results?		
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		
This meta-analysis shows that, as with findings in the general population, moderate alcohol consumption is associated with a lower risk of mortality and CHD in type 2 diabetic populations. Statistical pooling showed lower risks in alcohol consumers than in non-consumers (the reference category). The relative risk (RR) of total mortality was 0.64 (95% CI 0.49–0.82) in the <6 g/day category. In the higher alcohol consumption categories (6 to <18, and ≥18 g/day), the RRs of total mortality were not significant. Risks of fatal and total CHD were significantly lower in all three categories of alcohol consumers (<6, 6 to <18 and ≥18 g/day) than in non-consumers, with RRs ranging from 0.34 to 0.75.		

Template[1] for Intervention [2] Study – Randomised Controlled Trial

KEY QUESTION(S)	
Q. 24	
COMPLETED BY:	
Carly Hayman	
REFERENCE(S)	
Sierksma et al (2004) Effect of Moderate Alcohol Consumption on Parameters of Reverse Cholesterol Transport in Postmenopausal Women. *Alcoholism: Clinical and Experimental Research. 28(4); 662-666*	
SOURCE OF FUNDING	
METHOD	
Patient Eligibility Criteria	Non-smoking, postmenopausal women Consumption of 21 or fewer alcoholic beverages per week BMI between 19 and 30kg/m^2 Aged 75 years or younger.

Study design	Randomised crossover trial One three week period of consuming white wine (250ml) with evening meals and one three week period of drinking grape juice.
Setting	The Netherlands
Intervention(s)	**alcohol**
Primary outcome measure	Triglycerides; Total cholesterol ; HDL cholesterol ; Apo A-I
Additional outcome measures	Parameters of reverse cholesterol transport
Sample Size	**N total = 18**
Main results	**Numbers analysed: 18**
	Study duration: Two periods of 3 weeks
	Patients characteristics and group comparability: No difference between groups
	Effect size – primary outcome: No significant change in triglycerides, Apo A-I, or total cholesterol HDL cholesterol: grape juice: 1.79 (0.43) [1.57–2.00]; white wine: 1.88 (0.45) [1.65–2.11] p=0.02 HDL phospholipids: grape juice: 1.91 (0.29) [1.77–2.06]; white wine: 2.02 (0.36) [1.84–2.20] p= 0.008
	Effect size – additional outcomes: Cellular cholesterol efflux increased by 3.4%

QUALITY CHECK [3]

Patient selection	**YES/NO**	**Comment**
Were the eligibility criteria specified?	Yes	
Was a method of randomisation performed?	Yes	Details of allocation to counterbalanced alcohol first/juice first not discussed.
Was the treatment allocation concealed?	No	Participants and staff were unblended.
Were the groups similar at baseline regarding the most important prognostic indicators?	Yes	
Interventions		
Were the index and control interventions explicitly described?	Yes	
Was the care provider blinded for the intervention?	No	
Were co-interventions avoided or comparable?	No	Diet not controlled – may have influenced outcomes.
Was the compliance acceptable in all groups?	Yes	
Was the patient blinded to the intervention?	No	
Outcome measurement		
Was the outcome assessor blinded to the interventions?	No	
Were the outcome measures relevant?	Yes	
Were adverse effects described?	No	
Was the withdrawal/drop-out rate described and acceptable?	Yes	
Was a short-term follow-up measurement performed?	Yes	
Was a long-term follow-up measurement performed?	No	
Was the timing of the outcome assessment in both groups comparable?	Yes	
Statistics		
Was the sample size for each group described?	Yes	
Did the analysis include an intention-to-treat analysis?	n/a	
Were point estimates and measures or variability presented for the primary outcome measures?	Yes	

CLINICAL IMPLICATIONS

Benefits	Increased HDL cholesterol levels and cellular cholesterol efflux.
Harms	n/a
Comments	

REASON FOR EXCLUSION

RELEVANCE TO AN AUSTRALIAN CONTEXT	
Urban setting	
OVERALL CONCLUSIONS	
Moderate alcohol consumption increased serum HDL cholesterol levels and the capacity of plasma to induce cellular cholesterol efflux. Unlike previous study examining men and women, diet was not controlled in this study, which may explain the discrepancy for a 5.0% increase in serum HDL and a 12% increase in the previous study (Sierksam 2004 28(5).	

Template[1] for Intervention [2] Study – Randomised Controlled Trial

KEY QUESTION(S)	
Q. 24	
COMPLETED BY:	
Carly Hayman	
REFERENCE(S)	
Sierksma et al (2004) Effect of moderate alcohol consumption on plasma dehydroepiandrosterone sulfate, testosterone, and estradiol levels in middle-aged men and postmenopausal women: A diet-controlled intervention study. *Alcoholism: Clinical and Experimental Research. 28(5)(pp 780-785),*	
SOURCE OF FUNDING	
METHOD	
Patient Eligibility Criteria	Consumption of <28 alcohol containing beverages per week for men, <21 for women. BMI between 20 and 31kg/m^2 No history of alcoholism
Study design	Open-randomised cross-over trial 5 men and women were randomly allocated to beer sequence followed by no beer Other 5 men and women were allocated to no beer, followed by beer. Beer consumed during one period was 40 and 30g per day for men and women respectively. All food was provided by study.
Setting	TNO Nutrition and Food Research, Zeist, The Netherlands
Intervention(s)	
Primary outcome measure	Blood samples collected in the morning after last day of each experimental condition HDL cholesterol DHEAS (hormone with proposed protective effects against atherosclerosis)
Additional outcome measures	Testosterone Estradiol levels
Sample Size	Total N = 20 (10 men and 10 post-menopausal women) One women dropped out due to treatment unrelated causes.
Main results	**Numbers analysed:** N=19
	Study duration: Two three week periods
	Patients characteristics and group comparability: No discrepancies described.
	Effect size – primary outcome: Plasma DHEAS: level increased by 16.5% (95% CI 8.0 to 24.9) after beer consumption compared with no alcohol consumption. No gender differences observed. Serum HDL cholesterol level: after 3 week alcohol consumption, increase in cholesterol; 11.7% (95% CI 7.3 to 16.0) Similar changes in both men and women.

	Effect size – additional outcomes: Plasma testosterone level: Three weeks of beer consumption decreased testosterone by 6.8% (95% CI -1.0 to -12.5) in men. No effect on women. Plasma estradiol - no significant change for men or women.

QUALITY CHECK [3]		
Patient selection	**YES/NO**	**Comment**
Were the eligibility criteria specified?	Yes	
Was a method of randomisation performed?	Yes	But method of randomization not outlined.
Was the treatment allocation concealed?	No	
Were the groups similar at baseline regarding the most important prognostic indicators?	Yes	
Interventions		
Were the index and control interventions explicitly described?	Yes	
Was the care provider blinded for the intervention?	No	
Were co-interventions avoided or comparable?	Yes	
Was the compliance acceptable in all groups?	Yes	
Was the patient blinded to the intervention?	No	
Outcome measurement		
Was the outcome assessor blinded to the interventions?	Yes	
Were the outcome measures relevant?	Yes	Though did not measure LDL
Were adverse effects described?	No	
Was the withdrawal/drop-out rate described and acceptable?	Yes	Only one woman dropped out due to unrelated reasons.
Was a short-term follow-up measurement performed?	Yes	
Was a long-term follow-up measurement performed?	No	
Was the timing of the outcome assessment in both groups comparable?	Yes	
Statistics		
Was the sample size for each group described?	Yes	
Did the analysis include an intention-to-treat analysis?	n/a	Not mentioned
Were point estimates and measures or variability presented for the primary outcome measures?	Yes	

CLINICAL IMPLICATIONS	
Benefits	Increase in DHEAS which may provide protective effects against CVD
Harms	n/a
Comments	

REASON FOR EXCLUSION
Small sample size needs to be considered .

RELEVANCE TO AN AUSTRALIAN CONTEXT
Urban settings in the Netherlands, relevance to Australia?

OVERALL CONCLUSIONS
Protective effect of moderate alcohol consumption on CVD may be attributed to increased plasma DHEAS

Methodology Checklist: systematic reviews	
Guideline topic: alcohol	Question number: 24
Characteristics of study	

Checklist completed by: Jonathan Ucinek			
Study citation	TAYLOR, B. & REHM, J. (2006) When risk factors combine: the interaction between alcohol and smoking for aerodigestive cancer, coronary heart disease, and traffic and fire injury. Addict Behav, 31, 1522-35.		
Study design	Systematic review	N (total)	Overall, the review identified 37 studies from the literature search. All presented data of the interactive effects of alcohol and tobacco. The majority were articles on cancer (24), followed by those on fire injury (10), traffic injury (2), and coronary heart disease (1). Both male and female cases and controls were represented, and where available, sex and age-adjusted risk estimates are presented.
Search strategy	Systematic literature review identified articles on the interaction of alcohol and smoking on a number of outcomes related to both risk behaviours Articles included in this review were identified from searches of National Library of Medicine's Pubmed database and OVID from 1966 to March 2005, using the main search terms balcohol drinking or drinkingQ and btobacco smoking or smokingQ. In addition, the preceding key word searches were combined with each of: bneoplasmsQ or bcancerQ, bcoronary heart diseaseQ or bcoronary diseaseQ or bcardiovascular diseaseQ, btraffic accidentsQ or bmotor vehicle accidentsQ or baccidentsQ or binjuryQ, bfiresQ or bfire injuryQ or bhome accidentsQ or bburnsQ. In order not to miss any articles from specific outcome categories, this search was sometimes cast more widely than specific outcome categories. English articles only were selected for further review. After articles were identified from this initial search, articles were checked for data on the combined effect of alcohol and tobacco smoking.		
Selection criteria	Inclusion Criteria: Articles were case-control or cohort studies with data on the interaction or combined effects of alcohol and tobacco cigarette smoking with respect to oral cancer, pharyngeal cancer, laryngeal cancer, esophageal cancer, coronary heart disease, traffic accidents, or fire injury, either as a main or secondary finding Estimates of risk were presented when at all possible, either as odds ratios or relative risks between exposed and unexposed groups, and for each level of smoking and drinking. However, in doing this, coronary heart disease and injury outcomes were severely under-represented, so more descriptive statistics were accepted when risk estimates were not given or were very scarce. The article reported the number of cases and non-cases included in the study.		
Intervention	Smoking and alcohol comsumption		
Comparison			
Outcomes	Cancer, coronary heart disease and injury		
Quality of study			
Quality criteria (from SIGN)		*Met?	Comments

SECTION 1: Internal validity		
Study addresses an appropriate and clearly focused question	Y	The purpose of this review was to summarize the scientific evidence related to risks associated with the interaction of smoking and alcohol drinking and the impact of those risks on public health.
Description of the methodology used is included	Y	Poor method description
The literature search was sufficiently rigorous to identify all the relevant studies	Y	
Study quality was addressed and taken into account?	Y	
There were enough similarities between the studies to justify combining them.	N	Unclear There were significant differences between these studies in exposure measurement, however. The study by Znaor and colleagues (2003) focused on ever drinking and ever smoking (alcohol at least once a day, smoked once a day) and the article by Schlecht et al. (1999) used lifetime exposure measurements at three levels: pack-years for smoking and lifetime alcohol consumption (in kg, calculated from frequency and volume questions and years consumed)
SECTION 2: Overall assessment of the study		
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
	+	+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		
Section 3: Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.		
The interaction of smoking and alcohol significantly increases risk for aero digestive cancers, and may increase risk for traffic injury and fire injury, but there were very few quality studies on injury. The indication that the cardio protective effect of alcohol on coronary heart disease is only valid for smokers, but this result is inconclusive because of small evidence base The interaction between smoking and alcohol consumption seems to be responsible for a significant amount of disease. Unfortunately, little is known on the mechanisms and details of this interaction on disease outcomes. Future studies, especially for coronary heart disease and injury outcomes, are warranted		

Coronary heart disease does not have as clear a relationship as was seen for cancer. At this point, we have some indications that the cardio protective effect is limited to smokers, but this is based on only few studies, and other studies explicitly trying to confirm the effect did not find this interaction. More research is needed, especially including alcohol consumption measures

* Assessment of whether the criteria has been met should be made according to one of the following descriptors
Well covered
Adequately addressed
Poorly addressed
Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
Not applicable.

Subgroup evidence for question 24:

a. Those deemed clinically high risk as outlined in the assessment guidelines (those with SBP >180 or DBP>110mmHg, diabetes >60yrs, diabetes with microalbuminuria, CKD [see levels below], familial hypercholesterolaemia, cholesterol >7.5mmol/L)

b. Those with atrial fibrillation

(may not be relevant) Conen 2008 reported among healthy middle-aged women, consumption of up to 2 alcoholic beverages per day was not associated with an increased risk of incident atrial fibrillation. Heavier consumption of 2 or more drinks per day, however, was associated with a small but statistically significant increased risk of atrial fibrillation.

c. High, medium and low absolute risk of CVD

No evidence

d. Abnormal BP and normal BP

Malinski 2004 – cohort study - Their results, which require confirmation in other large-scale studies, suggest that light to moderate alcohol consumption is associated with a reduction in risk of total and CVD mortality in hypertensive men.

e. Hypercholesterol and normal cholesterol

No evidence

f. Diabetes and no diabetes

Howard 2004 – SR – compared to no alcohol, moderate consumption (1-3 drinks/day) assoc with 33-56% lower incidence of diabetes and 34-55% lower incidence of diabetes-related CHD. Heavy consumption (>3 d/d) may be assoc with up to 43% increased incidence of diabetes. Moderate consumption does not acutely impair glycaemic control in persons with diabetes (abstract).

Koppes 2006 – SR - meta-analysis shows that, as with findings in the general population, moderate alcohol consumption is associated with a lower risk of mortality and CHD in type 2 diabetic populations.

g. Chronic kidney disease and no chronic kidney disease (break down into GFR <45 ml/min, GFR 45-60 ml/min and GFR >60 ml/min)

No evidence

FORM framework Question 24

Qestion 24. What is the evidence that the patterns and levels of alcohol consumption alter CVD events and all cause mortality? Report evidence for secondary outcomes: Blood pressure; Lipid parameters

1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*

Four Systematic reviews (note mostly high quality SR but few found RCT level – mostly cohort): Bagnardi 2008; Burger 2004; Corroa 2004; Di Castelnuovo 2006 and two high quality RCTs on secondary measures: Djousse 2009 and Sierksma 2004.	A	**One or more level I studies with a low risk of bias or several level II studies with a low risk of bias**
	B	**One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias**
	C	**One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias**
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**

2. Consistency *(if only one study was available, rank this component as 'not applicable')*

All reviews report a level of protection against CVD generally for low to moderate alcohol intake, and an increased risk for heavy/binge: the so-called J curve. This varies between men and women and there may be an age effect as well as an ethnicity effect that could account for varying reporting levels There is some question that these effects are different for ischaemic versus haemorrhagic stroke	A	**All studies consistent**
	B	**Most studies consistent and inconsistency can be explained**
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
	NA	**Not applicable (one study only)**

3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*

The impact on risk reduction at either end of the j-curve needs to be confirmed by the WG but appears substantial.	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*

The majority of the studies were in developed countries with a population profile similar to Australia however ethnicity is an important modifier in alcohol effects so caution needs to be applied to generalising to specific groups.	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*

The evidence is applicable to our context	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**

	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The SRs are clear about the protective effects and the increased risk (j-curve). The RCTs attempt to tease out the mechanisms by looking at various lipid parameters.

Reporting is often in different units so it is difficult to make a judgement about the absolute levels overall. This would be available in the recently produced NHMRC Alcohol guidelines for the Australian context.

The SRs have been downgraded from A to B as they are predominantly reviews of cohort studies or lesser. However it should also be acknowledged that RCTs are difficult in this area and relatively rare/unlikely – ie it is unlikely that there will ever be a study that randomises people to heavy/binge drinking.

EWG discussed value in making recommendations outside current national guidelines. While the national guidelines take a risk approach the recommendation to restrict alcohol intake to modest levels aligns with evidence for increased risk of CHD. Agreed to be consistent and current guidelines and hence while recognizing evidence basis include practice point linking to current national guidelinjes.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account

Component	Rating	Description
1.Evidence base	B	The rating of B seems conservative given the number of SRs however they are reviews of predominantly cohort studies and lower.
2.Consistency	B	Generally consistent although actual levels differ
3.Clinical impact	A	Needs to be confirmed by WG but appears high
4. Generalisability	B	Caveats as noted – WG to discuss impact of ethnicity from clinical knowledge
5. Applicability	A	

Evidence statement

Alcohol consumption has an effect on CVD events and mortality – with the so-called J-curve pattern where low to moderate consumption has a protective effect on most CVD events (but possibly not haemorrhagic stroke) and high/binge patterns increase risk for CVD events and all-cause mortality. Blood pressure increases linearly with intake and lipid parameters follow a similar J curve of benefit/harm. Gender, age and ethnicity are significant modifiers for these effects.

RECOMMENDATION	**GRADE OF RECOMMENDATION**	
What recommendation(s) does the guideline development group draw from this evidence? Use action		

All adults should be advised to follow the current *Australian guidelines to reduce health risks from drinking alcohol (2009).* (Practice point)

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up*	
IMPLEMENTATION OF RECOMMENDATION	
Will this recommendation result in changes in usual care?	**NO**
Are there any resource implications associated with implementing this recommendation?	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**NO**

12.Smoking cessation (Q25)

Search results

Sources	Dates	Total hits	Retrieval list	Final inclusions
Databases Medline; Embase ; Cinahl; PsychINFO Cochrane Library, including CENTRAL Cochrane Controlled Trial Register (CCTR) **Other sources:** pearling; expert working group.	**2002-2010**	**417**	**79**	**1** Anthosien 2005
Search terms:	Smoking Cessation; "TOBACCO USE DISORDER" ; TOBACCO; NICOTINE;Tobacco, Smokeless; SMOKING; (quit$ or stop$ or ceas$ or giv$) adj2 smoking;TOBACCO; SMOKE POLLUTION; Second hand smoking; Passive smoking			

Literature identified

Q 25 Does smoking cessation reduce CVD events and all cause mortality?	
References	**Comments / Quality**
Anthonisen, N R, Skeans, M A, Wise, R A, Manfreda, J, Kanner, R E and Connett, J E (2005). *The effects of a smoking cessation intervention on 14.5 year mortality: a randomized clinical trial*. Ann Intern Med, 142, 233-9.	Moderate quality RCT. There is evidence that smoking cessation reduces disease progression and further CVD events in those already with CVD. This strengthens the case that smoking cessation is an important primary prevention strategy.
References SIGN Guidelines	**The articles below were retrieved by SIGN and relate to the link between smoking and CVD in primary prevention.**
Ellingsen I, Hjermann I, Abdelnoor M, Hjerkinn E,	RCT (Oslo Diet and Antismoking Trial); 1232 participants (males, 40-49yrs with high or normal triglycerides) 23

and Tonstad S. *Dietary and antismoking advice and ischemic heart disease mortality in men with normal or high fasting triacylglycerol concentrations: a 23-y follow-up study.* Am J Clin Nutr 2003;78:935–40.	year followup. Intervention: Lifestyle advice for diet and smoking Outcome: IHD mortality Results: In men with a high triglyceride, intervention group vs control the intervention significantly reduced IHD death. Adjusted hazard ratio of 0.56 (95% CI: 0.34, 0.93; P 0.027). In the men with a normal triglyceride concentration, the intervention had no detectable effect on IHD mortality (adjusted hazard ratio: 1.10; 95% CI: 0.66, 1.83; P 0.7).
Doll R, Peto R, Boreham J, Sutherland I. *Mortality in relation to smoking: 50 years' observations on maleBritish doctors.* BMJ, doi:10.1136/bmj.38142.554479.AE (published 22 June 2004)	Prospective cohort; 34,439 male British doctors followed for 50 years Outcome: Overall mortality by smoking habit Results: The cigarette smoker versus non-smoker probabilities of dying in middle age (35-69) were 42% v 24% (a twofold death rate ratio) for those born in 1900-1909, but were 43% v 15% (a threefold death rate ratio) for those born in the 1920s. At older ages, the cigarette smoker versus non-smoker probabilities of surviving from age 70 to 90 were 10% v 12% at the death rates of the 1950s (that is, among men born around the 1870s) but were 7% v 33% (again a threefold death rate ratio) at the death rates of the 1990s (that is, among men born around the 1910s). Cessation at age 60, 50, 40, or 30 years gained, respectively, about 3, 6, 9, or 10 years of life expectancy.
Prescott, E., Scharling, H., Osler, M. and Schnohr, P.. *Importance of light smoking and inhalation habits on risk of myocardial infarction and all cause mortality. A 22 year follow-up of 12 149 men and women in The Copenhagen City Heart Study*. Journal of Epidemiology and Community Health 2002:56;702-6.	Cohort; 12,149 in total, 6505 females and 5644 males Study: Light smoking and inhalation habits Outcome: Adjusted relative risk of MI by tobacco consumption for both men and women. Adjusted relative risk of all causes of mortality by tobacco consumption for both men and women Results: Adjusted relative risk (95% CI). 'Never Smokers' as reference. Example results Relative Risk MI Women Men Ex-smokers 0.83 (0.58-1.19) 1.10 (0.82-1.47) Non-Inhalers - <3 g/day 0.90 (0.28-2.86) 2.03 (0.49-8.30) - 6-9 g/day 1.58 (1.03-2.43) 0.87 (0.53-1.44) - 15-24 g/day 1.87 (1.27-2.74) 1.39 (0.96-2.01) Inhalers - <3 g/day 1.40 (0.34-5.70) 0.76 (0.19-3.13) - 6-9 g/day 2.44 (1.52-3.93) 2.10 (1.40-3.14) - 15-24 g/day 3.15 (2.33-4.25) 1.61 (1.21-2.15) Relative Risk All

	Causes Mortality Women Men Ex-smokers 1.16 (1.00-1.33) 1.00 (0.85-1.18) Non-Inhalers - <3 g/day 1.24 (0.79-1.94) 1.32 (0.49-3.56) - 6-9 g/day 1.24 (1.01-1.53) 0.86 (0.67-1.13) - 15-24 g/day 1.57 (1.31-1.88) 1.17 (0.96-1.44) Inhalers - <3 g/day 1.10 (0.54-2.21) 0.55 (0.25-1.25) - 6-9 g/day 1.86 (1.47-2.35) 1.76 (1.39-2.23) - 15-24 g/day 2.87 (2.51-3.30) 1.98 (1.69-2.32) Smoking without inhaling or smoking as little as 3-5gms of tobacco per day is associated with a significantly increased risk of developing MI and of all causes of mortality in both men and women. For women the risk is even higher than for men.
Jacobs, E. J., Thun, M. J. and Apicella, L. F. *Cigar smoking and death from coronary heart disease in a prospective study of US men.* Archives of Internal Medicine 1999:159;2413-8.	Cohort study; 121,768 participants Cigar smoking Outcome: CHD mortality Results: Rate ratios (95% CI). CHD Status Deaths Age Adj Multv Adj Age 30-74 y - never smoker 1085 1.00 (ref) 1.00 (ref) - former 78 1.09 (0.86-1.37) 1.03 (0.82-1.30) - current 98 1.37 (1.11-1.68) 1.30 (1.05-1.62) Age ≥75 y - never smoker 1054 1.00 (ref) 1.00 (ref) - former 129 1.12 (0.94-1.35) 1.10 (0.91-1.32) - current 64 0.98 (0.76-1.26) 0.93 (0.72-1.21) Smoking cigars increases the risk of early death from CHD. The association between cigar smoking and death from CHD was stronger among current younger smokers. No increased risk noted among cigar smokers aged 75yrs and older or for former cigar smokers of any age.
Wannamethee, S.G, Shaper, A.G, Whincup, P.H,	Prospective cohort study Participants: 7735 men aged 40 - 59 years drawn at random from

Walker, M. *Smoking Cessation and the Risk of Stroke in Middle-aged Men.* JAMA, July 12, 1995, Vol. 274 – No. 2. P155-160.	the age-sex registers of one general practice in each of 24 British towns from 1978-1980 (the British Regional Heart Study).Follow up of 12.75 years Outcome Measure: fatal and nonfatal strokes Results: Current smokers had a nearly fourfold relative risk (RR) of stroke compared with never smokers (RR, 3.7; 95% confidence interval [CI], 2.0 to 6.9). Ex-smokers showed lower risk than current smokers but showed excess risk compared with never smokers (RR, 1.7; 95% CI, 0.9 to 3.3; P=.11); those who switched to pipe or cigar smoking showed a significantly increased risk (RR, 3.3; 95% CI, 1.6 to 7.1) similar to that of current light smokers. Primary pipe or cigar smokers also showed increased risk (RR, 2.2; 95% CI, 0.6 to 8.0), but the number of subjects involved was small. The benefit of giving up smoking completely was seen within 5 years of quitting, with no further consistent decline in risk thereafter, but this was dependent on the amount of tobacco smoked. Light smokers (<20 cigarettes/d) reverted to the risk level of those who had never smoked. Heavy smokers retained a more than twofold risk compared with never smokers (RR, 2.2; 95% CI, 1.1 to 4.3). The age-adjusted RR of stroke in those who quit smoking during the first 5 years of follow-up (recent quitters) was reduced compared with continuing smokers (RR, 1.8; 95% CI, 0.7 to 4.6 vs RR, 4.3; 95% CI, 2.1 to 8.8). The benefit of quitting smoking was observed in both normotensive and hypertensive men, but the absolute benefit was greater in hypertensive subjects.
Kawachi, I., Colditz, G.A., Stampfer, M.J., Willett, W.C., MD; Manson, J.E., Rosner, B., Hunter, D.J., Hennekens, C.H., and Speizer, F.E. *Smoking Cessation in Relation to Total Mortality Rates in Women : A Prospective Cohort Study. 15 November 1993*. Annals of Internal Medicine, Volume 119, Number 10. P992-1000	Prospective cohort 12 years of follow up Participants: 117 001 female registered nurses, ages 30 to 55 years, who were free of manifest coronary heart disease, stroke, and cancer (except non-melanoma skin cancer) in 1976. Outcome Measures: Total mortality, further categorized into deaths from cardiovascular diseases, cancers, and violent deaths. Results: The multivariate relative risks for total mortality compared with never smokers were 1.87 (95% CI, 1.65 to 2.13) for current smokers and 1.29 (CI, 1.14 to 1.46) for former smokers. Participants who started smoking before the age of 15 years had the highest risks for total mortality (multivariate relative risk, 3.15; CI, 2.16 to 4.59), cardiovascular disease mortality (relative risk, 9.94; CI, 5.15 to 19.19), and deaths from external causes of injury (relative risk, 5.39; CI, 1.84 to 15.78). Compared with continuing smokers, former smokers had a 24% reduction in risk for cardiovascular disease mortality within 2 years of quitting. The excess risks for total mortality and both cardiovascular disease and total cancer mortality among former smokers approached the level of that for never smokers after 10 to 14 years of abstinence. The health benefits of cessation were clearly present regardless of the age at starting and daily number of cigarettes smoked.
Sauer, W. H., Berlin, J. A., Strom, B. L., Miles, C.,	Case control; 3272 total participants, cases = 587 control = 2685

Carson, J. L. and Kimmel, S. E. *Cigarette yield and the risk of myocardial infarction in smokers*. Archives of Internal Medicine 2002:162;300-6.	Study: Secondary post hoc evaluation of the role of tar yield in MI. This is a sub-study of a primary study examining the effect of nicotine patch exposure and the risk of MI in smokers Results: Odds ratio (95% CI) Bivariable Multivariable Low tar 1.0 (reference) 1.0 (reference) Medium tar 1.26 (0.88-1.82) 1.86 (1.21-2.87) High tar 1.89 (1.34-2.66) 1.26 (1.47-3.34) Smoking higher yield cigarettes is associated with an increased risk of MI and there is a close response relationship between tar intake per day and MI, regardless of the type of cigarette smoked.
Huhtasaari, F., Lundberg, V., Eliasson, M., Janlert, U. and Asplund, K.. *Smokeless tobacco as a possible risk factor for myocardial infarction: a population-based study in middle-aged men.* Journal of the American College of Cardiology 1999:34;1784-90.	Case Control; Target population =139,215; Cases=687, Referents=687 Study: Snuff affect on risk of MI vs smokers and never smokers Results: Odds ratio (95% CI) MI Cigarette smokers - vs never tobacco users 3.65 (2.67-4.99) Non smoking regular snuff dippers - vs never tobacco users 0.96 (0.65-1.41) Multiple cardiovascular risk factors Regular smokers 3.53 (2.45-5.03) Regular snuff dippers 0.58 (0.35-0.94) Fatal cases of myocardial death Snuff dippers 1.50 (0.45-5.03 Snuff dippers had no overall excess risk for MI. Nicotine is probably not an important contributor to IHD in smokers. But a possible small or modest detrimental effect of snuff dipping on the risk for sudden death could not be excluded. However the results of this study cannot be extrapolated to other countries because the method of snuff preparation is different from that found in other countries.

Evidence details

Template[1] for Intervention [2] Study – Randomised Controlled Trial

KEY QUESTION(S)	
25	
COMPLETED BY:	
Jonathan Ucinek	
REFERENCE(S)	
ANTHONISEN, N. R., SKEANS, M. A., WISE, R. A., MANFREDA, J., KANNER, R. E. & CONNETT, J. E. (2005) The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Ann Intern Med, 142, 233-9.	
SOURCE OF FUNDING	
This study was funded by a contract and grants from the National Heart, Lung, and Blood Institute of the National Institutes of Health. The funding source had a role in the design of the study and approved the manuscript before it was submitted for publication.	
METHOD	
Patient Eligibility Criteria	Not described
Study design	RCT The Lung Health Study was a randomized clinical trial of smoking cessation. Special intervention participants received the smoking intervention program and were compared with usual care participants. Vital status was followed up to 14.5 years
Setting	
Intervention(s)	10-week smoking cessation program that included a strong physician message and 12 group sessions using behaviour modification and nicotine gum, plus either ipratropium or a placebo inhaler
Primary outcome measure	All-cause mortality
Additional outcome measures	mortality due to cardiovascular disease, lung cancer, and other respiratory disease
Sample Size	5887 middle-aged volunteers with asymptomatic airway obstruction.
Main results	Numbers analysed:
	Study duration: 10 weeks, 14.5 years follow up.
	Patients characteristics and group comparability: applies to individuals with airways obstruction

	Effect size – primary outcome: all cause mortality8.83 per 1000 intervention group cf 10.38 per 1000 in non-intervention
	Effect size – additional outcomes: death rate from CV event lower in intervention group

QUALITY CHECK [3]		
Patient selection	**YES/NO**	**Comment**
Were the eligibility criteria specified?	Y	
Was a method of randomisation performed?	Y	
Was the treatment allocation concealed?	Y	
Were the groups similar at baseline regarding the most important prognostic indicators?	N	Not described
Interventions		
Were the index and control interventions explicitly described?	Y	
Was the care provider blinded for the intervention?	N	Not described
Were co-interventions avoided or comparable?	N	Not described
Was the compliance acceptable in all groups?	NR	Compliance recorded
Was the patient blinded to the intervention?	N	Not possible
Outcome measurement		
Was the outcome assessor blinded to the interventions?	Y	
Were the outcome measures relevant?	Y	
Were adverse effects described?	N	Not described
Was the withdrawal/drop-out rate described and acceptable?	Y	Intention to treat analysis
Was a short-term follow-up measurement performed?	Y	
Was a long-term follow-up measurement performed?	Y	
Was the timing of the outcome assessment in both groups comparable?	Y	
Statistics		
Was the sample size for each group described?	Y	
Did the analysis include an intention-to-treat analysis?	Y	
Were point estimates and measures or variability presented for the primary outcome measures?	Y	

CLINICAL IMPLICATIONS	
Benefits	

Harms	
Comments	
REASON FOR EXCLUSION	
RELEVANCE TO AN AUSTRALIAN CONTEXT	
OVERALL CONCLUSIONS	
Smoking cessation intervention programs can have a substantial effect on subsequent mortality, even when successful in a minority of participants	

FORM framework Question 25

Key question(s): Q 25. Does smoking cessation reduce CVD events and all cause mortality?	**Evidence table ref:**

1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*

One high quality RCT (Anthosien 2005) confirmed that a smoking cessation intervention reduced long term mortality (all cause and cardiovascular) at 14 years follow-up even though only a minority successfully stopped smoking (the group that were successful had a greater reduction than those who didn't).
Secondary analysis of a longitudinal study (Unal 2003) propose that large declines in smoking prevalence accounted for 29,460 fewer CHD deaths in England and Wales in 2000 compared with 1981.

A	**One or more level I studies with a low risk of bias or several level II studies with a low risk of bias**
B	**One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias**
C	**One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias**
D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**

2. Consistency *(if only one study was available, rank this component as 'not applicable')*

A	**All studies consistent**
B	**Most studies consistent and inconsistency can be explained**
C	**Some inconsistency, reflecting genuine uncertainty around question**
D	**Evidence is inconsistent**
NA	**Not applicable (one study only)**

3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*

A	**Very large**
B	**Substantial**
C	**Moderate**
D	**Slight/Restricted**

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*

A	**Evidence directly generalisable to target population**
B	**Evidence directly generalisable to target population with some caveats**
C	**Evidence not directly generalisable to the target population but could be sensibly applied**
D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*

A	**Evidence directly applicable to Australian healthcare context**
B	**Evidence applicable to Australian healthcare context with few caveats**
C	**Evidence probably applicable to Australian healthcare context with some caveats**

	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The literature often states smoking cessation as a key CVD primary prevention strategy however the search failed to turn up studies bar the one reported. This makes the grading difficult as the key literature appeared <2002. The recommendation grade therefore needs to be modified based on existing guidelines with literature <2002. The EWG agreed no RCTs will now be undertaken for smoking cessation and hence the strength of the observational studies meant an upgrade to the strength of the recommendation.

There is evidence that smoking cessation reduces disease progression and further CVD events in those already with CVD (see accompanying articles). This strengthens the case that smoking cessation is an important primary prevention strategy.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account

Component	Rating	Description
1.Evidence base	B*	An existing RCT and other longitudinal data support reduction in mortality (+CVD) as a result of smoking reduction however it appears key literature is <2002
2.Consistency	A	
3.Clinical impact	A	
4. Generalisability	A	
5. Applicability	A	

Evidence statement

Any interventions that reduce smoking will have a favourable effect on primary prevention of CVD.

Indicate any dissenting opinions

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action*	**GRADE OF RECOMMENDATION**	A

a) All smokers should be advised to stop smoking.

b) All smokers should be offered advice about methods to aid smoking cessation, including counselling services, and if assessed as nicotine dependent, nicotine replacement therapy or other appropriate pharmacotherapy should be used. (Practice point)

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up*	
IMPLEMENTATION OF RECOMMENDATION	
Will this recommendation result in changes in usual care?	**NO**
Are there any resource implications associated with implementing this recommendation?	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**NO**

13.Depression (Q26)

Search results

Sources	Dates	Total hits	Retrieval list	Final inclusions
Sources a/a	**2002-2010**	**1178**	**22**	**0 (3 related papers)**
Search terms:	Depressive disorder; Dysthymic disorder; depression/ depression, involutional/ depression, postpartum/ ; Seasonal affective disorder; Major depressive disorder; Treatment pharmacological or other Screening for depression			

Literature identified

Question 26. Does treatment (pharmacological and non pharmacological) of depression reduce CVD events and all cause mortality?	
References	**Comments / Quality**
GALLAGHER D. Depression and cardiovascular disease: Does antidepressant treatment improve cardiac outcome? Irish Journal of Psychological Medicine. 2007, vol.24 ,no4, pp.156-158	Moderate quality. Secondary prevention only.
Summers et al 2010. Impact and clinical management of depression in patients with CAD. Pharmacotherapy. 30: 302-322	Moderate quality. Secondary prevention studies only
WONG, M. L., DONG, C., ESPOSITO, K., THAKUR, S., LIU, W., ELASHOFF, R. M. & LICINIO, J. (2008) Elevated stress-hemoconcentration in major depression is normalized by antidepressant treatment: secondary analysis from a randomized, double-blind clinical trial and relevance to cardiovascular disease risk. PLoS One, 3, e2350	Low quality RCT. No CVD endpoints. Not specific to primary prevention

Evidence details

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS

Guideline topic: Depression			Question number: Q 26
Characteristics of study			
Checklist completed by:			
Study citation	GALLAGHER D. Depression and cardiovascular disease: does antidepressant treatment improve cardiac outcome? Irish Journal of Psychological Medicine. 2007, vol.24 ,no4, pp.156-158		
Study design	**Systematic review**	**N (total)**	No trials with people without CVD; 4 trials with people with mixed CAD/MI
Search strategy	MEDLINE search of RCTs, date not specified. Searching of identified studies for further trials		
Selection criteria	English only, RCTs investigating effect of antidepressant treatment on cardiac outcomes – any population		
Intervention	Antidepressant treatment		
Comparison	Not specified		
Outcomes	CVD		
Quality of study			
Quality criteria (from SIGN)		***Met?**	**Comments**
SECTION 1: Internal validity			
Study addresses an appropriate and clearly focused question		WC	
Description of the methodology used is included		NR	
The literature search was sufficiently rigorous to identify all the relevant studies		NA	Not strong - Medline
Study quality was addressed and taken into account?		NR	
There were enough similarities between the studies to justify combining them.		NR	
SECTION 2: Overall assessment of the study			
How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.			++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
		+	+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
			- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?		Poorly reported SR methodology but with strong RCT studies	
SECTION 3: Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your			

own view of its strengths and weaknesses, and how it will help to answer the key question.
THIS SR IS POORLY REPORTED BUT DISCUSSES HIGH QUALITY RCTS. IT DISCUSSES THE LINK BETWEEN DEPRESSION AND POOR CV HEALTH. IT CONFIRMS THAT THERE ARE NO CURRENT STUDIES THAT HAVE DEMONSTRATED A LINK BETWEEN IMPROVED CARDIAC OUTCOMES AND TREATMENT OF DEPRESSION. IT CONCLUDES THAT THIS LACK OF EVIDENCE SHOULD NOT DETRACT FOR THE NEED TO ADDRESS DEPRESSION AS A CLINICAL ISSUE IN ITS OWN RIGHT.

METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS

Guideline topic: Depression			**Question number: Q 26**
Characteristics of study			
Checklist completed by: SH			
Study citation	Summers et al 2010. Impact and clinical management of depression in patients with CAD. Pharmacotherapy. 30: 302-322		
Study design	**Systematic review**	**N (total)**	No trials with people without CVD; 6 trials with people with CAD
Search strategy	MEDLINE search of RCTs until 2009. Searching of identified studies for further trials		
Selection criteria	English only, RCTs investigating effect of antidepressant treatment on cardiac outcomes – patients with CAD		
Intervention	Antidepressant treatment		
Comparison	Not specified		
Outcomes	CVD		

Quality of study		
Quality criteria (from SIGN)	***Met?**	**Comments**
SECTION 1: Internal validity		
Study addresses an appropriate and clearly focused question	WC	
Description of the methodology used is included	PC	
The literature search was sufficiently rigorous to identify all the relevant studies	NA	Not strong – Medline only
Study quality was addressed and taken into account?	NR	
There were enough similarities between the studies to justify combining them.	NR	
SECTION 2: Overall assessment of the study		

How well was the study done to minimise bias? Determine the methodological quality of the study according to this ranking, based on responses above.		++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
	+	+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
		- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.
If coded as +, or - what is the likely direction in which bias might affect the study results?	Poorly reported SR methodology but with strong RCT studies	
SECTION 3: **Identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.**		
THIS SR HAS POORLY REPORTED METHODOLOGY BUT DISCUSSES HIGH QUALITY RCTS. IT REVIEWS THE EFFECT OF ANTI-DEPRESSIVE MANAGEMENT ON CVD OUTCOMES IN PEOPLE WITH CAD. IT DOES NOT DEMONSTRATE A DIRECT REDUCTION IN CVD OUTCOMES WITH DEPRESSION INTERVENTION BUT STRESSES THAT DEPRESSION AND CAD ARE OFTEN COMORBID AND REQUIRE SCREENING AND MANAGEMENT FOR BOTH. IT INCLUDES A DISCUSSION ON VARIOUS FORMS OF ANTI-DEPRESSIVE MANAGEMENT.		

Template[1] for Intervention [2] Study – Randomised Controlled Trial

KEY QUESTION(S)	
COMPLETED BY:	
REFERENCE(S)	
SOURCE OF FUNDING	
WONG, M. L., DONG, C., ESPOSITO, K., THAKUR, S., LIU, W., ELASHOFF, R. M. & LICINIO, J. (2008) Elevated stress-hemoconcentration in major depression is normalized by antidepressant treatment: secondary analysis from a randomized, double-blind clinical trial and relevance to cardiovascular disease risk. PLoS One, 3, e2350.	
METHOD	
Patient Eligibility Criteria	We studied 146 outpatient depressed subjects, all of whom were Mexican-Americans (defined as having at least 3 grandparents born in Mexico) aged 19–65 years, who were participating in an ongoing randomized, double-blind pharmacogenetic study of antidepressant response to desipramine or fluoxetine and completed the 8-week treatment trial (see Table 1 for population characteristics). All depressed subjects had a current episode of unipolar major depression as diagnosed by the Structured Clinical Interview for DSM-IV (SCID). Severity of depression was assessed with the 21- Item Hamilton Depression Rating Scale (HAM-D21) [24]; a score of 18 or greater, with item number 1 (depressed mood) rated 2 or greater, was required for inclusion. The SCID and HAM-D21 have been

	validated in English and Spanish, and all assessments were conducted in the subject's primary language. Exclusion criteria included any primary Axis I disorder other than MDD (e.g. dementia, psychotic illness, bipolar disorder, adjustment disorder); electroconvulsive therapy in the last 6 months; previous lack of response to desipramine or fluoxetine; current, active suicidal ideation with a plan and strong intent; or any other antidepressant treatment within the 2 weeks prior to enrollment. Patients enrolled in this protocol were either drug-naı¨ve or drug-free for at least two weeks; in that case, their antidepressant medication had been discontinued for clinical reasons or because of non-adherence. Subjects with any active medical illnesses that could be etiologically related to the ongoing depressive episode (e.g. untreated hypothyroidism, cardiovascular accident within the past 6 months, uncontrolled hypertension or diabetes), and who were pregnant, lactating, currently using medications with significant central nervous system activity (e.g. benzodiazepines), exhibiting illicit drug use and/or alcohol abuse in the last 3 months, or currently enrolled in psychotherapy were also excluded. Female patients were required to use contraception during our treatment trial, but only 4 used hormonal contraceptive agents. Our patients were predominantly non-smokers (only 6 were smokers), and 37 patients were taking other medications during our trial.
Study design	Randomized, Double-Blind Clinical Trial
Setting	Mexican-American Los Angeles community and evaluated by the same bilingual, clinical research team at the Center for Pharmacogenomics and Clinical Pharmacology, David Geffen School of Medicine at UCLA
Intervention(s)	8 weeks of antidepressant treatment response to either fluoxetine 10–40 mg/day or desipramine 50–200 mg/day, with a dose escalation based on clinical outcomes. All subjects had 9 weeks of structured follow-up assessments. Our primary clinical outcome measure within the depressed group receiving antidepressant treatment was the. Remitter was defined as the patients who had a final HAM-D21 score ,8.
Primary outcome measure	HAM-D21 (depression rating scale)
Additional outcome measures	Hematologic and hemorheologic measures of stress-hemoconcentration included blood cell counts, hematocrit, hemoglobin, total serum protein, and albumin, and whole blood viscosity
Sample Size	146 outpatient depressed subjects and 46 non-depressed controls
Main results	**Numbers analysed:**
	Study duration:
	Patients characteristics and group comparability:
	Effect size – primary outcome:
	Effect size – additional outcomes:

QUALITY CHECK [3]		
Patient selection	**YES/NO**	**Comment**

Were the eligibility criteria specified?	Y	
Was a method of randomisation performed?	Y	
Was the treatment allocation concealed?	Y	
Were the groups similar at baseline regarding the most important prognostic indicators?	Y	
Interventions		
Were the index and control interventions explicitly described?	Y	
Was the care provider blinded for the intervention?	N	Not described
Were co-interventions avoided or comparable?	Y	
Was the compliance acceptable in all groups?	Y	
Was the patient blinded to the intervention?	N	Not described
Outcome measurement		
Was the outcome assessor blinded to the interventions?	N	Not described
Were the outcome measures relevant?	Y	
Were adverse effects described?	N	
Was the withdrawal/drop-out rate described and acceptable?	N	
Was a short-term follow-up measurement performed?	Y	
Was a long-term follow-up measurement performed?	N	
Was the timing of the outcome assessment in both groups comparable?	N	Only one measure taken from control while follow up conducted weekly for
Statistics		
Was the sample size for each group described?	Y	
Did the analysis include an intention-to-treat analysis?	N	
Were point estimates and measures or variability presented for the primary outcome measures?	Y	

CLINICAL IMPLICATIONS

Benefits	Secondary data analyses indicate that hemorheologic measures of stress-hemoconcentration are present in Mexican-American individuals with mild to moderate MDD and that these measures decrease significantly after 8 weeks of antidepressant treatment to levels which were the same as those of controls.
Harms	
Comments	

REASON FOR EXCLUSION

RELEVANCE TO AN AUSTRALIAN CONTEXT

OVERALL CONCLUSIONS

Our secondary data analyses indicate that hemorheologic measures of stress-hemoconcentration are present in Mexican- American individuals with mild to moderate MDD and that these measures decrease significantly after 8 weeks of antidepressant treatment to levels which were the same as those of controls.

FORM framework Question 26

Key question(s): Q 26. Does treatment (pharmacological and non pharmacological) of depression reduce CVD events and all cause mortality?	**Evidence table ref:**

1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*

No studies were retrieved which investigated the effect of depression treatment on CVD events and all cause mortality in people without CVD.

Gallagher 2007 (poorly reported SR) confirmed there are no trial data to support a link between depression treatment and improved CVD outcomes, despite the acknowledgment of depression as a major risk factor for CVD. (they only retrieved trials with populations already with CAD or MI).

A	**One or more level I studies with a low risk of bias or several level II studies with a low risk of bias**
B	**One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias**
C	**One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias**
D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**

2. Consistency *(if only one study was available, rank this component as 'not applicable')*

A	**All studies consistent**
B	**Most studies consistent and inconsistency can be explained**
C	**Some inconsistency, reflecting genuine uncertainty around question**
D	**Evidence is inconsistent**
NA	**Not applicable (one study only)**

3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*

A	**Very large**
B	**Substantial**
C	**Moderate**
D	**Slight/Restricted**

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*

A	**Evidence directly generalisable to target population**
B	**Evidence directly generalisable to target population with some caveats**
C	**Evidence not directly generalisable to the target population but could be sensibly applied**
D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*

A	**Evidence directly applicable to Australian healthcare context**
B	**Evidence applicable to Australian healthcare context with few caveats**
C	**Evidence probably applicable to Australian healthcare context with some caveats**
D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

A PhD thesis by Arbelaez 2005 reports a SR that identifies that there is a positive association between depression and stroke. Many articles cite depression as a risk factor for CVD in general and there is much debate on the nature of the association and the mechanisms underlying it, including shared biological mechanisms and parameters. Wong et al 2008, in a secondary analysis of an RCT, concluded that antidepressant management may reduce CVD events by positively influencing blood viscosity.

However we failed to identify any studies that investigated if there is a reduction in CVD endpoints with antidepression management **as a primary prevention.**

SRs in 2007 and 2010 also failed to find any data to support that treatment of depression in people with CAD improved CVD endpoints (Gallagher 2007, Summers 2010), despite the association between the two.

The EWG felt this topic warranted the development of a practice point related to assessment rather than management where existing guidelance is available.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account

Component	Rating	Description
1.Evidence base		
2.Consistency		
3.Clinical impact		
4. Generalisability		
5. Applicability		

Evidence statement

There is no evidence available to support the promotion of antidepressive interventions to favourably influence CVD. However depression is a condition that requires intervention irrespective of other effects.

Indicate any dissenting opinions

RECOMMENDATION	**GRADE OF RECOMMENDATION**	Not able to be graded
What recommendation(s) does the guideline development group draw from this evidence? Use action		

Adults being assessed for CVD risk should also be assessed for depression (and other psychosocial factors). Cardiovascular risk assessment using the Framingham Risk Equation may underestimate risk in adults with depression. (Practice point)

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up*	
IMPLEMENTATION OF RECOMMENDATION	
Will this recommendation result in changes in usual care?	**NO**
Are there any resource implications associated with implementing this recommendation?	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**NO**

Appendix 1. Additional evidence details

Additional hand searching was conducted by the NSF project team in several key journals to identify any major trials or meta-analysis published after the systematic literature review. Where a new meta-analysis or RCT was deemed important to include a formal appraisal was conducted. Where the information was deemed useful background information for the text a summary only is provided below.

Assessment

Reference: Emerging Risk Factors Collaboration, Wormser D, Kaptoge S, Di Angelantonio E, Wood AM, Pennells L, Thompson A, Sarwar N, Kizer JR, Lawlor DA, Nordestgaard BG, Ridker P, Salomaa V, Stevens J, Woodward M, Sattar N, Collins R, Thompson SG, Whitlock G, Danesh J. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. Lancet. 2011 Mar 26;377(9771):1085-95.

Summary: Individual records were available for 221,934 people in 17 countries (14,297 incident cardiovascular disease outcomes; 1.87 million person-years at risk) from 58 prospective cohort studies. Serial adiposity assessments were made in up to 63,821 people (mean interval 5.7 years [SD 3.9]). In people with BMI of 20 kg/m(2) or higher, HRs for cardiovascular disease were 1.23 (95% CI 1.17-1.29) with BMI, 1.27 (1.20-1.33) with waist circumference, and 1.25 (1.19-1.31) with waist-to-hip ratio, after adjustment for age, sex, and smoking status. After further adjustment for baseline systolic blood pressure, history of diabetes, and total and HDL cholesterol, corresponding HRs were 1.07 (1.03-1.11) with BMI, 1.10 (1.05-1.14) with waist circumference, and 1.12 (1.08-1.15) with waist-to-hip ratio. Addition of information on BMI, waist circumference, or waist-to-hip ratio to a cardiovascular disease risk prediction model containing conventional risk factors did not importantly improve risk discrimination (C-index changes of -0.0001, -0.0001, and 0.0008, respectively), nor classification of participants to categories of predicted 10-year risk (net reclassification improvement -0.19%, -0.05%, and -0.05%, respectively). Findings were similar when adiposity measures were considered in combination. Reproducibility was greater for BMI (regression dilution ratio 0.95, 95% CI 0.93-0.97) than for waist circumference (0.86, 0.83-0.89) or waist-to-hip ratio (0.63, 0.57-0.70).

Authors conclusion: “BMI, waist circumference, and waist-to-hip ratio, whether assessed singly or in combination, do not importantly improve cardiovascular disease risk prediction in people in developed countries when additional information is available for systolic blood pressure, history of diabetes, and lipids.”

Comment: extensive observational data questioning the additional benefit of measures of obesity where traditional CVD risk factor information is available. Confirms previous data that effect of obesity is seen in effects on other risk factors such as BP and lipid levels. Noted in the text. No change made to the recommendation from the assessment guidelines.

Lifestyle topics

Reference: Ebrahim S, Taylor F, Ward K, Beswick A, Burke M, Davey Smith G. Multiple risk factor interventions for primary prevention of coronary heart disease. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD001561. DOI: 10.1002/14651858.CD001561.pub3.

Summary: A previous version of this Cochrane review was included. As it was updated the outcomes were checked and updated contents included. 16 new trials were identified since the previous search (2006) bringing total number of trials to 55 (163,471 participants) with a median duration of 12 month follow up. Fourteen trials (139,256 participants) with reported clinical event endpoints; total mortality (OR 1.00, 95% CI 0.96-1.05) and CHD mortality (OR 0.99, 95% CI 0.92-1.07). Total mortality and combined fatal and non-fatal cardiovascular events showed benefits from intervention when confined to trials involving people with hypertension (16 trials) and diabetes (5 trials): OR 0.78 (95% CI 0.68 to 0.89) and OR 0.71 (95% CI 0.61 to 0.83), respectively. Net changes (weighted mean differences) in systolic and diastolic blood pressure (53 trials) and blood cholesterol (50 trials) were -2.71 mmHg (95% CI -3.49 to -1.93), -2.13 mmHg (95% CI -2.67 to -1.58) and -0.24 mmol/l (95% CI -0.32 to -0.16), respectively. The OR for reduction in smoking prevalence (20 trials) was 0.87 (95% CI 0.75 to 1.00). Heterogeneity (I^2 > 85%) was noted for all risk factor analysis.

Authors' conclusions
"Interventions using counselling and education aimed at behaviour change do not reduce total or CHD mortality or clinical events in general populations but may be effective in reducing mortality in high-risk hypertensive and diabetic populations. Risk factor declines were modest but owing to marked unexplained heterogeneity between trials, the pooled estimates are of dubious validity. Evidence suggests that health promotion interventions have limited use in general populations."

Reference: Brien SE, Ronksley PE, Turner BJ, Mukamal KJ, Ghali WA. Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: systematic review and meta-analysis of interventional studies. BMJ. 2011; 342: d636.

Summary: (from study)
Of 63 eligible studies, 44 on 13 biomarkers were meta-analysed in fixed or random effects models. Quality was assessed by sensitivity analysis of studies grouped by design. Analyses were stratified by type of beverage (wine, beer, spirits). Alcohol significantly increased levels of high density lipoprotein cholesterol (pooled mean difference 0.094 mmol/L, 95% confidence interval 0.064 to 0.123), apolipoprotein A1 (0.101 g/L, 0.073 to 0.129), and adiponectin (0.56 mg/L, 0.39 to 0.72). Alcohol showed a dose-response relation with high density lipoprotein cholesterol (test for trend P = 0.013). Alcohol decreased fibrinogen levels (-0.20 g/L, -0.29 to -0.11) but did not affect triglyceride levels. Results were similar for crossover and before and after studies, and across beverage types.
Authors conclusion: "Favourable changes in several cardiovascular biomarkers (higher levels of high density lipoprotein cholesterol and adiponectin and lower levels of fibrinogen) provide indirect pathophysiological support for a protective effect of moderate alcohol use on coronary heart disease."

Robust SR of observation studies provides potential reasons for link between modest alcohol and CHD. Included in text.

Appraised by Kelvin Hill	
REFERENCE	**SYSTEMATIC REVIEW**
Patra J, Taylor B, Irving H, Roerecke M, Baliunas D, Mohapatra S, et al. Alcohol consumption and the risk of morbidity and mortality for different stroke types--a systematic review and meta-analysis. BMC Public Health. 2010; 10: 258.	
SOURCE OF FUNDING	
SUMMARY	

Inclusion criteria	Types of studies	26 observational studies (17 cohort & 9 case-control) with ischemic or hemorrhagic strokes. (1) had to be an original research study (not a review); (2) cohort or case-control study in which medically confirmed ischemic or hemorrhagic stroke were end points (i.e., not self-reported endpoint); (3) reporting of RRs or ORs or HRs (or data to calculate these risks) of stroke associated with alcohol consumption compared to abstention; (4) having three or more alcohol drinking exposure groups (i.e., dose-response information was required).
	Participants	General population
	Interventions	Alcohol intake
	Primary outcome	Stroke (both ischaemic and heamorrhagic)
	Additional outcomes	
Search		MEDLINE, EMBASE, CINAHL, CABS, WHOlist, SIGLE, ETOH, and Web of Science databases between 1980 to June 2009 was performed followed by manual searches of bibliographies of key retrieved articles.
Methods of review	Method of applying inclusion criteria	Two reviewers independently extracted the information on study design, participant characteristics, level of alcohol consumption, stroke outcome, control for potential confounding factors, risk estimates and key criteria of study quality using a standardized protocol.
	Assessment of methodological quality	As above two reviewers reviewed study quality.
Comparisons		Different levels of alcohol intake
Main results		The dose-response relationship for hemorrhagic stroke had monotonically increasing risk for increasing consumption, whereas ischemic stroke showed a curvilinear relationship, with a protective effect of alcohol for low to moderate consumption, and increased risk for higher exposure. For more than 3 drinks on average/day, in general women had higher risks than men, and the risks for mortality were higher compared to the risks for morbidity.

QUALITY CHECK

Process	**Questions**	**Answer**	**Comment**
Search:	**Are**:		
	two or more databases named and used	Yes	
	reference lists of selected articles searched	Yes	
	experts and trialists contacted	No	
	any journals searched by hand	Yes	But not stated which
	databases searched from their inception	No	But long enough 1980
	all languages accepted	Yes	
Selection:	**Is there a clear definition of**:		
	the population being studied	Yes	
	the interventions being investigated	Yes	
	the principal outcomes being studied	Yes	
	the study designs included (and excluded)	Yes	
Validity:	**Does the review process**:		
	assess (measure, quantify) the quality of studies identified	Yes	
	blind reviewers to study origin (authors, journal etc)	No	Not stated
	abstract data into a structured database	Yes	
	use two independent people to abstract data and assess study quality	Yes	

	measure heterogeneity and bias of studies included	Yes	
Data:	**For each study are the details (or their absence) noted of**:		
	participants included in study (number and type)	Yes	
	interventions studied	Yes	
	outcome	Yes	
Analysis:	**Does the review process**:		
	undertake meta-analysis or state why not done	Yes	
	investigate agreement between independent assessors	Yes	
	give confidence intervals for outcomes reported	Yes	

CLINICAL IMPLICATIONS	
Benefits	Modest intake may be protective of stroke but increased input increases both IS and HS.
Harms	Increased stroke with increased intake
Comments (ischeamic v heamorraghic, quality issues etc.)	Good quality SR of relevance.

REASON FOR EXCLUSION (Poor quality +not clinically relevant / interesting or if relevant for preamble)	
Include	

RELEVANCE TO AN AUSTRALIAN CONTEXT (Urban and rural / non urban settings)	
Relevant	

OVERALL CONCLUSION

Light to moderate alcohol consumption is associated with a reduced risk of stroke but increased intake increases stroke.

Important new meta-analysis simply confirming previous data to be inclued. No change to the recommendation.

Appraised by Leah Wright

REFERENCE	**SYSTEMATIC REVIEW**
Paul E Ronksley, Susan E Brien, 1 Barbara J Turner, Kenneth J Mukamal, William A Ghali. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis, BMJ 2011;342:d671 doi:10.1136/bmj.d671	

SOURCE OF FUNDING

Contracted operating grant from Program of Research Integrating Substance Use Information into Mainstream Healthcare (PRISM) funded by the Robert Wood Johnson Foundation, project No 58529, with cofunding by the Substance Abuse and Mental Health Services and the Administration Center for Substance Abuse Treatment.

SUMMARY

Inclusion criteria	Types of studies	84 prospective cohort studies
	Participants	Adults >18 years old without pre-existing cardiovascular disease
	Interventions	Active alcohol consumption

	Primary outcome	Presence or absence of death from cardiovascular disease (that is, fatal cardiovascular or stroke events), incident coronary heart disease (fatal or non-fatal incident myocardial infarction, angina, ischaemic heartdisease, or coronary revascularisation), death from coronary heart disease (fatal myocardial infarction or ischaemic heart disease), incident stroke (ischaemic or haemorrhagic events), or death from stroke.
	Additional outcomes	
Search		Medline (1950 through September 2009) and Embase (1980 through September 2009) supplemented by manual searches of bibliographies and conference proceedings
Methods of review	Method of applying inclusion criteria	Prospective cohort studies on the association between alcohol consumption and overall mortality from cardiovascular disease, incidence of and mortality from coronary heart disease, and incidence of and mortality from stroke.
	Assessment of methodological quality	The number of years that participants were followed and adjustment for confounding.
Comparisons		Active alcohol consumption vs life-time abstainers
Main results		The pooled adjusted relative risks for alcohol drinkers relative to non-drinkers in random effects models for the outcomes of interest were 0.75 (95% confidence interval 0.70 to 0.80) for cardiovascular disease mortality (21 studies), 0.71 (0.66 to 0.77) for incident coronary heart disease (29 studies), 0.75 (0.68 to 0.81) for coronary heart disease mortality (31 studies), 0.98 (0.91 to 1.06) for incident stroke (17 studies), and 1.06 (0.91 to 1.23) for stroke mortality (10 studies). Dose-response analysis revealed that the lowest risk of coronary heart disease mortality occurred with 1.2 drinks a day, but for stroke mortality it occurred with .1 drink per day. Secondary analysis of mortality from all causes showed lower risk for drinkers compared with non-drinkers (relative risk 0.87 (0.83 to 0.92)).

QUALITY CHECK

Process	**Questions**	**Answer**	**Comment**
Search:	**Are**:		
	two or more databases named and used	Yes	
	reference lists of selected articles searched	Yes	
	experts and trialists contacted	Yes	
	any journals searched by hand	No	Unclear
	databases searched from their inception	Yes	
	all languages accepted	No	Not stated
Selection:	**Is there a clear definition of**:		
	the population being studied	Yes	
	the interventions being investigated	Yes	
	the principal outcomes being studied	Yes	
	the study designs included (and excluded)	Yes	
Validity:	**Does the review process**:		
	assess (measure, quantify) the quality of studies identified	Yes	
	blind reviewers to study origin (authors, journal etc)	No	Not stated
	abstract data into a structured database	Yes	
	use two independent people to abstract data and assess study quality	Yes	
	measure heterogeneity and bias of studies included	Yes	
Data:	**For each study are the details (or their absence) noted of**:		
	participants included in study (number and type)	Yes	
	interventions studied	Yes	

	outcome	Yes	
Analysis:	**Does the review process**:		
	undertake meta-analysis or state why not done	Yes	
	investigate agreement between independent assessors	Yes	
	give confidence intervals for outcomes reported	Yes	

CLINICAL IMPLICATIONS	
Benefits	There is a positive association between low-moderate alcohol consumption and reduced CV risk.
Harms	
Comments (ischeamic v heamorraghic, quality issues etc.)	
REASON FOR EXCLUSION (Poor quality +not clinically relevant / interesting or if relevant for preamble)	
N/A	
RELEVANCE TO AN AUSTRALIAN CONTEXT (Urban and rural / non urban settings)	
Relevant	
OVERALL CONCLUSION	
Light to moderate alcohol consumption is associated with a reduced risk of multiple cardiovascular outcomes. Important new meta-analysis simply confirming previous data.	

Blood pressure

Template for Intervention Study – Systematic Review		
Topic Blood pressure		
Completed by: Leah Wright		
REFERENCE Sebastiano Sciarretta, MD; Francesca Palano, MD; Giuliano Tocci, MD; Rossella Baldini, PhD; Massimo Volpe, MD. Antihypertensive Treatment and Developmentof Heart Failure in Hypertension, Arch Intern Med. 2011;171(5):384-394.		
SOURCE OF FUNDING		
SUMMARY		
Inclusion criteria	Types of studies	26 RCTs
	Participants	Selected trials included patients with hypertension or a high-risk population with a predominance of patients with hypertension.
	Interventions	antihypertensive strategies in heart failure prevention
	Primary outcome	Absolute incidence of HF

	Additional outcomes	Other major cardiovascular events
Search		1997 through 2009 in peer-reviewed journals indexed in the Pub Med and EMBASE databases were selected.
Methods of review	Method of applying inclusion criteria	RCTs
	Assessment of methodological quality	
Comparisons		Different antihypertensive medications and incidence of HF
Main results		Network meta-analysis showed that diuretics (odds ratio [OR], 0.59; 95% credibility interval [CrI], 0.47-0.73), angiotensin-converting enzyme (ACE) inhibitors (OR, 0.71; 95% CrI, 0.59-0.85) and angiotensin II receptor blockers (ARBs) (OR, 0.76; 95% CrI, 0.62-0.90) represented the most efficient classes of drugs to reduce the heart failure onset compared with placebo. On the one hand, a diuretic-based therapy represented the best treatment because it was significantly more efficient than that based on ACE inhibitors (OR, 0.83; 95% CrI, 0.69-0.99) and ARBs (OR, 0.78; 95% CrI, 0.63-0.97). On the other hand, diuretics (OR, 0.71; 95% CrI, 0.60-0.86), ARBs (OR, 0.91; 95% CrI, 0.78-1.07), and ACE inhibitors (OR, 0.86; 95% CrI, 0.75-1.00) were superior to calcium channel blockers, which were among the least effective first-line agents in heart failure prevention, together with beta-blockers and apha-blockers.

QUALITY CHECK			
Process	Questions	Answer	Comment
Search:	Are:		
	two or more databases named and used	Yes	
	reference lists of selected articles searched	Yes	
	experts and trialists contacted	No	
	any journals searched by hand	No	
	databases searched from their inception	No	
	all languages accepted	No	Not stated
Selection:	Is there a clear definition of:		
	the population being studied	Yes	
	the interventions being investigated	Yes	
	the principal outcomes being studied	Yes	
	the study designs included (and excluded)	Yes	
Validity:	Does the review process:		
	assess (measure, quantify) the quality of studies identified	Yes	
	blind reviewers to study origin (authors, journal etc)	No	
	abstract data into a structured database	yes	
	use two independent people to abstract data and assess study quality	Yes	
	measure heterogeneity and bias of studies included	Yes	
Data:	For each study are the details (or their absence) noted of:		
	participants included in study (number and type)	Yes	

	interventions studied	Yes	
	outcome	Yes	
Analysis:	Does the review process:		
	undertake meta-analysis or state why not done	Yes	
	investigate agreement between independent assessors	No	
	give confidence intervals for outcomes reported	Yes	

CLINICAL IMPLICATIONS	
Benefits	
Harms	
Comments / quality	Moderate quality SR.

REASON FOR EXCLUSION (Poor quality +not clinically relevant / interesting or if relevant for preamble)
Include in text –after systematic review

RELEVANCE TO AN AUSTRALIAN CONTEXT
yes

OVERALL CONCLUSION
Diuretics represented the most effective class of drugs in preventing heart failure, followed by renin-angiotensin system inhibitors. Thus, our findings support the use of these agents as first-line antihypertensive strategy to prevent heart failure in patients with hypertension at risk to develop heart failure. Calcium channel blockers and beta-blockers were found to be less effective in heart failure prevention.

Confirms existing data. Added to text.

Template for Intervention Study – Systematic Review

Topic Blood pressure

Completed by: Leah Wright

REFERENCE Kronish IM, Woodward M, Sergie Z, Ogedegbe G, Falzon L, Mann DM. Meta-analysis: impact of drug class on adherence to antihypertensives. Circulation. 2011 Apr 19;123(15):1611-21.

SOURCE OF FUNDING L. Falzon is supported by grant HL04458-05 from the National Heart, Lung, and Blood Institute. Dr Kronish is supported by grant 1K23HL098359 from the National Heart, Lung, and Blood Institute. Dr Mann is supported by grant 1K23DK081665 from the National Institute of Diabetes, Digestive, and Kidney Diseases.

SUMMARY

Inclusion criteria	Types of studies	Observational cohorts
	Participants	Community-dwelling patients >= 18 years of age
	Interventions	Adherence to antihypertensive medications
	Primary outcome	Pooled hazard ration (HR) of adherence

	Additional outcomes	
Search		The search included all articles and abstracts (including unpublished doctoral theses) referenced from database inception to February 1, 2009, in MEDLINE, the Database of Abstracts of Reviews of Effects, the National Health Service Economic and Evaluation Database, the Health Technology Assessment Database, EMBASE, and PsycINFO.
Methods of review	Method of applying inclusion criteria	Adherence to antihypertensives using medication refill data and contained sufficient data to calculate a measure of relative risk of adherence and its variance.
	Assessment of methodological quality	Sensitivity analyses
Comparisons		Adherence between pairs of drug classes
Main results		The pooled mean adherence by drug class ranged from 28% for -blockers to 65% for angiotensin II receptor blockers. There was better adherence to angiotensin II receptor blockers compared with angiotensin converting enzyme inhibitors (HR, 1.33; 95% confidence interval, 1.13 to 1.57), calcium channel blockers (HR, 1.57; 95% confidence interval, 1.38 to 1.79), diuretics (HR, 1.95; 95% confidence interval, 1.73 to 2.20), and beta-blockers (HR, 2.09; 95% confidence interval, 1.14 to 3.85). Conversely, there was lower adherence to diuretics compared with the other drug classes. The same pattern was present when studies that used odds ratios were pooled. After publication bias was accounted for, there were no longer significant differences in adherence between angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors or between diuretics and beta-blockers.

QUALITY CHECK

Process	Questions	Answer	Comment
Search:	Are:		
	two or more databases named and used	Yes	
	reference lists of selected articles searched	Yes	
	experts and trialists contacted	No	Not stated
	any journals searched by hand	Yes	
	databases searched from their inception	Yes	
	all languages accepted	No	English only
Selection:	Is there a clear definition of:		
	the population being studied	Yes	
	the interventions being investigated	Yes	
	the principal outcomes being studied	Yes	
	the study designs included (and excluded)	Yes	
Validity:	**Does the review process**:		
	assess (measure, quantify) the quality of studies identified	Yes	
	blind reviewers to study origin (authors, journal etc)	No	
	abstract data into a structured database	Yes	

	use two independent people to abstract data and assess study quality	Yes	
	measure heterogeneity and bias of studies included	Yes	
Data:	**For each study are the details (or their absence) noted of**:		
	participants included in study (number and type)	Yes	
	interventions studied	Yes	
	outcome	Yes	
Analysis:	**Does the review process**:		
	undertake meta-analysis or state why not done	Yes	
	investigate agreement between independent assessors	Yes	
	give confidence intervals for outcomes reported	Yes	

CLINICAL IMPLICATIONS	
Benefits	
Harms	
Comments / quality	Observational studies

REASON FOR EXCLUSION (Poor quality +not clinically relevant / interesting or if relevant for preamble)
Include in text –after systematic review

RELEVANCE TO AN AUSTRALIAN CONTEXT
yes

OVERALL CONCLUSION
In clinical settings, there are important differences in adherence to antihypertensives in separate classes, with lowest adherence to diuretics and -blockers and highest adherence to angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors. However, adherence was suboptimal regardless of drug class.

More robust SR based on observational data for compliance. Added to text as doesn't impact on recommendations.

Template for Intervention Study – Systematic Review		
Topic Blood pressure		
Completed by: Kelvin Hill		
REFERENCE Chen N, Zhou M, Yang M, Guo J, Zhu C, Yang J, Wang Y, Yang X, He L. Calcium channel blockers versus other classes of drugs for hypertension. Cochrane Database of Systematic Reviews 2010, Issue 8. Art. No.: CD003654. DOI: 10.1002/14651858.CD003654.pub4.		
SOURCE OF FUNDING West China Hospital, Sichuan University, China. (internal)		
SUMMARY		
Inclusion criteria	Types of studies	Eighteen RCTs (14 dihydropyridines, 4 non-dihydropyridines) with a total of 141,807 participants were included.
	Participants	Participants all had a baseline BP of at least 140 mm Hg systolic or 90 mm Hg diastolic, measured in a standard way on at least 2 occasions. If a trial was not limited to patients with elevated BP it must separately reported outcome data on patients with elevated BP as defined above.

	Interventions	CCBs v placebo or other
	Primary outcome	All cause mortality; CV mortality; MI; stroke; congestive heart failure; major cardiovascular events (MI, congestive heart failure, stroke and cardiovascular mortality); systolic and diastolic BP
	Additional outcomes	
Search		Electronic searches of the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASEand the WHO-ISH Collaboration Register (up to May 2009) were performed. We also checked the references of published studies to identify additional trials.
Methods of review	Method of applying inclusion criteria	Randomized controlled trial (RCT) comparing first-line CCBs with other antihypertensive classes, with at least 100 randomized hypertensive participants and with a follow-up of at least two years. Two authors independently selected the included trials, evaluated the risk of bias and entered the data for analysis.
	Assessment of methodological quality	As per cochrane
Comparisons		
Main results		All-cause mortality was not different between first-line CCBs and any other first-line antihypertensive classes. CCBs reduced the following outcomes as compared to β-blockers: total cardiovascular events (RR 0.84, 95% CI [0.77, 0.92]), stroke (RR 0.77, 95% CI [0.67, 0.88]) and cardiovascular mortality (RR 0.90, 95% CI [0.81, 0.99]). CCBs increased total cardiovascular events (RR 1.05 , 95% CI [1.00, 1.09], p = 0.03) and congestive heart failure events (RR 1.37, 95% CI [1.25, 1.51]) as compared to diuretics. CCBs reduced stroke (RR 0.89, 95% CI [0.80, 0.98]) as compared to ACE inhibitors and reduced stroke (RR 0.85, 95% CI [0.73, 0.99]) and MI (RR 0.83, 95% CI [0.72, 0.96]) as compared to ARBs. CCBs also increased congestive heart failure events as compared to ACE inhibitors (RR 1.16, 95% CI [1.06, 1.27]) and ARBs (RR 1.20, 95% CI [1.06, 1.36]). The other evaluated outcomes were not significantly different.

QUALITY CHECK

Process	**Questions**	**Answer**	**Comment**
Search:	**Are**:		
	two or more databases named and used	Y	
	reference lists of selected articles searched	Y	
	experts and trialists contacted	Y	
	any journals searched by hand	Y	
	databases searched from their inception	Y	
	all languages accepted	Y	
Selection:	**Is there a clear definition of**:		
	the population being studied	Y	
	the interventions being investigated	Y	
	the principal outcomes being studied	Y	
	the study designs included (and excluded)	Y	
Validity:	**Does the review process**:		

	assess (measure, quantify) the quality of studies identified	Y	
	blind reviewers to study origin (authors, journal etc)	N	Not stated
	abstract data into a structured database	Y	
	use two independent people to abstract data and assess study quality	Y	
	measure heterogeneity and bias of studies included	Y	
Data:	**For each study are the details (or their absence) noted of**:		
	participants included in study (number and type)	Y	
	interventions studied	Y	
	outcome	Y	
Analysis:	**Does the review process**:		
	undertake meta-analysis or state why not done	Y	
	investigate agreement between independent assessors	Y	
	give confidence intervals for outcomes reported	Y	

CLINICAL IMPLICATIONS

Benefits	CCBs better than β-blockers. CCBs reduced stroke (RR 0.89, 95% CI [0.80, 0.98]) as compared to ACE inhibitors and reduced stroke (RR 0.85, 95% CI [0.73, 0.99]) and MI (RR 0.83, 95% CI [0.72, 0.96]) as compared to ARBs.
Harms	CCBs increased congestive heart failure events as compared to ACE inhibitors (RR 1.16, 95% CI [1.06, 1.27]) and ARBs (RR 1.20, 95% CI [1.06, 1.36] and increased CVD events compared to diuretics.
Comments / quality	High quality SR.

REASON FOR EXCLUSION (Poor quality +not clinically relevant / interesting or if relevant for preamble)
Include in text –after systematic review

RELEVANCE TO AN AUSTRALIAN CONTEXT
yes

OVERALL CONCLUSION
No overall difference to other classes for all-cause mortality with some variation in CVD endpoints. Fairly consistent with existing reviews –add to text.

Authors concluded:
“Diuretics are preferred first-line over CCBs to optimize reduction of cardiovascular events. The review does not distinguish between CCBs, ACE inhibitors or ARBs, but does provide evidence supporting the use of CCBs over β-blockers. Many of the differences found in the current review are not robust and further trials might change the conclusions. More well-designed RCTs studying the mortality and morbidity of patients taking CCBs as compared with other antihypertensive drug classes are needed for patients with different stages of hypertension, different ages, and with different co-morbidities such as diabetes.”

Template for Intervention Study – Systematic Review		
Topic/question: Blood pressure targets		
Completed by: Leah Wright		
REFERENCE: Sripal Bangalore, MD, MHA; Sunil Kumar, MD; Iryna Lobach, PhD; Franz H. Messerli, MD. Blood Pressure Targets in Subjects With Type 2 Diabetes Mellitus/Impaired Fasting Glucose Observations From Traditional and Bayesian Random-Effects Meta-Analyses of Randomized Trials. Circulation. 2011;123:2799-2810		
SOURCE OF FUNDING		
SUMMARY		
Inclusion criteria	Types of studies	13 RCTs
	Participants	37 736 participants with type 2 diabetes mellitus or impaired fasting glucose/impaired glucose tolerance
	Interventions	Antihypertensive therapy with achieved systolic BP of 135 mm Hg in the intensive BP control group and 140 mm Hg in the standard BP control group
	Primary outcome	All cause mortality; CV mortality; MI; stroke
	Additional outcomes	Microalbuminuria; nephropathy; retinopathy; neoropathy
Search		
Methods of review	Method of applying inclusion criteria	(1) randomized clinical trials of participants with type 2 diabetes mellitus/IFG/IGT (2) reporting >= 1-year outcomes (3) and enrolling at least 100 patients (4) who achieved systolic BP =< 140 mm Hg in both arms.
	Assessment of methodological quality	9 were considered trials with low risk of bias asdescribed in the Methods section. The rest were considered to have an unclear or a high risk of bias
Comparisons		Systolic BP was =<135 mm Hg (intensive group) vs systolic BP =<140 mm Hg (standard group)
Main results		The present body of evidence suggests that intensive BP control (=< 135 mm Hg) reduces the risk of macrovascular (death, stroke) events in patients with type 2 diabetes mellitus/IFG/IGT. A treatment goal of 130 to 135 mm Hg, similar to the achieved BP of 133.5 mm Hg in the standard therapy group of the ACCORD trial, is therefore acceptable, and more aggressive goals to 120 mm Hg can be considered in patients at higher risk of stroke. However, at a systolic BP =< 130 mm Hg, there may be target organ heterogeneity, and these cerebrovascular benefits have to be balanced against an increased risk of SAEs and a lack of benefit for cardiac, renal, and retinal outcomes.
CLINICAL IMPLICATIONS		

QUALITY CHECK			
Process	**Questions**	**Answer**	**Comment**
Search:	**Are**:		
	two or more databases named and used	Y	
	reference lists of selected articles searched	Y	
	experts and trialists contacted	Y	
	any journals searched by hand	N	Not stated

	databases searched from their inception	Y	
	all languages accepted	Y	
Selection:	**Is there a clear definition of**:		
	the population being studied	Y	
	the interventions being investigated	Y	
	the principal outcomes being studied	Y	
	the study designs included (and excluded)	Y	
Validity:	**Does the review process**:		
	assess (measure, quantify) the quality of studies identified	Y	
	blind reviewers to study origin (authors, journal etc)	N	Not stated
	abstract data into a structured database	Y	
	use two independent people to abstract data and assess study quality	Y	
	measure heterogeneity and bias of studies included	Y	
Data:	**For each study are the details (or their absence) noted of**:		
	participants included in study (number and type)	Y	
	interventions studied	Y	
	outcome	Y	
Analysis:	**Does the review process**:		
	undertake meta-analysis or state why not done	Y	
	investigate agreement between independent assessors	Y	
	give confidence intervals for outcomes reported	Y	

Benefits	
Harms	20% increase in serious adverse events at targets of 135/85. 40% increase in serious events at targets of 130/80 although there is heterogeneity.
Comments / quality	High quality systematic review updating all major trials.

REASON FOR EXCLUSION **(Poor quality +not clinically relevant / interesting or if relevant for preamble)**

Note as important new meta-analysis incorporating large new trials included in the current systematic review.

RELEVANCE TO AN AUSTRALIAN CONTEXT

Directly relevant

OVERALL CONCLUSION

Lowering blood pressure greater than the normal targets of 140/90 mmHg reduces CVD outcomes with an increase in adverse events. Lower targets leads to reduced stroke outcomes only (not MI) and increases serious adverse events. A target between 130-135 systolic may be more realistic to balance the risk/benefits of lower targets.

Important to note in guidelines even though outside of literature review dates. Have flagged may lead to changes in BP targets over time but concensus to leave current targets until due consideration and debate in clinical community.

Template for Intervention Study – Systematic Review		
Completed by: Leah Wright		
Ashish Upadhyay, MD; Amy Earley, BS; Shana M. Haynes, DHSc; and Katrin Uhlig, MD, MS. Systematic Review: Blood Pressure Target in Chronic Kidney Disease and Proteinuria as an Effect Modifier, Ann Intern Med. 2011;154:541-548.		
SOURCE OF FUNDING The authors are supported by Kidney Disease: Improving Global Outcomes (KDIGO) to conduct systematic reviews and provide methods support for developing KDIGO guidelines, including the ongoing guideline on management of blood pressure in CKD. The funding source did not participate in the design, conduct, or reporting of the study.		
SUMMARY		
Inclusion criteria	Types of studies	3 RCTs
	Participants	2272 adult patients
	Interventions	Comparing lower versus higher blood pressure targets in adult patients with CKD and focus on proteinuria as an effect modifier
	Primary outcome	death, kidney failure, cardiovascular events, change in kidney function, number of antihypertensive agents, and adverse events
	Additional outcomes	
Search		MEDLINE and the Cochrane Central Register of Controlled Trials (July 2001 through January 2011)
Methods of review	Method of applying inclusion criteria	RCT
	Assessment of methodological quality	Studies graded – not clearly explained.
Comparisons		Comparing blood pressure targets in adults with non–dialysis-dependent CKD
Main results		Overall, trials did not show that a blood pressure target of less than 125/75 to 130/80 mm Hg is more beneficial than a target of less than 140/90 mm Hg. Lower-quality evidence suggests that a low target may be beneficial in subgroups with proteinuria greater than 300 to 1000 mg/d. Participants in the low target groups needed more antihypertensive medications and had a slightly higher rate of adverse events.

QUALITY CHECK			
Process	**Questions**	**Answer**	**Comment**
Search:	**Are**:		
	two or more databases named and used	Yes	
	reference lists of selected articles searched	Yes	
	experts and trialists contacted	No	
	any journals searched by hand	No	Not stated
	databases searched from their inception	No	July 2001 – Jan 2011
	all languages accepted	Yes	
Selection:	**Is there a clear definition of**:		
	the population being studied	Yes	

	the interventions being investigated	Yes	
	the principal outcomes being studied	Yes	
	the study designs included (and excluded)	Yes	
Validity:	**Does the review process**:		
	assess (measure, quantify) the quality of studies identified	Yes	
	blind reviewers to study origin (authors, journal etc)	No	Not stated
	abstract data into a structured database	Yes	
	use two independent people to abstract data and assess study quality	Yes	
	measure heterogeneity and bias of studies included	Yes	
Data:	**For each study are the details (or their absence) noted of**:		
	participants included in study (number and type)	Yes	
	interventions studied	Yes	
	outcome	Yes	
Analysis:	**Does the review process**:		
	undertake meta-analysis or state why not done	Yes	Small number of trials with different definitions of CKD
	investigate agreement between independent assessors	Yes	
	give confidence intervals for outcomes reported	No	NA

CLINICAL IMPLICATIONS	
Benefits	
Harms	
Comments / quality	Moderate to good quality. Only 3 included trials.

REASON FOR EXCLUSION (Poor quality +not clinically relevant / interesting or if relevant for preamble)

Include

RELEVANCE TO AN AUSTRALIAN CONTEXT

Relevant

OVERALL CONCLUSION

Available evidence is inconclusive but does not prove that a blood pressure target of less than 130/80 mm Hg improves clinical outcomes more than a target of less than 140/90 mm Hg in adults with CKD. Whether a lower target benefits patients with proteinuria greater than 300 to 1000 mg/d requires further study.

NOTE: This study has been included in draft CARI guideline on prevention of CVD in those with CKD which has been scrutinised by CARI guideline group with consensus for CKD in that guideline of 140/90 in those with CKD and 130/80 for those with CKD and protenuria. This is similar to draft international kidney guidelines so overwhelming agreement by EWG to align with these targets.

Template for Intervention Study – Randomised Controlled Trial

KEY QUESTION(S)	

BP –class of drug (Q19)	
COMPLETED BY:	
Kelvin Hill	
REFERENCE(S)	
Haller H, Ito S, Izzo JL Jr, Januszewicz A, Katayama S, Menne J, Mimran A, Rabelink TJ, Ritz E, Ruilope LM, Rump LC, Viberti G; ROADMAP Trial Investigators. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. N Engl J Med. 2011 Mar 10;364(10):907-17.	
SOURCE OF FUNDING	
Supported by Daiichi Sankyo.	
METHOD	
Patient Eligibility Criteria	white patients, 18 to 75 years of age, who had type 2 diabetes, normoalbuminuria. The mean duration of diabetes was 6.1 years, and the mean glycated hemoglobin level was 7.7%. More than 97% of the patients had at least two cardiovascular risk factors in addition to type 2 diabetes, and 67.7% had at least four. (33.4% had preexisting CVD).
Study design	Double blind, RCT
Setting	Multicentre trial across europe
Intervention(s)	ARB v placebo in addition to other BP agents
Primary outcome measure	time to the first onset of microalbuminuria, as determined by validated measurements of morning spot urine samples
Additional outcome measures	composite of cardiovascular complications and death from cardiovascular causes and renal events.
Sample Size	4449
Main results	Numbers analysed:4447
	Study duration:mean 3.2 years
	Patients characteristics and group comparability: yes except small diff in BMI, HDL and tryglycerides
	Effect size – primary outcome: hazard ratio for the primary end point was 0.75 (95.1% CI, 0.62 to 0.92; P = 0.006) after adjusting for baseline differences
	Effect size – additional outcomes:

QUALITY CHECK [3]		
Patient selection	YES/NO	Comment
Were the eligibility criteria specified?	Y	
Was a method of randomisation performed?	?Y	Previous publication
Was the treatment allocation concealed?	?	Previous publication
Were the groups similar at baseline regarding the most important prognostic indicators?	Y	Mostly, some differences in BMI, HDL and tryglycerides
Interventions		
Were the index and control interventions explicitly described?	Y	
Was the care provider blinded for the intervention?	Y	
Were co-interventions avoided or comparable?	Y	Other BP agents used in combination allowed and similar
Was the compliance acceptable in all groups?	Y	

Was the patient blinded to the intervention?	Y	
Outcome measurement		
Was the outcome assessor blinded to the interventions?	Y	Double blind
Were the outcome measures relevant?	Y	
Were adverse effects described?	Y	
Was the withdrawal/drop-out rate described and acceptable?	Y	
Was a short-term follow-up measurement performed?	Y	
Was a long-term follow-up measurement performed?	Y	Mean 3.2 years
Was the timing of the outcome assessment in both groups comparable?	Y	
Statistics		
Was the sample size for each group described?	Y	
Did the analysis include an intention-to-treat analysis?	y	
Were point estimates and measures or variability presented for the primary outcome measures?	Y	

CLINICAL IMPLICATIONS	
Benefits	Decrease renal complications and delay in renal complications.
Harms	Similar adverse events
Comments	Drug funded trial. 1/3 of patients had preexisting CVD. No difference in CVD events although increase in CVD mortality although numbers were small (15v3) and a high number occurred in those with CHD.

REASON FOR EXCLUSION
Note in text

RELEVANCE TO AN AUSTRALIAN CONTEXT
Yes –study conducted in European centres but applicable to Aust setting.

OVERALL CONCLUSIONS
ARBs reduce onset of renal complications. No difference in CVD events (esp primary prevention cohort) Similar outcomes to existing data. Hence include in text with no difference to recommendations.

Lipids

Template for Intervention Study – Systematic Review
Topic/question: Lipids Q 14
Completed by: Kelvin
REFERENCE: Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010 Nov 13;376(9753):1670-81.
SOURCE OF FUNDING UK Medical Research Council, British Heart Foundation, and, previously, the European Community Biomed Programme, Australian National Health and Medical Research Council and National Heart Foundation.
SUMMARY

Inclusion criteria	Types of studies	5 trials of more vs less intense (39,612 subjects –all with pre-existing CVD); 21 RCTs statin vs control (129,526 subjects); of which 54% (70025) had no prior CVD.
	Participants	Those with or without CVD
	Interventions	More intense statins v less intense
	Primary outcome	Cause-specifi c mortality, major coronary event (coronary death or non-fatal myocardial infarction), coronary revascularisation (angioplasty or bypass grafting), stroke (subdivided by type), and new cancer diagnosis (subdivided by site). a major vascular event was defi ned as the fi rst occurrence of any major coronary event, coronary revascularisation, or stroke.
	Additional outcomes	
Search		Not reported
Methods of review	Method of applying inclusion criteria	Trials were eligible for inclusion if: the main eff ect of the intervention was to lower LDL cholesterol; no other diff erences in risk factor modifi cation were intended; and at least 1000 participants were to be recruited with at least 2 years' scheduled treatment duration.
	Assessment of methodological quality	Yes as per Cochrane review
Comparisons		placebo
Main results		When all trials were combined, similar proportional reductions in major vascular events per 1·0 mmol/L LDL cholesterol reduction were found in all types of patient studied (RR 0·78, 95% CI 0·76–0·80; p<0·0001), including those with LDL cholesterol lower than 2 mmol/L on the less intensive or control regimen. Across all 26 trials, all-cause mortality was reduced by 10% per 1·0 mmol/L LDL reduction (RR 0·90, 95% CI 0·87–0·93; p<0·0001), largely reflecting significant reductions in deaths due to coronary heart disease (RR 0·80, 99% CI 0·74–0·87; p<0·0001) and other cardiac causes (RR 0·89, 99% CI 0·81–0·98; p=0·002), with no signifi cant effect on deaths due to stroke (RR 0·96, 95% CI 0·84–1·09; p=0·5) or other vascular causes (RR 0·98, 99% CI 0·81–1·18; p=0·8). No signifi cant effects were observed on deaths due to cancer or other non-vascular causes (RR 0·97, 95% CI 0·92–1·03; p=0·3) or on cancer incidence (RR 1·00, 95% CI 0·96–1·04; p=0·9), even at low LDL cholesterol concentrations. Effects on major vascular events per 1·0 mmol/L reduction in LDL cholesterol, reduced by 25% in those without CVD at baseline (1.4% vs 1.8% per year) RR 0・75 (0・69−0・82).
CLINICAL IMPLICATIONS		

QUALITY CHECK

Process	**Questions**	**Answer**	**Comment**
Search:	**Are**:		
	two or more databases named and used	N	Not stated
	reference lists of selected articles searched	N	
	experts and trialists contacted	Y	
	any journals searched by hand	N	Not stated
	databases searched from their inception	N	Built on previous systematic reviews.
	all languages accepted	?	

Selection:	**Is there a clear definition of**:		
	the population being studied	Y	
	the interventions being investigated	Y	
	the principal outcomes being studied	Y	
	the study designs included (and excluded)	Y	
Validity:	**Does the review process**:		
	assess (measure, quantify) the quality of studies identified	N	
	blind reviewers to study origin (authors, journal etc)	N	Not stated
	abstract data into a structured database	N	
	use two independent people to abstract data and assess study quality	N	
	measure heterogeneity and bias of studies included	Y	
Data:	**For each study are the details (or their absence) noted of**:		
	participants included in study (number and type)	Y	
	interventions studied	Y	
	outcome	Y	
Analysis:	**Does the review process**:		
	undertake meta-analysis or state why not done	Y	
	investigate agreement between independent assessors	Y	
	give confidence intervals for outcomes reported	Y	

Benefits	Reduced mortality and CVD endpoints.
Harms	No significant difference adverse events
Comments / quality	Important individual patient meta-analysis. Normal methodology for SR unclear.

REASON FOR EXCLUSION (Poor quality +not clinically relevant / interesting or if relevant for preamble)
Note as important new meta-analysis

RELEVANCE TO AN AUSTRALIAN CONTEXT
Directly relevant

OVERALL CONCLUSION
Important review with clear benefits of statins on CVD outcomes without harms. 25% reduction in CVD events per 1mmol/L reduction in LDL-C in primary prevention cohort. Does not change the overall summary/evidence of this topic or the recommendations (strengthens case).

KEY QUESTION(S)
Lipids and CKD Q14
COMPLETED BY:
Leah Wright
REFERENCE(S)
Colin Baigent, Martin J Landray, Christina Reith et al on behalf of the SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. The Lancet, Published Online June 9, 2011 DOI:10.1016/S0140-6736(11)60739-3
SOURCE OF FUNDING

Merck/Schering-Plough Pharmaceuticals	
METHOD	
Patient Eligibility Criteria	Pts 40 years and over with chronic kidney disease (3023 on dialysis and 6247 not) with no known history of myocardial infarction or coronary revascularisation.
Study design	Randomised double-blind trial
Setting	Out-patient, Oxford
Intervention(s)	Simvastatin 20 mg plus ezetimibe 10 mg daily versus matching placebo
Primary outcome measure	First major atherosclerotic event (non-fatal myocardial infarction or coronary death, non-haemorrhagic stroke, or any arterial revascularisation procedure).
Additional outcome measures	
Sample Size	9270 patients
Main results	**Numbers analysed:** 9270
	Study duration: 4 years
	Patients characteristics and group comparability: Good
	Effect size – primary outcome: 4650 patients were assigned to receive simvastatin plus ezetimibe and 4620 to placebo. Allocation to simvastatin plus ezetimibe yielded an average LDL cholesterol difference of 0·85 mmol/L (SE 0·02; with about two-thirds compliance) during a median follow-up of 4·9 years and produced a 17% proportional reduction in major atherosclerotic events (526 [11·3%] simvastatin plus ezetimibe vs 619 [13·4%] placebo; rate ratio [RR] 0·83, 95% CI 0·74–0·94; log-rank p=0·0021). Non-significantly fewer patients allocated to simvastatin plus ezetimibe had a non-fatal myocardial infarction or died from coronary heart disease (213 [4·6%] vs 230 [5·0%]; RR 0·92, 95% CI 0·76–1·11; p=0·37) and there were significant reductions in non-haemorrhagic stroke (131 [2·8%] vs 174 [3·8%]; RR 0·75, 95% CI 0·60–0·94; p=0·01) and arterial revascularisation procedures (284 [6·1%] vs 352 [7·6%]; RR 0·79, 95% CI 0·68–0·93; p=0·0036). After weighting for subgroup-specific reductions in LDL cholesterol, there was no good evidence that the proportional effects on major atherosclerotic events diff ered from the summary rate ratio in any subgroup examined, and, in particular, they were similar in patients on dialysis and those who were not. The excess risk of myopathy was only two per 10 000 patients per year of treatment with this combination (9 [0·2%] vs 5 [0·1%]). There was no evidence of excess risks of hepatitis (21 [0·5%] vs 18 [0·4%]), gallstones (106 [2·3%] vs 106 [2·3%]), or cancer (438 [9·4%] vs 439 [9·5%], p=0·89) and there was no significant excess of death from any non-vascular cause (668 [14·4%] vs 612 [13·2%], p=0·13).
	Effect size – additional outcomes:

QUALITY CHECK [3]		
Patient selection	**YES/NO**	**Comment**
Were the eligibility criteria specified?	Yes	
Was a method of randomisation performed?	Yes	Computer randomisation
Was the treatment allocation concealed?	Yes	
Were the groups similar at baseline regarding the most important	Yes	

prognostic indicators?		
Interventions		
Were the index and control interventions explicitly described?	Yes	
Was the care provider blinded for the intervention?	Yes	
Were co-interventions avoided or comparable?	Yes	
Was the compliance acceptable in all groups?	Yes	
Was the patient blinded to the intervention?	Yes	
Outcome measurement		
Was the outcome assessor blinded to the interventions?	Yes	
Were the outcome measures relevant?	Yes	
Were adverse effects described?	Yes	
Was the withdrawal/drop-out rate described and acceptable?	Yes	
Was a short-term follow-up measurement performed?	Yes	2, 6 and 12 months
Was a long-term follow-up measurement performed?	Yes	Every 6 months for 4 years
Was the timing of the outcome assessment in both groups comparable?	Yes	
Statistics		
Was the sample size for each group described?	Yes	
Did the analysis include an intention-to-treat analysis?	Yes	
Were point estimates and measures or variability presented for the primary outcome measures?	Yes	

CLINICAL IMPLICATIONS	
Benefits	Reductions in CVD events
Harms	Little difference in harms
Comments	Important outcomes from trial included in systematic review (early outcomes).

REASON FOR EXCLUSION
N/A
RELEVANCE TO AN AUSTRALIAN CONTEXT
Relevant
OVERALL CONCLUSIONS
Reduction of LDL cholesterol with simvastatin 20 mg plus ezetimibe 10 mg daily safely reduced the incidence of major atherosclerotic events in a wide range of patients with advanced chronic kidney disease. ACTION: included in text as important recent study published during guidelines finalisation. No additional recommendation made regarding combination therapy for lipid lowering in those with CKD.

Template for Intervention Study – Systematic Review		
Topic/question: Lipids Q 14		
Completed by: Kelvin Hill		
REFERENCE: Taylor F, Ward K, Moore THM, Burke M, Davey Smith G, Casas JP, Ebrahim S. Statins for the primary prevention of cardiovascular disease. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD004816. DOI: 10.1002/14651858.CD004816.pub4.		
SOURCE OF FUNDING Internal sources • Department of Social Medicine, University of Bristol, UK. External sources • Department of Health Funding for the Cochrane Heart Group, UK.		
SUMMARY		
Inclusion criteria	Types of studies	14 RCTs (16 trial arms; 34,272 participants)
	Participants	Those without CVD with high (or at high risk) of high cholesterol
	Interventions	Statin v placebo
	Primary outcome	All cause mortality, fatal and non-fatal CHD, CVD and stroke events, combined endpoints (fatal and non-fatal CHD, CVD and stroke events).
	Additional outcomes	change in blood total cholesterol concentration, revascularisation, adverse events, quality of life and costs
Search		Built on previous robust reviews. Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library (Issue1, 2007), MEDLINE (2001 to March 2007) and EMBASE (2003 to March 2007). A standard RCT filter was used for MEDLINE and EMBASE. No language restrictions were applied to either searching or trial inclusion. Reference lists of identified review articles and of all included RCTs were searched to find other potentially eligible studies.
Methods of review	Method of applying inclusion criteria	RCTs of statins with minimum duration of one year and follow-up of six months, in adults with no restrictions on their total low density lipoprotein (LDL) or high density lipoprotein (HDL) cholesterol levels, and where 10% or less had a history of CVD, were included.
	Assessment of methodological quality	Yes as per Cochrane review
Comparisons		Placebo
Main results		Eleven trials recruited patients with specific conditions (raised lipids, diabetes, hypertension, microalbuminuria). All-cause mortality was reduced by statins (RR 0.83, 95% CI 0.73 to 0.95) as was combined fatal and non-fatal CVD endpoints (RR 0.70, 95% CI 0.61 to 0.79). Benefits were also seen in the reduction of revascularisation rates (RR 0.66, 95% CI 0.53 to 0.83). Total cholesterol and LDL cholesterol were reduced in all trials but there was evidence of heterogeneity of effects. There was no clear evidence of any significant harm caused by statin prescription or of effects on patient quality of life.
CLINICAL IMPLICATIONS		

QUALITY CHECK			
Process	**Questions**	**Answer**	**Comment**
Search:	**Are**:		

	two or more databases named and used	Y	
	reference lists of selected articles searched	Y	
	experts and trialists contacted	Y	
	any journals searched by hand	N	Not stated
	databases searched from their inception	N	Built on previous systematic reviews.
	all languages accepted	Y	
Selection:	**Is there a clear definition of**:		
	the population being studied	Y	
	the interventions being investigated	Y	
	the principal outcomes being studied	Y	
	the study designs included (and excluded)	Y	
Validity:	**Does the review process**:		
	assess (measure, quantify) the quality of studies identified	Y	
	blind reviewers to study origin (authors, journal etc)	N	Not stated
	abstract data into a structured database	Y	
	use two independent people to abstract data and assess study quality	Y	
	measure heterogeneity and bias of studies included	Y	
Data:	**For each study are the details (or their absence) noted of**:		
	participants included in study (number and type)	Y	
	interventions studied	Y	
	outcome	Y	
Analysis:	**Does the review process**:		
	undertake meta-analysis or state why not done	Y	
	investigate agreement between independent assessors	Y	
	give confidence intervals for outcomes reported	Y	

Benefits	Reduced mortality and CVD endpoints.
Harms	No significant difference. Not enough details on quality of life
Comments / quality	High quality systematic review (new Cochrane review). Does not consider absolute risk approach but does suggest with uncertainly in trials that low risk may not benefit from treatment.

REASON FOR EXCLUSION (Poor quality +not clinically relevant / interesting or if relevant for preamble)
Include as important new meta-analysis

RELEVANCE TO AN AUSTRALIAN CONTEXT
Directly relevant

OVERALL CONCLUSION
Robust Cochrane review with clear benefits of statins on CVD outcomes without harms. Authors state “Caution should be taken in prescribing statins for primary prevention among people at low cardiovascular risk.”
NOTE: All trials had <10% previous CVD at baseline. Other previous SR have used <20% or Ray et al excluded all pre-existing CVD.

Does not change the overall summary of this topic or the recommendations (strengthens case) but important given confusion in interpretation in primary care setting. Added to text.

Antiplatelet

Template for Intervention Study – Randomised Controlled Trial

KEY QUESTION(S)	
Q18, antiplatelets	
COMPLETED BY:	
Leah Wright	
REFERENCE(S)	
Stuart J. Connolly, M.D., John Eikelboom, M.B., B.S., Campbell Joyner, M.D., Hans-Christoph Diener, M.D., Ph.D., Robert Hart, M.D., Sergey Golitsyn, M.D., Ph.D., Greg Flaker, M.D., Alvaro Avezum, M.D., Ph.D., Stefan H. Hohnloser, M.D., Rafael Diaz, M.D., Mario Talajic, M.D., Jun Zhu, M.D., Prem Pais, M.B., B.S., M.D., Andrzej Budaj, M.D., Ph.D., Alexander Parkhomenko, M.D., Ph.D., Petr Jansky, M.D., Patrick Commerford, M.B., Ch.B., Ru San Tan, M.B., B.S., Kui-Hian Sim, M.B., B.S., Basil S. Lewis, M.D., Walter Van Mieghem, M.D., Gregory Y.H. Lip, M.D., Jae Hyung Kim, M.D., Ph.D., Fernando Lanas-Zanetti, M.D., Antonio Gonzalez-Hermosillo, M.D., Antonio L. Dans, M.D., Muhammad Munawar, M.D., Ph.D., Martin O'Donnell, M.B., Ph.D., John Lawrence, M.D., Gayle Lewis, Rizwan Afzal, M.Sc., and Salim Yusuf, M.B., B.S., D.Phil., for the AVERROES Steering Committee and Investigators. Apixaban in Patients with Atrial Fibrillation, N Engl J Med 2011;364:806-17.	
SOURCE OF FUNDING	
Bristol-Myers Squibb and Pfizer. Clinical Trials.gov number, NCT00496769 Authors interests published.	
METHOD	
Patient Eligibility Criteria	Adult patients with atrial fibrillation who were at increased risk for stroke and for whom vitamin K antagonist therapy was unsuitable
Study design	**RCT**
Setting	**522 centres in 36 countries**
Intervention(s)	Apixaban (at a dose of 5 mg twice daily) vs aspirin (81 to 324 mg per day)
Primary outcome measure	Stroke or systemic embolism
Additional outcome measures	Rates of myocardial infarction, death from vascular causes, and death from any cause, as well as of composites of major vascular events.
Sample Size	5599
Main results	**Numbers analysed: 5599**
	Study duration: 3 years (although terminated early when analysis conducted on first 50% of primary efficacy events had accrued.
	Patients characteristics and group comparability: Equal
	Effect size – primary outcome: Before enrollment, 40% of the patients had used a vitamin K antagonist. The data and safety monitoring board recommended early termination of the study because of a clear benefit in favor of apixaban. There were 51 primary outcome events (1.6% per year) among patients assigned to apixaban and 113 (3.7% per year) among those assigned to aspirin (hazard ratio with apixaban, 0.45; 95% confidence interval [CI], 0.32 to 0.62; P<0.001). The rates of death were 3.5% per year in the apixaban group and 4.4% per year in the aspirin group (hazard ratio, 0.79; 95% CI, 0.62 to 1.02; P = 0.07). The risk of a first hospitalization for cardiovascular causes was reduced with apixaban as compared with aspirin (12.6% per year vs. 15.9% per year, P<0.001). The treatment effects were consistent among important subgroups.

	Effect size – additional outcomes: There were 44 cases of major bleeding (1.4% per year) in the apixaban group and 39 (1.2% per year) in the aspirin group (hazard ratio with apixaban, 1.13; 95% CI, 0.74 to 1.75; P = 0.57); there were 11 cases of intracranial bleeding with apixaban and 13 with aspirin.

QUALITY CHECK [3]		
Patient selection	**YES/NO**	**Comment**
Were the eligibility criteria specified?	Yes	
Was a method of randomisation performed?	Yes	24-hour central, computerized, automated voice-response system
Was the treatment allocation concealed?	Yes	
Were the groups similar at baseline regarding the most important prognostic indicators?	Yes	
Interventions		
Were the index and control interventions explicitly described?	Yes	
Was the care provider blinded for the intervention?	Yes	
Were co-interventions avoided or comparable?	Yes	
Was the compliance acceptable in all groups?		
Was the patient blinded to the intervention?	Yes	
Outcome measurement		
Was the outcome assessor blinded to the interventions?	Not sure	
Were the outcome measures relevant?	Yes	
Were adverse effects described?	Yes	
Was the withdrawal/drop-out rate described and acceptable?	NA	Trial terminated early
Was a short-term follow-up measurement performed?	Yes	
Was a long-term follow-up measurement performed?	Yes	Mean follow-up 1.1 years
Was the timing of the outcome assessment in both groups comparable?	Yes	
Statistics		
Was the sample size for each group described?	Yes	
Did the analysis include an intention-to-treat analysis?	Yes	
Were point estimates and measures or variability presented for the primary outcome measures?	yes	

CLINICAL IMPLICATIONS	
Benefits	Reduced CVD events. Possible reduction in mortality.
Harms	No difference in important harms such as bleeding
Comments	Important new trial to report in text.

REASON FOR EXCLUSION
Include but noted early termination and pharma sponsorship.

RELEVANCE TO AN AUSTRALIAN CONTEXT
yes

OVERALL CONCLUSIONS
In patients with atrial fibrillation for whom vitamin K antagonist therapy was unsuitable, apixaban reduced the risk of stroke or systemic embolism without significantly increasing the risk of major bleeding or intracranial hemorrhage. NOTE: important new study to include in text. No recommendations specific to AF made so no impact on recommendation.

Appendix 2. Data extraction and critical appraisal templates

Methodological quality of included systematic reviews and controlled trials was assessed initially using the Scottish Intercollegiate Guidelines Network (SIGN) *Methodology checklist for systematic reviews and meta-analyses* and *Randomised trials*. For diagnostic studies identified, the SIGN *Methodological checklist for diagnostic studies* was used. The SIGN templates are available online (http://www.sign.ac.uk/methodology/checklists.html). Other data extraction and critical appraisals undertaken by the NSF project team in conjunction with the Centre for Allied Health Evidence (iCAHE), University of South Australia, used a modified checklist based on the SIGN templates and the Guidelines International Network draft evidence tables. These checklists were developed and used previously by the NSF and provide additional detail. A copy of templates for systematic reviews and randomised controlled trials are included below.

Template[1] for Intervention [2] Study – Systematic Review

Completed by:

Date:

REFERENCE

SOURCE OF FUNDING

SUMMARY		
Inclusion criteria	**Types of studies**	
	Participants	
	Interventions	
	Primary outcome	
	Additional outcomes	
Search		

Methods of review	**Method of applying inclusion criteria**	
	Assessment of methodological quality	
Comparisons		
Main results		

QUALITY CHECK

Process	**Questions**	**Answer**	**Comment**
Search:	**Are**:		
	two or more databases named and used		
	reference lists of selected articles searched		
	experts and trialists contacted		
	any journals searched by hand		
	databases searched from their inception		
	all languages accepted		
Selection:	**Is there a clear definition of**:		
	the population being studied		
	the interventions being investigated		
	the principal outcomes being studied		
	the study designs included (and excluded)		
Validity:	**Does the review process**:		
	assess (measure, quantify) the quality of studies identified		
	blind reviewers to study origin (authors, journal etc)		
	abstract data into a structured database		
	use two independent people to abstract data and assess study quality		
	measure heterogeneity and bias of studies included		
Data:	**For each study are the details (or their absence) noted of**:		
	participants included in study (number and type)		
	interventions studied		
	outcome		
Analysis:	**Does the review process**:		
	undertake meta-analysis or state why not done		
	investigate agreement between independent assessors		
	give confidence intervals for outcomes reported		

CLINICAL IMPLICATIONS

Benefits	
Harms	
Comments	

(ischeamic v heamorraghic, quality issues etc.)	

REASON FOR EXCLUSION (Poor quality +not clinically relevant / interesting or if relevant for preamble)

RELEVANCE TO AN AUSTRALIAN CONTEXT (Urban and rural / non urban settings)

OVERALL CONCLUSION

Instructions to complete the table:

REFERENCE

SOURCE OF FUNDING
Specify the source of funding: public research funds, government, non government organisation, healthcare industry or other (give name of organisation or corporation). Note if no funding source listed.

SUMMARY		
Inclusion criteria	**Types of studies**	**Specify type and number of studies in the review**
	Participants	**Specify number and type of participants**
	Interventions	Precise details of the interventions for the review
	Primary outcome	State primary outcome measure for the intervention
	Additional outcomes	Describe other outcome measures reviewed
Search		
Methods of review	**Method of applying inclusion criteria**	**State reasons for inclusion**
	Assessment of methodological quality	How did you assess the quality of papers selected for inclusion in review
Comparisons		Describe controls
Main results		Describe the results

QUALITY CHECK
When reading the systematic review, use this checklist which primarily applies to the methods used in the review process. The questions do not apply to the studies included in the review. Occasionally you may only find the answer in the Results section. For each question you should answer, on the basis of the information you can find easily: Answer either: Yes, if there is no doubt No, if there is doubt or it cannot be determined easily.

CLINICAL IMPLICATIONS	
Benefits	Describe discrepancies between the studies
Harms	Describe discrepancies between the studies
Comments	

REASON FOR EXCLUSION (Poor quality +not clinically relevant / interesting or if relevant for preamble)

RELEVANCE TO AN AUSTRALIAN CONTEXT (Urban and rural / non urban settings)

OVERALL CONCLUSION
Report the review's conclusion.

[1] Minimum data abstracted from a single study to allow consistent comparison across studies and to inform a group process in evidence synthesis.

[2] This template is based on evidence tables developed by Guidelines International Network (G-I-N).

[3] The quality check is from the *UK National Clinical Guidelines for Stroke 2008* and is based on the QUOROM (Quality Of Reporting Of Meta-analysis) statement.

Template[1] for Intervention [2] Study – Randomised Controlled Trial

KEY QUESTION(S)

COMPLETED BY:

REFERENCE(S)

SOURCE OF FUNDING

METHOD	
Patient Eligibility Criteria	
Study design	
Setting	
Intervention(s)	
Primary outcome measure	
Additional outcome measures	
Sample Size	
Main results	Numbers analysed:
	Study duration:
	Patients characteristics and group comparability:
	Effect size – primary outcome:
	Effect size – additional outcomes:

QUALITY CHECK [3]		
Patient selection	YES/NO	Comment
Were the eligibility criteria specified?		
Was a method of randomisation performed?		
Was the treatment allocation concealed?		
Were the groups similar at baseline regarding the most important prognostic indicators?		
Interventions		
Were the index and control interventions explicitly described?		
Was the care provider blinded for the intervention?		
Were co-interventions avoided or comparable?		
Was the compliance acceptable in all groups?		
Was the patient blinded to the intervention?		
Outcome measurement		
Was the outcome assessor blinded to the interventions?		
Were the outcome measures relevant?		

Were adverse effects described?		
Was the withdrawal/drop-out rate described and acceptable?		
Was a short-term follow-up measurement performed?		
Was a long-term follow-up measurement performed?		
Was the timing of the outcome assessment in both groups comparable?		
Statistics		
Was the sample size for each group described?		
Did the analysis include an intention-to-treat analysis?		
Were point estimates and measures or variability presented for the primary outcome measures?		

CLINICAL IMPLICATIONS	
Benefits	
Harms	
Comments	

REASON FOR EXCLUSION

RELEVANCE TO AN AUSTRALIAN CONTEXT

OVERALL CONCLUSIONS

Instructions to complete the table:

When no element can be added under one or more heading, state:

“Not applicable” when an item is not to be informed (according to the type of study);

“Not described” when an item must be informed but no information is given in the publication.

Describe all the results given in the manuscript even if those are not relevant to the study aim.

Refer to the addendum for added results calculated or reconstructed by the reviewer.

REFERENCE(S)

SOURCE OF FUNDING
Specify the source of funding: public research funds, government, non government organisation, healthcare industry or other (give name of organisation or corporation). Note if no funding source listed.

METHOD	
Patient Eligibility Criteria	State the inclusion and exclusion criteria
Study design	Specify the study design: Prospective study, randomized study, cross sectional study, retrospective study, cohort study, case control study etc
Setting	Number of centres, countries involved, healthcare setting, urban/rural/mixed
Intervention(s)	Precise details of the interventions for each group (including dose, length, regimen and timing if relevant)
Primary outcome measure	State primary outcome measure, usually the one used for sample size calculation
Additional outcome measures	Brief description
Sample Size	Give the calculated number in each group and the actual number of patients in each group
Main results	Numbers analysed – give the number of patients in each group, in particular in the intention to treat analysis in comparative studies
	Study duration: Start and end dates of the study, inclusion of follow up periods
	Patients characteristics and group comparability: Describe discrepancies between the groups
	Effect size – primary outcome: Summary of the primary outcome in each and between groups: effect size and its precision (p value, CI)
	Effect size – additional outcomes: Brief description

QUALITY CHECK [3]	Assessment: YES; definitely satisfied/described clearly in text NO; not satisfied, or unable to determine from text.
Patient selection	
Were the eligibility criteria specified?	In order to score a 'YES', there must be explicit description of inclusion and/or exclusion criteria
Was a method of randomisation performed?	A random (unpredictable) assignment sequence (eg numbered opaque sealed envelopes). Methods of allocation using date of birth, date of admission, hospital numbers or alternation are not regarded as appropriate ('NO').
Was the treatment allocation concealed?	Assignment generated by an independent person not responsible for determining eligibility of the patient. This person has no information about the people included in the trial and no influence on the assignment sequence of the decision about eligibility of the patient.
Were the groups similar at baseline regarding the most important prognostic indicators?	In order to score a 'YES', groups have to be similar at baseline with regard to age, the outcome variables (if recorded) and any known and recorded prognostic factors. If a baseline difference exists in one of these factors, a 'NO' is scored.
Interventions	
Were the index and control interventions explicitly described?	Adequate description of type, modality, application technique, intensity, duration and frequency of sessions for both the index intervention and control intervention(s) in order to be able to replicate the study.
Was the care provider blinded for the intervention?	The reviewer determines when enough information about the blinding is given in order to score a 'Yes'. For exercise therapy a 'No' is always scored for this item.
Were co-interventions avoided or comparable?	Co-interventions should either be avoided or comparable between the index and

	control groups.
Was the compliance acceptable in all groups?	The reviewer determines when compliance with the interventions is acceptable, based on the reported intensity, duration, number and frequency of sessions for both the experimental intervention and control intervention. Compliance >70% in all groups is considered to be sufficient.
Was the patient blinded to the intervention?	The reviewer determines (per outcome parameter) when enough information about the blinding is given to score a 'Yes'. For exercise therapy a 'No' is always scored for this item.
Outcome measurement	
Was the outcome assessor blinded to the interventions?	The reviewer determines (per outcome parameter) when enough information about blinding is given to score a 'Yes'.
Were the outcome measures relevant?	The reviewer determines whether the outcome measures were relevant. Usually in rehabilitation it will be an activity or participation measure, but in other trials mortality, length of stay, impairment severity or even computed tomography (CT) scan data may be appropriate.
Were adverse effects described?	Each event should be described and correctly attributed to allocated treatment: if it is explicitly reported that 'no adverse effects' have occurred, a 'Yes' is scored.
Was the withdrawal/drop-out rate described and acceptable?	Participants who were included in the study but did not complete the observation period, or were not included in the analysis, must be described. If the percentage of withdrawals and drop-outs does not exceed 20% for short-term follow-up and 30% long-term follow up, and does not lead to substantial bias, a 'Yes' is scored. No report of drop-outs is scored as 'Don't know'.
Was a short-term follow-up measurement performed?	Outcome assessment at the end of the intervention period.
Was a long-term follow-up measurement performed?	Outcome assessment ≥3 months after the end of the intervention period.
Was the timing of the outcome assessment in both groups comparable?	Timing of outcome assessment identical for all intervention groups; for all important outcome assessments
Statistics	
Was the sample size for each group described?	To be presented for each group at randomisation and for the most important outcome assessments.
Did the analysis include an intention-to-treat analysis?	All randomised patients are reported/analysed for the most important moments of effect measurement (minus missing values), irrespective of non-compliance and co-interventions.
Were point estimates and measures or variability presented for the primary outcome measures?	For all of the important outcome measures both point estimates and measures of variability should be presented separately. Point estimates are: means, medians, modes, etc; measures of variability are: standard deviations, 95% confidence intervals, etc. For dichotomous or categorical data, proportions have to be presented.

CLINICAL IMPLICATIONS	
Benefits	Describe discrepancies between the groups
Harms	Describe discrepancies between the groups
Comments	ischaemic v haemorrhagic, quality issues etc

REASON FOR EXCLUSION
Poor quality +not clinically relevant / interesting or if relevant for preamble

RELEVANCE TO AN AUSTRALIAN CONTEXT
ie. Urban and rural / non urban settings

OVERALL CONCLUSIONS
Report the authors' conclusion

[1] Minimum data abstracted from a single study to allow consistent comparison across studies and to inform a group process in evidence synthesis.

[2] This template is based on evidence tables developed by Guidelines International Network (G-I-N).

[3] The quality check is from the *UK National Clinical Guidelines for Stroke 2008* and is based on the QUOROM (Quality Of Reporting Of Meta-analysis) statement.