Appendix A: Summary of evidence from surveillance

4-year surveillance (2018) – Cardiovascular disease: risk assessment and reduction, including lipid modification (2014) NICE guideline CG181

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Summary of evidence from surveillance

Identifying and assessing cardiovascular disease (CVD) risk

181-01 Identification of people requiring assessment of CVD risk

Recommendations in this section of the guideline

1.1.1 For the primary prevention of CVD in primary care, use a systematic strategy to identify people who are likely to be at high risk. [2008, amended 2014]

1.1.2 Prioritise people on the basis of an estimate of their CVD risk before a full formal risk assessment. Estimate their CVD risk using CVD risk factors already recorded in primary care electronic medical records. [2008]

1.1.3 People older than 40 should have their estimate of CVD risk reviewed on an ongoing basis. [2008]

1.1.4 Prioritise people for a full formal risk assessment if their estimated 10‑year risk of CVD is 10% or more. [2008, amended 2014]

1.1.5 Discuss the process of risk assessment with the person identified as being at risk, including the option of declining any formal risk assessment. [2008]

1.1.6 Do not use opportunistic assessment as the main strategy in primary care to identify CVD risk in unselected people. [2008]

Surveillance decision

This review question should be updated.

4-year surveillance summary

Monitoring intervals

A systematic review(1) (115 studies, 138 datasets, n=unreported) examined the clinical value and cost-effectiveness of different lipid measures and monitoring intervals for managing primary and secondary cardiovascular disease (CVD) prevention. For assessing monitoring frequencies, computer models were used based on routine general practice data. Results indicated that more frequent monitoring strategies were cost-effective compared with others. In cost-effectiveness analyses, strategies with annual

monitoring dominated 3 yearly monitoring for both primary and secondary prevention.

An RCT(2) (n=64 GP practices and n=3245 patients) evaluated the impact of general practitioner's systematic and planned intervention on total CVD risk reduction and a change in individual CVD risk factors. The intervention group practitioners followed up their examinees after 1, 3, 6, 12, and 18 months. The control group received standard care. Results showed that the proportion of patients with very high CVD risk was lower in the intervention group. The mean blood pressure, triglycerides, body mass index and waist and hip circumference was also significantly reduced.

Targeting relatives of patients

An RCT(3) (n=144) aimed to increase CVD risk assessment in adult first degree relatives of patients with premature ischaemic heart disease (PIHD), using written and verbal advice distributed by the patients. The primary outcome was the proportion of relatives who attended their GP for CVD risk assessment within 6 months of the patients' PIHD event. The results indicated that a larger number of relatives of patients in the intervention group attended their GP for a CVD assessment, including those with moderate to very high 5-year absolute risk for CVD. However, the statistical significance of the difference was not reported in the abstract, and PIHD was not clearly defined.

Topic expert feedback

A systematic review on lipid levels and monitoring intervals was cited(1) and is included in the evidence summary.

Expert feedback highlighted that clarification of the strategies to prioritise people for assessment was not included in guideline recommendations. Further guidance was considered necessary on methods to use across the healthcare pathway to identify people with an estimated increased risk of CVD, how frequently this identification should be done and which healthcare professionals should carry it out. However, no relevant studies were cited.

This area has been prioritised by the NICE Quality Standards Advisory Committee, but for which no source guidance is currently available, and indicates the need for evidence−based guidance to be developed in this area. New evidence will be considered at the next surveillance review point.

Lifetime Risk

Topic expert feedback indicated that lifetime risk should also be calculated as an alternative to 10-year risk, which is relevant to recommendation 1.1.4 and 1.1.8. A study was cited(4) relating to different methods of comparing lifetime risk and is included in the evidence summary for question 181-02.

Impact statement

Monitoring intervals

The new systematic review evidence indicating that more frequent monitoring strategies with annual monitoring are cost effective partially supports the current recommendation 1.1.1 to use a systematic strategy to identify people who are likely to be at high risk, and recommendation 1.1.6 advising against the use opportunistic assessment as the main strategy in primary care to identify CVD risk in unselected people. CG181 does not stipulate monitoring frequencies, but does refer to the NHS health check and states that the programme is the responsibility of local authorities. Strategies to prioritise people for assessment were not included in CG181.

Since the new evidence for annual monitoring was derived from computer models, there is unlikely to be an impact on the guideline until further validation studies become available to substantiate the findings. New research will be considered in this area at the next surveillance review.

Targeting relatives of patients

The new RCT evidence supporting the targeting of relatives of patients with PIHD is based on a small sample with unknown statistical significance and is therefore unlikely to impact on the guideline.

Strategies to prioritise people for assessment

Topic expert feedback highlighted that clarification of the strategies to prioritise people for assessment was not included in guideline and that further clarification in this area is needed. This is an area of care that has been prioritised by the Quality Standards Advisory Committee, but for which no source guidance is currently available, and indicates the need for evidence−based guidance to be developed in this area. In the absence of new evidence, no impact is anticipated. Further studies will be considered at the next surveillance review point

on methods to use across the healthcare pathway to identify people with an estimated increased risk of CVD, how frequently this identification should be done and which healthcare professionals should carry it out.

Lifetime risk

New evidence supporting the use of lifetime risk calculation to more accurately assess patients for lifestyle changes and eventually lipid lowering drugs was not specific to the UK population. However, topic expert and stakeholder feedback indicating the need to review this area, combined with the fact that the surveillance literature search strategy did not extend to observational studies, raises a potential impact on recommendation 1.1.4 to consider lifetime risk as an alternative to 10-year risk. This may also have consequential impacts on recommendation 1.1.26 for communicating risk and on recommendations 1.3.18 and 1.3.26 for primary prevention of CVD.

New evidence identified that may change current recommendations.

181-02 Which risk assessment tools are the most accurate for predicting the risk of CVD events in adults without established CVD (primary prevention)?

Recommendations in this section of the guideline

1.1.7 Be aware that all CVD risk assessment tools can provide only an approximate value for CVD risk. Interpretation of CVD risk scores should always reflect informed clinical judgement. [2008]

1.1.8 Use the QRISK2 risk assessment tool to assess CVD risk for the primary prevention of CVD in people up to and including age 84 years. [new 2014]

1.1.9 Do not use a risk assessment tool to assess CVD risk in people with type 1 diabetes. See recommendations 1.3.23, 1.3.24 and 1.3.25 for advice on treatment with statins for people with type 1 diabetes. [new 2014]

1.1.10 Use the QRISK2 risk assessment tool to assess CVD risk in people with type 2 diabetes. [new 2014]

1.1.11 Do not use a risk assessment tool to assess CVD risk in people with an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m2 and/or albuminuria[1]. These people are at increased risk of CVD. See recommendation 1.3.27 for advice on treatment with statins for people with chronic kidney disease (CKD). [new 2014]

1.1.12 Complete as many fields of the risk assessment tool as possible. [new 2014]

1.1.13 Routinely record ethnicity, body mass index and family history of premature CVD in medical records. [2008]

1.1.14 Consider socioeconomic status as an additional factor that contributes to CVD risk. [2008]

1.1.15 Do not use a risk assessment tool for people with pre‑existing CVD. [2008, amended 2014]

1.1.16 Do not use a risk assessment tool for people who are at high risk of developing CVD because of familial hypercholesterolaemia (see familial hypercholesterolaemia [NICE guideline CG71]) or other inherited disorders of lipid metabolism. [2008, amended 2014]

1.1.17 When using the risk score to inform drug treatment decisions, particularly if it is near to the threshold for treatment, take into account other factors that:

- may predispose the person to premature CVD and
- may not be included in calculated risk scores. [2008, amended 2014]

1.1.18 Recognise that standard CVD risk scores will underestimate risk in people who have additional risk because of underlying medical conditions or treatments. These groups include:

- people treated for HIV
- people with serious mental health problems
- people taking medicines that can cause dyslipidaemia such as antipsychotic medication, corticosteroids or immunosuppressant drugs people with autoimmune disorders such as

[1] People on renal replacement therapy are outside the scope of this guideline.

systemic lupus erythematosus, and other systemic inflammatory disorders. [2008, amended 2014]

1.1.19 Recognise that CVD risk will be underestimated in people who are already taking antihypertensive or lipid modification therapy, or who have recently stopped smoking. Use clinical judgement to decide on further treatment of risk factors in people who are below the CVD risk threshold for treatment. [2008, amended 2014]

1.1.20 Severe obesity (body mass index greater than 40 kg/m2) increases CVD risk. Take this into account when using risk scores to inform treatment decisions in this group (see obesity [NICE guideline CG43]). [2008]

1.1.21 Consider people aged 85 or older to be at increased risk of CVD because of age alone, particularly people who smoke or have raised blood pressure. [2008, amended 2014]

Surveillance decision

This review question should be updated.

4-year surveillance summary

Impact of risk scores on CVD outcomes

A Cochrane systematic review(5) (41 studies, n=194,035) assessed the effects of evaluating and providing CVD risk scores in adults without prevalent CVD on cardiovascular outcomes, risk factor levels, preventive medication prescribing, and health behaviours. Low-quality evidence indicated that providing CVD risk scores may have little or no effect on CVD events compared with usual care. Providing CVD risk scores reduced total cholesterol, systolic blood pressure, and multivariable CVD risk. Providing risk scores may increase preventive medication prescribing in higher-risk people without evidence of harm, although the results were imprecise.

Ankle brachial index

A secondary analysis of a cohort study(6) (n=5248) assessed whether the inclusion of ankle brachial index (ABI) improved the predictive capacity of the Framingham-REGICOR risk function among adults aged 35-74. During the median 5.9 year follow up, pathological ABI was associated with increased coronary heart disease (CHD) and CVD risk. Including ABI in the Framingham-REGICOR function was found to improve its discrimination and its reclassification capacity for CVD events but not for CHD events.

A validation study(7) (n=24,375 men and n=20,377 women) developed and evaluated a risk model for CVD events incorporating the ABI and Framingham risk score (FRS). The FRS+ABI led to a non-significant improvement in risk prediction in men and to a significant increase in women. Restricting the FRS+ABI model to those with FRS intermediate 10-year risk of 10 to 19% resulted in significantly higher net reclassification improvements in both men and women. However, incorporating ABI in an improved newly fitted risk factor model had a non-significant effect.

A secondary analysis(8) of a cohort study (n=13,150) found that an ABI of 1.00 or less was significantly associated with an increased risk for heart failure, independent of traditional heart failure risk factors, prevalent coronary heart disease, carotid atherosclerosis, and interim myocardial infarction (MI).

Biomarkers

N-terminal pro-B-type natriuretic peptide (NT-proBNP) and Troponin

Several studies examined NT-proBNP and troponin T as additional biomarkers in risk prediction for CVD:

A nested case-cohort study(9) (n=3,098) examined the individual and combined effect NT-proBNP, high-sensitivity cardiac troponin T (hs-cTnT), interleukin-6 (IL-6), and hs-CRP on the prediction of heart failure incidence or progression in patients with type 2 diabetes. Only NT-proBNP significantly and consistently improved the prediction of heart failure in patients with type 2 diabetes, measured by 5-year risk-predictive performance metrics.

A nested cohort study(10) (n=3,862) and two secondary analyses of a cohort study(11,12) (N=1510 and n=970) found that both troponin T and NTproBNP were independent predictors of incident CVD events among patients with diabetes. The addition of either marker to established risk factors improved 5-year risk classification for CVD events and mortality. The combination of both markers provided optimal risk discrimination. One study(12) also found that a simple score combining cTnT and NT-proBNP with age and race was non-inferior to the established and more complex ARIC Heart Failure model.

A secondary analysis(13) of 2 cohort studies (n=3757 and n=2226) found that NT-proBNP and high-sensitivity troponin T, but not midregional pro adrenomedullin, were significantly associated with increased primary CVD risk in both the studies. However, the improvement in treatment allocation gained by adding troponin T and NTproBNP to risk scores was dependant on the risk threshold chosen for commencing preventative treatments. Using 28% 14-year risk as a proxy for 20% 10-year risk, NT-proBNP improved risk classification for primary CVD cases, but only improved classification of non-cases at a 14% 14-year risk threshold. In the other study, improvements in risk classification were only seen using NT-proBNP and high-sensitivity troponin T among cases using the 28% 14-year risk threshold.

An individual patient data (IPD) meta-analysis(14) (n=95,617) assessed whether or not measurement of NT-proBNP concentration could predict heart failure and enhance CHD and stroke risk assessment. Primary outcomes were the combination of coronary heart disease and stroke, and the combination of coronary heart disease, stroke, and heart failure. The results indicated that in people without baseline CVD, NT-proBNP concentration assessment strongly predicted first-onset heart failure and provided additive value beyond conventional risk assessment in coronary heart disease and stroke prediction.

A two centre prospective cohort study(15) (n=528) found that advanced endothelial dysfunction significantly correlated with near future CVD events in high-risk patients. This physiological vascular measurement improved risk discrimination when added to the FRS, NT-proBNP, and SYNTAX scores. CVD events consisted of cardiovascular death, MI, unstable angina, ischemic stroke, coronary revascularisation, heart failure-induced hospitalisation, aortic disease, and peripheral arterial disease.

A secondary analysis(16) of an RCT (n=2348) assessed, for older people, predictive values for recurrent CVD of models with age and sex, traditional cardiovascular risk markers, and 'SMART risk score', all with and without addition of NT-proBNP. Addition of NT-proBNP improved prediction of recurrent CVD, cardiovascular mortality and treatment effect of pravastatin. A minimal model including age, sex and NT-proBNP predicted as accurately as complex risk models including NT-proBNP.

A meta-analysis(17) (3 studies, n=10,723) found that patients with high-sensitivity cardiac troponin T (hs-cTnT) concentrations between the limit of blank (3 ng/L) and limit of detection (5 ng/L) were older, more likely to be male, and have a higher burden of cardiovascular risk factors and structural pathology. The meta-analysis of the 3 cohorts showed participants with hs-cTnT between the limit of blank and limit of detection were at increased risk of new-onset heart failure and cardiovascular mortality.

An IPD meta-analysis(18) (74,738) found that in people without CVD, the addition of troponin I to variables of established risk score improved prediction of CVD, calculated by measures of discrimination (C-index) and net reclassification improvement.

A cohort study(11) (n=8402) examined the potential of N-terminal prohormone brain natriuretic peptide (NTproBNP) and high-sensitivity troponin T to enhance CVD risk stratification in patients with diabetes. Both troponin T and NTproBNP were independent predictors of incident CVD events. Addition of circulating cardiac biomarkers to traditional risk factors, abnormal electrocardiogram, and conventional markers of diabetes complications improved CVD risk prediction.

Lipoprotein(a) [(Lp(a)]

A secondary analysis of an RCT(19) (n=9612) investigated whether Lp(a) was a determinant of residual risk in the setting of low-density lipoprotein cholesterol (LDL-C) cholesterol after potent statin therapy. Results showed that for patients treated with rosuvastatin 20 mg/d, Lp(a) was a significant determinant of residual risk.

Risk prediction in mental illness

A cohort study (20) (n=38,824) developed and validated a risk model exclusive to predicting

CVD events in people with serious mental illness (SMI) (schizophrenia, bipolar disorder, or other nonorganic psychosis), incorporating established cardiovascular risk factors and additional variables. The primary outcome was ten-year risk of the first CVD event (MI, angina pectoris, cerebrovascular accidents, or major coronary surgery). Predictors included age, sex, height, weight, systolic blood pressure, diabetes mellitus, smoking, body mass index (BMI), lipid profile, social deprivation, SMI diagnosis, prescriptions for antidepressants and antipsychotics, and reports of heavy alcohol use. Two risk models were developed, the PRIMROSE BMI model and the PRIMROSE lipid model. These models mutually excluded lipids and BMI. Both models performed better in SMI compared with models that include only established CVD risk factors.

Carotid intima-media thickness (IMT) and Coronary Artery Calcium (CAC)

A cohort study(21) (n=unreported) found that a carotid IMT score, based on age, sex, and race/ethnicity IMT percentiles improved CHD prediction of first-time CHD among adults aged 45 to 84 years old when added to Framingham risk factors in an ethnically diverse cohort.

A further sub-analysis(22) (n=6779) of the same cohort study found that in adults without CVD, CAC presence improved prediction of CVD and CHD more than carotid plaque presence or high carotid IMT.

A cost effectiveness study(23) (n=unreported) modelled the cost-effectiveness of CAC for cardiovascular risk stratification in asymptomatic, intermediate risk patients not taking a statin. Data were derived from the Multi-Ethnic Study of Atherosclerosis (MESA). Scanning intermediate-risk patients for CAC and treating those with CAC of at least 1 unit, compared to treatment based on established risk-assessment guidelines, was found to be both cost saving and more effective.

A cohort study(24) (n=988) was conducted to define the relative value of coronary artery calcium score (CACS), exercise treadmill testing (ETT), and stress myocardial perfusion single-photon emission computed tomography (SPECT) variables in predicting long-term risk stratification in asymptomatic or symptomatic low-risk patients without prior coronary artery disease (CAD). The results showed that CACS significantly improved long-term risk stratification beyond FRS, ETT, and SPECT results across the spectrum of clinical risk.

Lifetime risk

A cohort study(4) (n=259,834) estimated short-term (10-year) and lifetime cardiovascular risk using the American College of Cardiology (ACC) and the American Heart Association (AHA) tool and the QRISK2 and QRISK. Application of lifetime cardiovascular risk was found to identify greater numbers of individuals at high risk with substantial differences between the different methods available.

Complete blood count (CBC) risk score

A secondary analysis(25) of an RCT found that in a population of lower-risk individuals initially free from CVD (n=6568 female and n=10,629 males), the CBC risk score was strongly associated with all-cause mortality among JUPITER trial participants and had good discrimination. It also predicted CV-specific outcomes. The CBC score had been previously derived and validated.

QRISK tools

A cohort study(26) compared (n=8783) QRISK2, an electronic health data-based risk score, to the Framingham Risk Score (FRS) and atherosclerotic cardiovascular disease (ASCVD) score. Over the 30 month follow up period, QRISK2 classified more patients in the higher-risk groups than FRS but a similar number to ASCVD. QRISK2 showed increased discrimination with area under the curve statistics, compared to the FRS and ASCVD. The statistical significance of the comparisons was not reported in the abstract, however.

A cohort study(27) (n=1309 practices, n=7.89 million patients in the derivation cohort and n=2.67 million patients in the validation cohort) aimed to develop and validate updated QRISK3 prediction algorithms to estimate the 10 year risk of CVD in women and men accounting for potential new risk factors (chronic kidney disease (stage 3, 4, or 5), a measure of systolic blood pressure variability (standard deviation of repeated measures), migraine, corticosteroids, systemic lupus erythematosus, atypical antipsychotics, severe mental illness, and HIV/AIDs). Patients were free of CVD and not prescribed statins at baseline. Overall performance of the updated QRISK3 algorithms was found to be non-inferior to the QRISK2 algorithms.

Diabetes specific risk models

A systematic review(28) (11 studies) evaluated the evidence on direct comparisons of the performance of general population versus

diabetes-specific CVD risk models in people with diabetes. The results indicated a discriminatory advantage of diabetes-specific over general population-based models for CVD risk stratification in diabetes. However, the sample sizes of included studies and the general population-based models were not specified in the abstract.

Patients with hypertension

A subgroup analysis of a cohort study(29) (n=13052) identified risk factors for CVD in hypertensive patients with no history of CVD being treated with antihypertensive drugs. The factors significantly related to CVD were female gender, older age, family history of CHD, diabetes, current smoking and alcohol drinking socially. Results also indicated that the risk of CHD in patients with dyslipidaemia and hypertension who were on statin treatment was comparable to the risk in patients without dyslipidaemia. However, in dyslipidaemia patients not on statin treatment, the risk increased to a significant level.

Genetic risk scores

An RCT(30) (n=203), investigated whether incorporating a genetic risk score in CHD risk estimates lowers LDL-C levels. Patients were 45-65 years of age, at intermediate risk for CHD, and not on statins. Risk was disclosed by a genetic counsellor followed by shared decision making regarding statin therapy with a physician. The results indicated that disclosure of CHD risk estimates that incorporated genetic risk information led to lower LDL-C levels than disclosure of CHD risk based on conventional risk factors alone.

A secondary analysis(31) of an RCT (n=4,910) and 2 cohort studies (n=1,154 and n=4,392) found that people at high genetic risk of CVD had a greater burden of subclinical atherosclerosis and derived greater relative and absolute benefit from statin therapy to prevent a first CHD event. The genetic risk was calculated from a polygenic risk score derived from up to 57 common DNA sequence variants previously associated with CHD.

A cohort study(32) (n=5899) examined the incremental predictive value of genetic risk scores of CHD in the 10-year risk prediction of incident CHD. A total of 152 single nucleotide polymorphisms (SNPs) associated with CAD were used to construct three weighted genetic risk scores: (i) GRSgws based on 49 genome-wide significant SNPs; (ii) GRSfdr based on 103 suggestively associated SNPs; and (iii) GRSall based on all 152 SNPs. The results showed that the risk scores were associated with incident CHD but did not improve risk prediction.

Lifestyle based risk

A secondary analysis(33) (n=61 025 women and n=34 478 men) of two cohort studies involved the development of a lifestyle-based CVD prediction model over a follow up period of 24 years. The Healthy Heart Score included age, smoking, body mass index, exercise, alcohol, and a composite diet score to generate 20 year risk prediction model. In the validation cohort, the risk score demonstrated good discrimination, fit, and calibration, particularly among individuals without baseline hypertension or hypercholesterolemia.

A secondary analysis(34) (n=2020) of a cohort study examined whether the inclusion of physical activity status in a CVD risk model improved its predictive accuracy. The HellenicSCORE (that incorporates age, sex, smoking, total cholesterol, and systolic blood pressure levels) was calculated to estimate the baseline 10-year CVD risk; assessment of PA status was based on the International Physical Activity Questionnaire. The estimated CVD risk was tested against the observed 10-year incidence. PA status significantly predicted future CVD events and reduced the estimating classification bias when it was included in the model.

Secondary prevention: Thrombolysis in Myocardial Infarction (TIMI) score

A secondary analysis(35) of the IMPROVE-IT trial (n=17,717) examined the value of atherothrombotic risk stratification in identifying post-acute coronary syndrome (ACS) patients who have the greatest potential for benefit from the addition of ezetimibe to statin therapy. The TIMI risk score, comprising 9 variables, was found to identify high-risk patients who derived greatest benefit from combined ezetimibe and statin therapy for secondary prevention after ACS.

Topic expert feedback

Troponin

Topic experts noted that cardiac troponin measurements have an established role in diagnosis of acute MI. However recent studies with both cardiac troponin T and cardiac troponin I have shown that these may be applied in risk stratification, particularly among

older patients without established CVD in whom the risk of adverse effects of high intensity statin therapy is greater. Two studies were cited(17,18) and are included in the evidence summary above.

A further study(11) was cited on the role of troponin in CVD risk prediction in diabetes and is included in the evidence summary.

Carotid IMT and Coronary Artery Calcium

A study(21) was cited on the role of the Carotid IMT Score and Positive CAC Score and is included in the evidence summary.

Topic experts noted that several large studies have shown that CAC Score on ultra-fast computed tomography adds discrimination to conventional CV risk scores and can be used to identify higher risk groups in whom additional or second line lipid lowering therapies may be cost effective in primary prevention, and low risk groups in whom intervention may be of little value. A study was cited but was specific to United States guideline evaluation and was therefore ineligible. A recent economic analysis(23) was cited relating to CAC based risk stratification and is included in the evidence summary. CAC was also highlighted to be of value in predicting cerebrovascular disease risk. A study was cited but was outside the remit of CG181.

Addition of imaging to risk assessment

A topic expert considered it premature to add imaging to risk assessment or treatment outcome monitoring, but that this should be discussed for future consideration. Example techniques noted were carotid Doppler, CAC and Intravascular ultrasound.

Lp(a)

Topic experts highlighted the need to consider two biomarkers for risk calculation and potentially LDL/non-HDL-C on-treatment targets. The position of measurement of lipoprotein(a), and possibly the significance of the 'new' category of polygenic hypercholesterolaemia were recommended. One study was cited(31) and is included in the evidence summary. Topic experts also noted that there is a growing body of evidence that measurement of lipoprotein(a) may improve cardiovascular risk prediction independently of other lipid associated measures and may be of value in younger people in whom measurement of cardiac troponins appears to be of lesser predictive value. A study was cited but was not included due to being an ineligible study design.

QRISK tools

Topic experts highlighted the need to review the implementation of the recommended 10% QRISK score threshold utilised by the NHS Check programme.

A topic expert highlighted the potential value of the electronic health record in risk assessment. A study was cited(26) and is included in the evidence summary.

Topic expert feedback indicated that QRISK2 should not be the only tool that is used, and that lifetime risk should also be calculated (relevant to Rec 1.1.8 and more). A study was cited(4) relating to different methods of comparing lifetime risk and is included in the evidence summary.

Topic expert feedback also highlighted that people with type 2 diabetes should not have cardiovascular risk assessment - they should be considered automatically at high risk, but no evidence was cited in support of this.

TIMI risk score

Topic experts noted that in CG181 risk stratification was not applied in patients with established CVD. However it was stated that the TIMI risk score has been demonstrated to be an effective means of identifying a higher risk group among CVD patients who benefit from ezetimibe added to statin therapy. A study was cited(35) and is included in the evidence summary. With the introduction of risk stratification in defining eligibility for anti-PCSK9 based therapies in secondary prevention in NICE technology appraisals TA393 and TA394 other approaches such as the TIMI score were felt to be worthy of consideration.

However, additional expert feedback indicated that TA393 and TA394 are recent and include eligibility criteria that do not reference the TIMI score.

Impact statement

QRISK tools

NICE CG181 recommends (1.1.8) using the QRISK2 risk assessment tool to assess CVD risk for the primary prevention of CVD in people up to and including age 84 years. The collective new evidence and topic expert feedback indicates that the inclusion of additional clinical variables in QRISK3 has potential value to identify those at most risk of

heart disease and stroke, beyond QRISK2. Incorporating additional data from the electronic health record may improve CVD risk stratification. The new evidence suggests that QRISK3 performs well for people with type 1 diabetes and chronic kidney disease, and may help some people with these conditions to make an informed choice on whether to take statins. There is therefore a potential impact on recommendations 1.1.9 and 1.1.11 to review the advice against using risk tools for people with type 1 diabetes and chronic kidney disease, respectively. This may also have a consequential impact on recommendations 1.3.23, 1.3.24, and 1.3.27 (see 181-11).

There is also potential need to amend recommendations 1.1.8 and 1.1.10 to advise the use of QRISK3 in place of QRISK2 because QRISK2 is due to be superseded by QRISK3 in 2018.

Alternative tools and additional variables

New evidence and expert feedback also indicates potential value of other tools as alternatives or in conjunction with QRISK:

- Condition specific risk models; particularly the Primrose lipid model for people with mental illness
- Genetic risk scores
- Lifestyle based risk scores; the Healthy heart score, and the modified HELENIC score with physical activity incorporated
- Additive value of biomarkers
  - carotid intima-media thickness
  - coronary artery calcium
  - troponin for risk stratification, particularly in older people
  - NTproBNP
  - Ankle Brachial Index added to Framingham risk score
  - Lp(a).

However, these alternative tools and additional biomarkers are unlikely to impact on CG181 for any of the following groups of people, because QRISK3 has been validated in all of them in England and Wales, and there does not appear to be any evidence that any of the alternative tools or variables have been shown to improve on QRISK3:

- the general population aged 25-84
- people with type 2 diabetes mellitus
- people with serious mental illness
- people with hypertension.

Risk tools for secondary prevention

Although new evidence supports the use of the TIMI score in patients with established CVD, topic expert feedback indicated that the relevant technology appraisals are recent and set out eligibility criteria for people with pre-existing CVD, without reference to the TIMI score. Further evidence on the TIMI score will be monitored for consideration in future reviews of:

TA385 Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (February 2016).

TA393 Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (June 2016)

TA394 Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (June 2016)

There is therefore unlikely to be an impact on recommendation 1.1.15, which advises against the use of a risk tool for people with pre-existing CVD.

Lifetime risk

New evidence supporting the use of lifetime risk calculation to more accurately assess patients for lifestyle changes and eventually lipid lowering drugs was not specific to the UK population. However, topic expert and stakeholder feedback indicating the need to review this area, combined with the fact that the surveillance literature search strategy did not extend to observational studies, raises a potential impact on recommendation 1.1.4 to consider lifetime risk as an alternative to 10-year risk. This may also have consequential impacts on recommendation 1.1.26 for communicating risk and on recommendations 1.3.18 and 1.3.26 for primary prevention of CVD.

Overall impact of risk tools on CVD outcomes

New systematic review evidence indicating that risk tools have an effect on CVD risk factors but not on CVD outcomes is largely consistent with recommendation 1.1.7 to be aware that all CVD risk assessment tools can provide only an approximate value for CVD risk, and that their interpretation should always reflect informed clinical judgement. It should be noted that the included primary studies had multiple limitations and substantial heterogeneity across

the interventions, outcomes, and analyses, thereby limiting the impact of the evidence.

New evidence identified that may change current recommendations.

181-03 Communication about risk assessment and treatment

Subquestion

What is the effectiveness of the different methods (decision aids) of presenting/communicating risk to patients that are at risk of CVD?

Recommendations in this section of the guideline

1.1.22 NICE has produced guidance on the components of good patient experience in adult NHS services. These include recommendations on the communication of risk. Follow the recommendations in patient experience in adult NHS services (NICE guidance CG138). [new 2014]

1.1.23 Use everyday, jargon-free language to communicate information on risk. If technical terms are used, explain them clearly. [2008]

1.1.24 Set aside adequate time during the consultation to provide information on risk assessment and to allow any questions to be answered. Further consultation may be required. [2008]

1.1.25 Document the discussion relating to the consultation on risk assessment and the person's decision. [2008]

1.1.26 Offer people information about their absolute risk of CVD and about the absolute benefits and harms of an intervention over a 10-year period. This information should be in a form that:

- presents individualised risk and benefit scenarios and
- presents the absolute risk of events numerically and
- uses appropriate diagrams and text. [2008]

1.1.27 To encourage the person to participate in reducing their CVD risk:

- find out what, if anything, the person has already been told about their CVD risk and how they feel about it explore the person's beliefs about what determines future health (this may affect their attitude to changing risk)
- assess their readiness to make changes to their lifestyle (diet, physical activity, smoking and alcohol consumption), to undergo investigations and to take long-term medication
- assess their confidence in making changes to their lifestyle, undergoing investigations and taking medication
- inform them of potential future management based on current evidence and best practice
- involve them in developing a shared management plan
- check with them that they have understood what has been discussed. [2008, amended 2014]

1.1.28 If the person's CVD risk is at a level where intervention is recommended but they decline the offer of treatment, advise them that their CVD risk should be reassessed again in the future. Record their choice in their medical notes. [2008, amended 2014]

Surveillance decision

This review question should be updated.

4-year surveillance summary

Impact of risk model provision to patients and professionals

A systematic review(36) (17 studies) assessed how provision of a CVD risk model to either professionals or patients impacts their decision-making, behaviour and ultimately patient health. The results indicated that provision of a CVD risk model estimate increased prescribing of lipid-lowering and blood pressure medication, with greatest effects in those with CVD risk >20%. Overall, there was a trend towards reductions in cholesterol and blood pressure and a statistically significant reduction in modelled CVD risk after an average of 12 months follow up.

Decision aids

A secondary analysis(37) of an RCT (n=160) of a CHD adherence intervention (second generation decision aid plus tailored messages) versus usual care explored how the decision aid facilitates adherence. Within the decision aid group, the decision aid significantly increased knowledge of effective CHD prevention strategies and the accuracy of perceived CHD risk, and significantly decreased decisional conflict. Comparing between study groups, the decision aid also significantly increased CHD prevention discussions with providers and improved perceptions of some features of patient-provider interactions. It also increased participants' intentions for any effective CHD risk reducing strategies, with a majority of the effect from the educational component of the decision aid.

Topic expert feedback

Lifetime risk

Topic expert and stakeholder feedback indicated the need to consider lifetime risk calculation in place of 10-year risk calculation (see 181-02 for further details).

Impact statement

Lifetime risk

The topic expert and stakeholder feedback indicating the need to consider lifetime risk calculation in place of 10-year risk calculation, as discussed in 181-02, may also have a consequential impact on recommendation 1.1.26 for the communication of risk to patients.

Risk model provision to patients and professionals

The new systematic review evidence highlighting the value of provision of a CVD risk model estimate to professionals and patients is consistent with CG181 recommendations to use a risk assessment tool and to communicate information on risk to patients.

Decision aids

The new evidence based on RCT data indicates the potential educational value of a decision aid plus tailored messages in increasing knowledge and improving perceptions of professional-patient interaction. However, the evidence was derived from a small sample size and is unlikely to impact on the guideline until further evidence becomes available to substantiate the findings.

New evidence identified that may change current recommendations.

Lifestyle modifications for the primary and secondary prevention of CVD

181-04 What is the clinical and cost effectiveness of dietary intervention strategies versus usual diet for adults without established CVD (primary prevention) and with established CVD (secondary prevention)?

Recommendations derived from this review question

1.2.1 Advise people at high risk of or with CVD to eat a diet in which total fat intake is 30% or less of total energy intake, saturated fats are 7% or less of total energy intake, intake of dietary cholesterol is less than 300 mg/day and where possible saturated fats are replaced by mono-unsaturated and polyunsaturated fats. Further information and advice can be found at NHS Choices. [new 2014]

1.2.2 Advise people at high risk of or with CVD to:

- reduce their saturated fat intake.
- increase their mono-unsaturated fat intake with olive oil, rapeseed oil or spreads based on these oils and to use them in food preparation.

Further information and advice on healthy cooking methods can be found at NHS Choices. **[new 2014]**

1.2.3 Advise people at high risk of or with CVD to do all of the following:

- choose wholegrain varieties of starchy food
- reduce their intake of sugar and food products containing refined sugars including fructose
- eat at least 5 portions of fruit and vegetables per day
- eat at least 2 portions of fish per week, including a portion of oily fish
- eat at least 4 to 5 portions of unsalted nuts, seeds and legumes per week.

Further information and advice can be found at NHS Choices. **[new 2014]**

1.2.4 Advise pregnant women to limit their oily fish to no more than 2 portions per week and to avoid marlin, shark and swordfish. Further information and advice on oily fish consumption can be found at NHS Choices. **[new 2014]**

1.2.5 Take account of a person's individual circumstances – for example, drug therapy, comorbidities and other lifestyle modifications when giving dietary advice. **[new 2014]**

1.2.6 Advise and support people at high risk of or with CVD to achieve a healthy diet in line with behaviour change: the principles for effective interventions (NICE guideline PH6). **[new 2014]**

Surveillance decision

This review question should be updated.

4-year surveillance summary

Dietary advice

A Cochrane systematic review(38) (44 studies) assessed the effects of providing dietary advice to achieve sustained dietary changes or improved cardiovascular risk profile among healthy adults. Dietary advice reduced total serum cholesterol and LDL cholesterol after 3 to 24 months. Mean HDL cholesterol levels and triglyceride levels were unchanged. Compared to no advice, dietary advice increased fruit and

vegetable intake and dietary fibre intake, while reducing total dietary fat and saturated fat as a percentage of total energy intake.

Nut consumption

A total of 9 systematic reviews(39–47) (included studies ranging from 5 to 31 and n=509 to n=501,791), assessed nut consumption and incident risk of CVD. A Cochrane review(39) (5 studies, n=509) examined the effectiveness of nut consumption for the primary prevention of CVD. All trials examined the provision of nuts to increase consumption rather than dietary advice. There were variable and inconsistent effects of nut consumption on CVD risk factors lipid levels and blood pressure.

All the other systematic reviews found that higher nut intake was associated with reduced risk of CVD, including CAD.

Legume consumption

A systematic review(48) (26 studies, n=1037) found that diets emphasising dietary pulse intake at a median dose of 130 g/d (about 1 serving daily) significantly lowered LDL cholesterol levels compared with the control diets (isocaloric diet that did not include dietary pulses). Treatment effects on apolipoprotein B and non-HDL cholesterol were not observed, however.

A systematic review(49) (14 studies, n=367,000) found that compared with lower legume consumption, the highest category of consumption was associated with a significantly decreased risk in both CVD and CHD.

Mediterranean diet

Two systematic reviews(50,51) examined the effectiveness of a Mediterranean dietary pattern for the primary prevention of CVD. The Cochrane review(50) (11 trials, 52,044) defined the Mediterranean dietary pattern as comprising at least two of 7 components: (1) high monounsaturated/saturated fat ratio, (2) low to moderate red wine consumption, (3) high consumption of legumes, (4) high consumption of grains and cereals, (5) high consumption of fruits and vegetables, (6) low consumption of meat and meat products and increased consumption of fish, and (7) moderate consumption of milk and dairy products. Results indicated small reductions in total and LDL cholesterol. Subgroup analyses revealed statistically significant greater reductions in total cholesterol in those trials describing the intervention as a Mediterranean diet.

The other review(51) (6 studies, n=10,950) did not define the Mediterranean diet in the abstract. It found evidence of protection against vascular events and stroke from the Mediterranean diet, but the quantity and quality of the available evidence was limited and highly variable in quality.

A total of 12 secondary analyses(52–63) of the Predimed trial, were identified. The original trial covered Mediterranean diet supplemented with either extra virgin olive oil or nuts reduced cardiovascular events and was included in the CG181 evidence review. The secondary analyses indicated that:

- The Mediterranean diet may counteract the harmful effects of increased adiposity on the risk of CVD, as measured by waist to height ratio, body mass index and waist circumference.
- Participants with higher baseline concentrations of short-, medium-, and long-chain acylcarnitines who were randomly assigned to the control group had a higher risk of CVD than did subjects with lower concentrations of acylcarnitines who were assigned to the Mediterranean diet group.
- Adherence to the Mediterranean diet is associated with an increase in serum markers of atheroma plaque stability.
- The PREDIMED trial provided strong evidence that a vegetable-based Mediterranean diet rich in unsaturated fat and polyphenols can be an effective and sustainable model for CVD prevention.
- A high-unsaturated fat and antioxidant-rich dietary pattern such as the Mediterranean diet is a useful tool in the prevention of CVD.
- Increases in polyphenol intake measured as urinary total polyphenol excretion were associated with decreased inflammatory biomarkers, suggesting a dose-dependent anti-inflammatory effect of polyphenols. High polyphenol intake improved cardiovascular risk factors- mainly BP and the lipid profile, and reduced all cause and CVD mortality.
- In high-risk individuals, most with treated hypertension, Mediterranean diet supplemented with extra virgin olive oil or nuts reduced 24-hour ambulatory blood

pressure, total cholesterol, and fasting glucose.

- A Mediterranean dietary intervention may mitigate potential deleterious effects of elevated plasma ceramide concentrations on CVD.

Dietary Fibre

A Cochrane review(64) (23 studies, n=1513) determined the effectiveness of dietary fibre for the primary prevention of CVD. Pooled analyses for CVD risk factors suggested reductions in total cholesterol and LDL cholesterol with increased fibre intake, and reductions in diastolic blood pressure. There were no obvious effects of subgroup analyses by type of intervention or fibre type but the number of studies included in each of these analyses were small. Risk of bias was unclear in the majority of studies and high for some quality domains.

A further 4 systematic reviews(65–68) (22 studies, 18 studies n= 672,408, 14 studies, and 15 studies) examined dietary fibre intake, including both fruit and cereal fibre, and risk of CVD. Greater dietary fibre intake was associated with a lower risk of both CVD and CAD.

A total of 5 systematic reviews(69–73) (10 studies n=782,251; 45 studies; 14 studies, n=786,076; 11 studies, n=816 599; 20 studies, n=2,282,603) found observational study evidence of inverse associations of intake of whole grains with risk of mortality from all-cause, CVD, and CHD. Follow-up periods ranged from 5.5 to 26 years.

A secondary analysis of a cohort study(74) (n=26,445) found that individuals with a high consumption of whole grains had a decreased risk of CVD. A higher consumption of foods rich in added sugar (sugar and sweets, and sugar-sweetened beverages) had a significant cross-sectional association with higher triglyceride concentrations and lower HDL-C concentrations. A stronger positive association between a high consumption of sugar and sweets on iCVD risk was observed among those with low genetic risk score for triglycerides.

Fruit and vegetable consumption

A total of 4 systematic reviews(75–78) (23 studies, n= 937,665; 16 studies, n=833,234; 38 studies, n=1,498,909; 22 studies, n=1,251) examined the association between fruit and vegetable consumption and risk of CVD. The collective results provided further evidence that a higher consumption of fruit and vegetables is associated with a lower risk of CVD and all-cause mortality. An RCT(79) (n=174) also found that increasing fruit and vegetable intake sequentially by 2, 4, and 6 portions per day every 6 weeks over habitual intakes improved microvascular reactivity, arterial stiffness, pulse wave analysis, ambulatory blood pressure and biomarkers of nitric oxide. The benefits were most apparent in men with an increased risk of CVD. These data support recommendations to increase fruit and vegetable intake to more than 6 portions daily.

A further secondary analysis(80) of the Predimed trial (n=7216) found a significant inverse association with CVD incidence for the sum of fruit and vegetable consumption. Participants who consumed in total nine or more servings per day of fruits plus vegetables had lower risk of CVD in comparison with those consuming under 5 servings.

Flavonoids

The collective results from 3 systematic reviews(81–83) (14 studies; 15 studies n=452,564; 10 studies) examining the effects of dietary flavonoids indicated that increased intake of flavonoids had a protective effect against CVD. One of the systematic reviews(81) found that six classes of flavonoids, specifically flavonols, anthocyanidins, proanthocyanidins, flavones, flavanones and flavan-3-ols, significantly decrease the risk of CVD.

A prospective cohort study(84) (n=43,880) found that during 24 year follow up, higher intakes of fruit-based flavonoids were associated with a lower risk of nonfatal MI and ischemic stroke in healthy men who had no prior diagnosed CVD or cancer.

Beta Glucan

Two systematic reviews(85,86) investigated the cholesterol-lowering potential of beta-glucan on LDL-cholesterol, non-HDL-cholesterol and Apolipoprotein B (apoB) for the risk reduction of CVD.

The first (58 studies, n=3974) found that oat beta-glucan had a lowering effect on LDL-cholesterol, non-HDL-cholesterol and Apolipoprotein B. The second (14 studies, n=615) found that barley beta-glucan had a lowering effect on LDL-C and non-HDL-C.

Dietary Cholesterol

A meta-analysis (87) (40 cohort studies, n=361,923 and 19 trials n=632) examined the effects of dietary cholesterol on CVD risk in healthy adults. Dietary cholesterol was not statistically significantly associated with CAD. However, dietary cholesterol statistically significantly increased both serum total cholesterol and LDL cholesterol, but increases in LDL cholesterol were no longer statistically significant when intervention doses exceeded 900 mg/d. Dietary cholesterol also statistically significantly increased serum HDL cholesterol and the LDL to HDL ratio. Dietary cholesterol did not statistically significantly change serum triglycerides or very-low-density lipoprotein concentrations. It should be noted that the specific food sources of dietary cholesterol were not reported in the abstract.

Egg consumption

Four studies(88–91) examined the effect of egg consumption on CV risk.

An RCT(88) (n=152) found that high egg consumption (2 eggs per day for 6 weeks) compared with a low-egg diet (less than 2 eggs per week) did not have an adverse effect on the lipid profile of people with type 2 diabetes, measured by total cholesterol, low-density lipoprotein cholesterol, triglycerides, or glycaemic control.

A secondary analysis(89) (n=7216) of an RCT found that low to moderated egg consumption was not associated with an increased CVD risk in diabetic or non-diabetic individuals at high cardiovascular risk. The main outcome was the rate of major CVD events (MI, stroke or death from cardiovascular causes).

A sub-study(90) of a population based cohort study (n=1429) found no association between egg consumption and risk of clinical vascular outcomes, over a mean follow up of 11 years and after adjustment for covariates.

A further cohort study(91) (n=1032) of men aged 42-60 years old, found that, over a 5 year follow up, egg or cholesterol intakes were not associated with increased CAD risk, even in men considered at higher genetic risk.

Dairy fat

A systematic review(92) (13 studies n=7,680) investigated biomarkers of dairy fat intake and the risk of CVD. The results showed no association between levels of circulating pentadecanoic acid, heptadecanoic acid and trans-palmitoleic acid, and the risk of CVD.

A systematic review(93) (22 studies) found an inverse association between dairy consumption and overall risk of CVD and stroke. CHD risk was significantly lowered by cheese consumption.

A third systematic review(94) (9 studies, n=636,151) focussed on butter consumption. This was found to be weakly associated with all-cause mortality, was not significantly associated with any CVD, coronary heart disease or stroke, and was inversely associated with incidence of diabetes.

A systematic review(95) (15 studies) found nonlinear inverse relationships between cheese consumption and risks of total CVD and stroke. Most of the studies excluded prevalent CVD at baseline and had a duration of more than 10 years.

Calcium

A systematic review(96) (22 studies) found no significant association between total and dietary calcium intake and mortality from all-causes, CVD, and cancer. Subgroup analysis by the duration of follow-up revealed a significant positive association between total calcium intake and CVD mortality for cohort studies with a mean follow-up duration of >10 years. A significant inverse association was seen between dietary calcium intake and all-cause and CVD mortality for studies with a mean follow-up duration of <10 years.

Dietary fat

A total of 5 systematic reviews(97–101), 2 RCTs(102,103), a secondary analysis(104) of an RCT and 2 observational studies(105,106) examined the association between fat intake and risk of CVD, including comparisons between low and high fat diets, low carbohydrate and low fat diets, intake of saturated and trans-fats, and intake of polyunsaturated fats.

The results indicated that:

- Intakes of monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids were associated with a lower risk of CVD and death, whereas SFA and trans-fat intakes were associated with a higher risk of CVD.
- Reducing saturated fat by reducing or modifying dietary fat reduced the risk of cardiovascular events. However, moderate quality evidence indicated no beneficial

effects of reduced or modified fat diets in the secondary prevention of CHD.

- Compared with participants on low fat diets, participants on low carbohydrate diets experienced a greater reduction in body weight and tryglycerides, but a greater increase in HDL-cholesterol and LDL-cholesterol.

For people with prediabetes or diabetes, high fat regimens were found to result in a significant decrease in triglyceride levels and diastolic blood pressure and a significant increase in HDL-cholesterol levels. In addition, the mean difference in the reductions of fasting glucose levels were significantly higher in patients with type 2 diabetes adhering to a high fat diet.

Olive Oil

Three studies(107–109) focussed specifically on olive oil.

One systematic review(107) (32 studies, n=841,211) examined the association between MUFA and CVD, cardiovascular mortality as well as all-cause mortality, and explored differences between the different dietary sources of MUFA. MUFA of mixed animal and vegetable sources per se did not yield any significant effects on all-cause mortality, cardiovascular mortality, cardiovascular events, and stroke. However, olive oil alone was significantly associated with reduced risk.

One systematic review(108) (30 studies, n=3106) found that olive oil interventions (with daily consumption ranging approximately between 1 mg and 50 mg) resulted in a significantly more pronounced decrease in C-reactive protein and interleukin-6 as compared to controls. Potential effects on endothelial function as well as markers of inflammation and endothelial function.

A secondary analysis of an RCT(109) (n=7216) assessed the association between total olive oil intake, its varieties (extra virgin and common olive oil) and the risk of CVD and mortality in a Mediterranean population at high cardiovascular risk. Olive oil consumption, specifically the extra-virgin variety, was associated with reduced risks of CVD and mortality in individuals at high CV risk.

Omega-6 fatty acids

A Cochrane systematic review(110) (4 studies, n=660) examined the effectiveness of either increasing omega-6 intake in place of saturated or monounsaturated fats or carbohydrates for the primary prevention of CVD, or decreasing omega-6 intake in place of carbohydrates or protein (or both) for the primary prevention of CVD. Omega-6 comprised linoleic acid (LA), Gamma-linolenic acid (GLA), Dihomo-gamma-linolenic acid (DGLA), Arachidonic acid (AA), or any combination. None of the included RCTs of omega-6 intake reported CVD clinical events, but lipid levels were covered. There was insufficient evidence to show an effect of increased or decreased omega-6 intake on blood lipids and blood pressure.

Dietary Sodium intake

A secondary analysis(111) (n=2642) of a cohort study examined the association between dietary sodium intake and mortality, incident CVD, and incident heart failure in older adults. Results indicated that sodium intake was not associated with 10-year mortality, incident CVD, or incident heart failure.

Fructose

A systematic review(112) (51 isocaloric trials n=943 and 8 hypercaloric trials n=125) examined the effect of fructose on established therapeutic lipid targets for CVD (LDL-C, apolipoprotein B, HDL-C), and metabolic syndrome (triglycerides and HDL-C). Pooled analyses showed that fructose only had an adverse effect on established lipid targets when added to existing diets so as to provide excess calories (+21% to 35% energy). When isocalorically exchanged for other carbohydrates, fructose had no adverse effects on blood lipids.

Soft drink consumption

A systematic review(113) (7 studies, n=308,420) evaluated whether soft drink consumption independently leads to an increased risk of cardiovascular events and mortality. The pooled results indicated a greater risk of stroke, and MI, but not vascular events with incremental increase in sugar-sweetened beverage (SSB) consumption. With incremental increase in artificially sweetened beverage consumption, there was a greater risk of stroke, but not vascular events or MI.

A further systematic review(114) (4 studies n=173,753) found that consumption of SSBs increased the risk of CHD, especially among men.

The third systematic review, a dose-response meta-analysis(115) (6 studies n=240,726 for hypertension, 4 studies n=194 664 for CHD

and 4 studies, n=259,176 for stroke) found that every additional one serving/d increase in SSB consumption was associated with a higher risk of hypertension and CHD, but not with a higher risk of stroke.

Dietary strategies

A systematic review(116) (20 studies, n=1917) examined the effect of the Dietary Approach to Stop Hypertension (DASH) on cardiometabolic biomarkers. The pooled results indicated that the DASH diet significantly reduced total cholesterol and LDL, and appeared to have greater beneficial effects in people with an increased cardiometabolic risk.

Topic expert feedback

Expert feedback highlighted that the advice given on restricting dietary cholesterol in recommendation 1.2.1 is inaccurate. The feedback further highlighted that the British Heart Foundation does not recommend any restriction on dietary cholesterol intake.

Additional expert feedback highlighted that NHS Choices is not considered to be an authoritative source, and references to it in recommendations 1.2.1-1.2.4, 1.2.11 and 1.2.13 should be removed.

Topics expert feedback indicated that new evidence on all other diet and nutrition is consistent with current recommendations.

Impact statement

Dietary cholesterol

New evidence and expert feedback indicates that advice given on dietary cholesterol in recommendation 1.2.1, is inconsistent with new evidence indicating that dietary cholesterol, including egg consumption, may not have an adverse impact on CVD risk. There is a potential need to review recommendation 1.2.1, which advises limiting intake of dietary cholesterol to less than 300 mg/day.

Expert feedback highlighted that NHS Choices is not considered to be an authoritative source, and references to it in recommendations 1.2.1-1.2.4, should be removed. There is a further potential impact to review the wording of these recommendations.

Cardioprotective diet

The collective new evidence and topic expert feedback on the following aspects of the cardioprotective diet are consistent with CG181 recommendations, which cross refer to NHS choices advice on healthy eating and NICE guideline PH6 behaviour change: the principles for effective interventions:

- Dietary fibre intake
- Fruit and vegetable consumption, including flavonoids
- Dietary sodium intake
- Fat intake
- Fructose intake
- Nuts and legume consumption; evidence supports current dietary advice but does support the provision of nuts as an intervention. This is consistent with recommendation 1.2.3 which advises eating at least 4 to 5 portions of unsalted nuts, seeds and legumes per week, but does not advise provision of nuts.

Soft drink consumption

New evidence indicates that sugar sweetened drink consumption is associated with increased risk of CHD and hypertension. This is consistent with recommendation 1.2.3 which advises reducing sugar intake and intake of food products containing refined sugars including fructose.

Mediterranean diet

The guideline committee noted that there may be uncertainty as to what constitutes a Mediterranean diet. It concluded that recommendations should avoid using this dietary description as it is non-specific.

Evidence supporting specific elements of the reported diet, including nuts, olive oil, high-unsaturated fat and antioxidant-rich dietary pattern, is consistent with current recommendations to increase intake of these foods. Therefore no impact on the guideline is expected.

New evidence on dietary calcium and oat beta glucan was considered by topic expert feedback to be too specific to impact on the guideline.

New evidence identified that may change current recommendations.

181-05 Physical activity

Recommendations derived from this review question

1.2.7 Advise people at high risk of or with CVD to do the following every week:

- at least 150 minutes of moderate intensity aerobic activity **or**
- 75 minutes of vigorous intensity aerobic activity or a mix of moderate and vigorous aerobic activity in line with national guidance for the general population (see Physical activity guidelines for adults at NHS Choices). **[2008, amended 2014]**

1.2.8 Advise people to do muscle-strengthening activities on 2 or more days a week that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders and arms) in line with national guidance for the general population (see Physical activity guidelines for adults at NHS Choices). **[new 2014]**

1.2.9 Encourage people who are unable to perform moderate-intensity physical activity because of comorbidity, medical conditions or personal circumstances to exercise at their maximum safe capacity. **[2008, amended 2014]**

1.2.10 Advice about physical activity should take into account the person's needs, preferences and circumstances. Agree goals and provide the person with written information about the benefits of activity and local opportunities to be active, in line with four commonly used methods to increase physical activity (NICE guideline PH2). **[2008]**

Surveillance decision

This review question should not be updated.

4-year surveillance summary

Physical activity

A secondary analysis of an RCT(117) (n=9306) investigated whether baseline and change in objectively-assessed ambulatory activity is associated with the risk of a cardiovascular event in individuals at high CVD risk with impaired glucose. An inverse association was observed between daily ambulatory activity and the subsequent risk of a cardiovascular event.

A cohort study (118) (n=4207) found that greater physical activity was inversely associated with CHD, stroke (especially ischemic stroke), and total CVD, even in those >75 years. Walking pace, distance, and overall walking score, leisure-time activity, and exercise intensity were each associated with lower risk.

A secondary analysis of a cohort study(119) (n=5901) found that domestic work and cycling were associated with reduced CHD risk among older adults over a 15 year follow up.

An RCT(120) (n=1635) found that an aerobically based, moderately intensive physical activity programme was not associated with reduced cardiovascular events in older adults aged 70 to 89 years. The physical activity intervention was a structured moderate-intensity program, predominantly walking 2 times per week on site for 2.6 years on average.

A Cochrane review(121) (4 studies, n=823) assessed the effects of exercise training in people with increased CVD risk but without a concurrent CVD on general cardiovascular mortality, incidence of cardiovascular events, and total cardiovascular risk. Meta-analysis was not possible because the interventions (setting, type and intensity of exercise) and outcome measurements were not comparable, and the risk of bias in the identified studies was high. The available evidence was not sufficient to determine the effectiveness of exercise.

A systematic review(122) (36 studies, n=3,439,874) compared the association between physical activity and CVD and type 2 diabetes, both before and after adjustment for a measure of body weight. An increase from being inactive to achieving recommended

physical activity levels (150 minutes of moderate-intensity aerobic activity per week) was associated with lower risk of CVD mortality, CVD incidence, and type 2 diabetes incidence.

Sedentary time

A secondary analysis(123) of a cohort study (n=4516) found that among people free of CVD at baseline, the total amount of daily sitting was significantly associated with incident CVD over a mean follow up of 8.6 years.

Yoga

A Cochrane systematic review(124) (11 studies, n=800) aimed to determine the effect of any type of yoga on the primary prevention of CVD. Results indicated that yoga has favourable effects on diastolic blood pressure, HDL cholesterol and triglycerides, but uncertain effects on LDL cholesterol. No study reported cardiovascular mortality, all-cause mortality or non-fatal events, and most studies were small and short-term. However, the contributing studies were small, short-term and at unclear or high risk of bias.

A systematic review(125) (44 studies, n=3168) assessed the effects of yoga on modifiable biological CVD risk factors in the general population and in high-risk disease groups. Relative to usual care or no intervention, yoga improved lipid levels and insulin resistance. Relative to exercise, yoga improved HDL.

Another systematic review(126) (37 studies, n=unreported) found that compared to non-exercise controls, yoga for adults showed significant improvement for body mass index, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol, total cholesterol and triglycerides.

A Cochrane systematic review(127) aimed to determine the effectiveness of yoga for the secondary prevention of mortality and morbidity in, and on the health-related quality of life of, individuals with CHD. However, no eligible RCTs that met the inclusion criteria of the review were found.

A Cochrane systematic review(128) (4 studies, n=430) found insufficient evidence to determine the effectiveness of transcendental meditation for the primary prevention of CVD. The included trials were small, short term (three months) and at risk of bias. None of the included studies reported all-cause mortality, cardiovascular mortality or non-fatal endpoints as trials were short term.

Qijong

A Cochrane systematic review(129) (11 studies n=1369) found insufficient evidence (trials assessed as high risk of bias), to support the use of Qigong in the prevention of CVD. The only trial considered at low risk of selection and detection bias did not demonstrate statistically significant effects on CVD risk factors with qigong, but this study was small and was underpowered.

Tai Chi

A Cochrane systematic review(130) (13 studies, n=1520) aimed to determine the effectiveness of tai chi for the primary prevention of CVD. It found that no studies reported on cardiovascular mortality, all-cause mortality or non-fatal events as most studies were short term, and there was insufficient evidence to determine the effectiveness of tai chi.

Interval training

A systematic review(131) (6 studies, n=229) found that in patients with CAD, interval training was more effective than continuous training for the improvement of aerobic capacity in patients with CAD. However, the review only included small studies with unreported follow up periods.

Home based exercise

A systematic review(132) (7 studies n=1440) compared the longer-term effects (beyond 12 months) of home-based exercise programmes with usual care or centre-based rehabilitation in patients referred for cardiac rehabilitation. The results showed no significant differences in exercise capacity between home-based rehabilitation and usual care. There was a small but significant difference in exercise capacity in favour of home-based compared to centre-based rehabilitation.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

The collective new evidence on general aspects of physical activity is consistent with recommendations 1.2.7-1.2.10, which cross refer to NHS Choices and NICE public health guidance on physical activity.

Evidence on the following specific forms of exercise was either inconclusive or based on small trials with unknown follow up periods or unclear or high risk of bias:

- Yoga

- Qijong
- Tai Chi
- Meditation
- Interval training
- Home based exercise for cardiac rehabilitation.

No impact is anticipated on the guideline

New evidence is unlikely to change guideline recommendations.

181-06 Combined interventions (diet and physical activity)

Recommendations in this section of the guideline

1.2.11 Give advice on diet and physical activity in line with national recommendations (see NHS Choices). [2008]

Surveillance decision

This review question should be updated.

4-year surveillance summary

An RCT(133) (n=320) assessed the effects of a family-centred, physical activity and nutrition "brief" intervention (time-limited contact) in primary health care patients with an elevated 5-year risk of CVD. The intervention comprised a CVD risk assessment and up to five home sessions that aimed to reduce obesity by encouraging physical activity and healthy eating. The control group received a CVD risk assessment and one-time consultation. When compared with the control group, the intervention resulted in significant decreases in BMI, total cholesterol at 4 and 12 months, the total cholesterol to high-density lipoprotein cholesterol ratio at 4 months, 5-year CVD risk at 4 months, and fast food consumption at 12 months.

A systematic review(134) (22 studies, n=2574) aimed to determine whether lifestyle interventions focusing on behaviourally modifiable risk factors with or without an exercise programme are effective in terms of (1) preventing recurrent cardiovascular events, (2) reducing mortality, and (3) improving modifiable risk factors associated with CVD in patients after a transient ischemic attack or ischemic stroke. Pooled results showed a significant reduction in systolic blood pressure by the lifestyle interventions applied, compared with usual care. No significant effect was found on cardiovascular events, mortality, diastolic blood pressure, or cholesterol.

A post hoc analysis(135) (n=696) of an RCT aimed to determine the long-term effectiveness of a complex intervention in primary care aimed at improving outcomes for patients with CHD. There were no significant differences between the intervention and control practices in either total or cardiovascular hospital admissions. There were no significant differences in mortality or in the proportions of patients above target control for systolic blood pressure or total cholesterol.

A pilot RCT(136) (n=108) found that 'Waste the Waist', a group-based intervention designed to promote healthy eating and physical activity for people with high cardiovascular risk, achieved weight loss over a 12 month follow up but did not change physical activity.

Digital Health interventions

An RCT(137) and cost effectiveness analysis (n=330) found that an internet-based, nurse-led intervention in addition to usual care to improve vascular risk factors in patients with a clinical manifestation of a vascular disease (coronary, cerebral, or peripheral arteries) did not result in a QALY gain at 1 year, but had a small effect

on vascular risk factors and was associated with lower costs.

An RCT(138) (n=385) compared live counselling with a web-based format of delivering a lifestyle and medication intervention to reduce CAD risk. Included patients were aged 35 to 79 years, with no known CVD, and at moderate to high risk for CHD. Both intervention formats reduced CHD risk following the 12-month follow-up. The web format was less expensive, although this was not calculated in a UK NHS setting.

A systematic review(139) (51 studies) assessed the potential benefit of digital health interventions (DHIs) on CVD outcomes (CVD events, all-cause mortality, hospitalisations) and risk factors compared with non-DHIs. DHIs included telemedicine, Web-based strategies, e-mail, mobile phones, mobile applications, text messaging, and monitoring sensors. DHIs significantly reduced CVD outcomes. Concomitant reductions in weight and body mass index but not blood pressure were found in these DHI trials compared with usual care. The 10-year risk percentages were also significantly improved.

An RCT(140) (n=641) assessed whether non-clinical staff can effectively manage people at high risk of CVD using DHIs. The intervention was the Healthlines service (alongside usual care), comprising 13 regular telephone calls from trained lay health advisors following scripts generated by interactive software. Advisors facilitated self-management by supporting participants to use online resources to reduce risk factors, and sought to optimise drug use, improve treatment adherence, and encourage healthier lifestyles. The control group comprised usual care alone. The intervention was associated with small clinical benefits for a minority of people with high CVD risk, and there was no overall improvement in average risk. The Healthlines service was, however, associated with improvements in some risk behaviours, and in perceptions of support and access to care.

A cost effectiveness study(141) within the same RCT, (n=641) examined a telehealth intervention for primary care patients with raised CVD risk. Cost-effectiveness was measured by net monetary benefit at the end of 12 months of follow-up, calculated from incremental cost and incremental quality-adjusted life years (QALYs). The results suggested that the Healthlines telehealth intervention was likely to be cost-effective at a threshold of £20,000 per QALY.

A systematic review(142) (57 studies, n=19,862) evaluated whether Internet-based interventions for CV risk factor management reduce the risk of CVD in older people. Significant reductions were found in blood pressure, HbA1c level, LDL cholesterol level, weight. Physical activity levels significantly increased. However, the observed effects were more pronounced in studies with short (under 12 months) follow-up and studies that combined the Internet application with human support. No difference in incident CVD was found between groups.

Schizophrenia and lifestyle coaching

An RCT(143) (n=428) tested the efficacy of an intervention aimed to improve the cardiovascular risk profile and reduce mortality among people with schizophrenia spectrum disorders and abdominal obesity. The results did not support superiority of individual lifestyle coaching or care coordination compared to treatment as usual.

Topic expert feedback

Topic expert feedback highlighted that NHS Choices is not considered to be an authoritative source, and the reference to it in recommendation 1.2.11 should be removed.

Impact statement

Recommendation 1.2.11 states that advice should be given in line with national recommendations set out by NHS Choices.

Expert feedback highlighted that NHS Choices is not considered to be an authoritative source, and reference to it in recommendation 1.2.11 should be removed. There is a further potential impact to review the wording of this recommendation.

New evidence indicates the potential value of a family-centred, physical activity and nutrition "brief" intervention. However, the evidence was derived from a single RCT of limited sample size and is unlikely to impact on the guideline until further evidence becomes available to substantiate the findings.

New evidence on the following interventions is insufficient to impact on the guideline recommendations due to either unknown or small study sizes, lack of validation or inconclusive findings for lipid lowering and CVD outcomes:

- Internet-based, nurse-led interventions.

- Lifestyle interventions for behaviour change.
- Complex primary care interventions.
- Digital health interventions, including the Healthlines service; although evidence indicates this may be a cost effective intervention in the NHS, the intervention has not been validated.
- The 'Waste the Waist' group-based intervention.

New evidence identified that may change current recommendations.

181-07 Weight management

Recommendations in this section of the guideline

1.2.12 Offer people at high risk of or with CVD who are overweight or obese appropriate advice and support to work towards achieving and maintaining a healthy weight, in line with obesity (NICE guideline CG43). **[2008]**

Surveillance decision

This review question should not be updated.

4-year surveillance summary

A post hoc analysis(144) (n=5145) of an RCT examined whether the incidence of CVD in the trial varied by changes in weight or fitness. The RCT showed no significant reductions in the primary outcome of CVD incidence in adults with type 2 diabetes randomly assigned to an intensive lifestyle intervention for weight loss compared with those randomly assigned to diabetes support and education. However, in the post hoc analysis, individuals who lost at least 10% of their bodyweight in the first year of the study had a significantly lower risk of the primary and secondary outcomes compared with individuals with stable weight or weight gain. Achieving an increase of at least 2 metabolic equivalents in fitness change was associated with a significant reduction in the secondary outcome but not the primary outcome.

Mental illness

A systematic review(145) (33 studies n=unreported) evaluated pharmacologic and behavioural interventions to reduce CVD risk in adults with serious mental illness. Most studies targeted weight control (28 studies). Compared with control groups, weight control was improved with behavioural interventions, metformin, anticonvulsive medications topiramate and zonisamide, and adjunctive or antipsychotic switching to aripiprazole. Evidence was insufficient for all other interventions and for effects on glucose and lipid control.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

CG181 cross refers to NICE's guideline on obesity for weight management. As CG181 doesn't make specific recommendations for weight management in people with diabetes or with mental illness, the new evidence on the following interventions is unlikely to impact directly on CG181:

- an intensive lifestyle intervention in people with type 2 diabetes (lifestyle interventions are covered in NICE's guideline on Type 2 diabetes in adults: management)

- behavioural interventions, metformin, anticonvulsive medications topiramate and zonisamide, and adjunctive or antipsychotic switching to aripiprazole.

New evidence is unlikely to change guideline recommendations.

181-08 Alcohol consumption

Recommendations in this section of the guideline

1.2.13 Be aware that men should not regularly drink more than 3–4 units a day and women should not regularly drink more than 2–3 units a day. People should avoid binge drinking. Further information can be found at NHS Choices. [2008]

Surveillance decision

This review question should be updated.

4-year surveillance summary

A systematic review(146) (18 studies, n=214, 340), assessed the potential dose-response association betweenmay change alcohol consumption and risk of CAD. Alcohol consumption in moderation was associated with a reduced risk of CAD with 36 grams/d of alcohol conferring a lower risk than other levels.

Topic expert feedback

Topic expert feedback highlighted that NHS Choices is not considered to be an authoritative source, and the reference to it in recommendation 1.2.13 should be removed.

Impact statement

The new systematic review evidence indicating that alcohol consumption in moderation may reduce the risk of CAD is consistent with the national advice. However, Expert feedback highlighted that NHS Choices is not considered to be an authoritative source, and the reference to it in recommendation 1.2.13 should be removed. There is a further potential impact to review the accuracy and wording of this recommendation.

New evidence identified that may change current recommendations.

181-09 Smoking cessation

Recommendations in this section of the guideline

1.2.14 Advise all people who smoke to stop, in line with smoking cessation services (NICE guideline PH10). **[2008]**

1.2.15 Offer people who want to stop smoking support and advice, and referral to an intensive support service (for example, the NHS Stop Smoking Services). **[2008]**

1.2.16 If a person is unable or unwilling to accept a referral to an intensive support service, offer them pharmacotherapy in line with smoking cessation services (NICE guideline PH10) and varenicline for smoking cessation (NICE technology appraisal guidance 123). **[2008]**

Surveillance decision

This review question should not be updated.

4-year surveillance summary

Psychosocial interventions

A network meta-analysis(147) (7 pharmacotherapy trials, n=2809, 17 behavioural trials n=4666) evaluated the efficacy and safety of pharmacological and behavioural smoking cessation interventions in CVD patients. Individual and telephone counselling, were found to be effective for smoking cessation, whereas in-hospital behavioural interventions were not effective. Outcomes were smoking abstinence at 6 and 12 months.

An updated Cochrane systematic review(148) (40 studies in total, including 21 new studies) aimed to examine the efficacy of psychosocial interventions for smoking cessation in patients with CHD in short-term (6 to 12 month follow-up) and long-term follow up (more than 12 months). Psychosocial smoking cessation interventions were found to be effective in promoting abstinence up to 1 year, provided they were of sufficient duration. After one year, the studies showed favourable effects of smoking cessation intervention.

Varenicline

Two systematic reviews(147,149) were identified on varenicline for smoking cessation, including cardiovascular safety. The recommendations in this area are covered by the technology appraisal TA123: varenicline for smoking cessation (July 2007).

This information will be passed onto the TA team for consideration when the topic undergoes the review proposal process.

Smoking as a risk factor

An IPD meta-analysis(150) (n=503,905) investigated the impact of smoking and smoking cessation on CVD mortality, acute coronary events, and stroke events in people aged 60 and older. The results indicated that smoking is a strong independent risk factor of cardiovascular events and mortality even at older age, advancing cardiovascular mortality by more than five years.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

NICE CG181 does not make specific recommendations for smoking cessation in the context of CVD prevention, but cross refers to NICE's guideline on smoking cessation services.

The new systematic review evidence supporting the use of psychosocial interventions, including individual and telephone counselling, will be considered in the surveillance of this related guidance and no impact is anticipated on CG181.

New evidence is unlikely to change guideline recommendations.

181-010 What is the clinical and cost effectiveness of foods enriched with phytosterols (plant stanols and sterols) or phytosterol supplements versus

placebo for adults without established CVD (primary prevention) and with established CVD (secondary prevention)?

Recommendations derived from this review question

1.2.17 do not advise any of the following to take plant stanols or sterols for the prevention of CVD:

- people who are being treated for primary prevention
- people who are being treated for secondary prevention
- people with CKD
- people with type 1 diabetes
- people with type 2 diabetes. **[new 2014]**

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Lipid modification therapy for the primary and secondary prevention of CVD

181-011 What is the clinical and cost effectiveness of statin therapy for adults without established CVD (primary prevention) and with established CVD (secondary prevention)?

Recommendations derived from this review question

1.3.1 Be aware that when deciding on lipid modification therapy for the prevention of CVD, drugs are preferred for which there is evidence in clinical trials of a beneficial effect on CVD morbidity and mortality. **[2008]**

1.3.2 When a decision is made to prescribe a statin use a statin of high intensity[2] and low acquisition cost. **[new 2014]**

Lipid measurement and referral

1.3.3 Measure both total and high-density lipoprotein (HDL) cholesterol to achieve the best estimate of CVD risk. **[2008]**

1.3.4 Before starting lipid modification therapy for the primary prevention of CVD, take at least 1 lipid sample to measure a full lipid profile. This should include measurement of total cholesterol, HDL cholesterol, non-HDL cholesterol and triglyceride concentrations. A fasting sample is not needed. **[new 2014]**
For information about implementing this recommendation, see implementation: getting started.

1.3.5 Use the clinical findings, lipid profile and family history to judge the likelihood of a familial lipid disorder rather than the use of strict lipid cut-off values alone. **[new 2014]**

[2] See appendix A for statin classification.

1.3.6 Exclude possible common secondary causes of dyslipidaemia (such as excess alcohol, uncontrolled diabetes, hypothyroidism, liver disease and nephrotic syndrome) before referring for specialist review. **[new 2014]**

1.3.7 Consider the possibility of familial hypercholesterolaemia and investigate as described in familial hypercholesterolaemia (NICE guideline CG71) if they have:

- a total cholesterol concentration more than 7.5 mmol/litre **and**
- a family history of premature coronary heart disease. **[new 2014]**

1.3.8 Arrange for specialist assessment of people with a total cholesterol concentration of more than 9.0 mmol/litre or a non-HDL cholesterol concentration of more than 7.5 mmol/litre even in the absence of a first-degree family history of premature coronary heart disease. **[new 2014]**

1.3.9 Refer for urgent specialist review if a person has a triglyceride concentration of more than 20 mmol/litre that is not a result of excess alcohol or poor glycaemic control. **[new 2014]**

1.3.10 In people with a triglyceride concentration between 10 and 20 mmol/litre:

- repeat the triglyceride measurement with a fasting test (after an interval of 5 days, but within 2 weeks) **and**
- review for potential secondary causes of hyperlipidaemia **and**
- seek specialist advice if the triglyceride concentration remains above 10 mmol/litre. **[new 2014]**

1.3.11 In people with a triglyceride concentration between 4.5 and 9.9 mmol/litre:

- be aware that the CVD risk may be underestimated by risk assessment tools **and**
- optimise the management of other CVD risk factors present **and**
- seek specialist advice if non-HDL cholesterol concentration is more than 7.5 mmol/litre. **[new 2014]**

Statins for the prevention of CVD

Recommendations in this section update and replace those in statins for the prevention of cardiovascular events (NICE technology appraisal guidance 94)].

1.3.12 The decision whether to start statin therapy should be made after an informed discussion between the clinician and the person about the risks and benefits of statin treatment, taking into account additional factors such as potential benefits from lifestyle modifications, informed patient preference, comorbidities, polypharmacy, general frailty and life expectancy. **[new 2014]**

1.3.13 Before starting statin treatment perform baseline blood tests and clinical assessment, and treat comorbidities and secondary causes of dyslipidaemia. Include all of the following in the assessment:

- smoking status
- alcohol consumption
- blood pressure (see hypertension [NICE guideline CG127])
- body mass index or other measure of obesity (see obesity [NICE guideline CG43])
- total cholesterol, non-HDL cholesterol, HDL cholesterol and triglycerides
- HbA_{1c}
- renal function and eGFR
- transaminase level (alanine aminotransferase or aspartate aminotransferase)
- thyroid-stimulating hormone. **[new 2014]**

Primary prevention

1.3.14 Before offering statin treatment for primary prevention, discuss the benefits of lifestyle modification and optimise the management of all other modifiable CVD risk factors if possible. **[new 2014]**

1.3.15 Recognise that people may need support to change their lifestyle. To help them do this, refer them to programmes such as exercise referral schemes. (See behaviour change: individual approaches [NICE guideline PH49].) **[new 2014]**

1.3.16 Offer people the opportunity to have their risk of CVD assessed again after they have tried to change their lifestyle. **[new 2014]**

1.3.17 If lifestyle modification is ineffective or inappropriate offer statin treatment after risk assessment. **[new 2014]**

1.3.18 Offer atorvastatin 20 mg for the primary prevention of CVD to people who have a 10% or greater 10-year risk of developing CVD. Estimate the level of risk using the QRISK2 assessment tool. **[new 2014]**
For information about implementing this recommendation, see implementation: getting started.

1.3.19 For people 85 years or older consider atorvastatin 20 mg as statins may be of benefit in reducing the risk of non-fatal myocardial infarction. Be aware of factors that may make treatment inappropriate (see recommendation 1.3.12). **[new 2014]**

Secondary prevention

1.3.20 Start statin treatment in people with CVD with atorvastatin 80 mg[3]. Use a lower dose of atorvastatin if any of the following apply:

- potential drug interactions
- high risk of adverse effects
- patient preference. **[new 2014]**
  For information about implementing this recommendation, see implementation: getting started.

1.3.21 Do not delay statin treatment in secondary prevention to manage modifiable risk factors. **[2014]**

1.3.22 If a person has acute coronary syndrome, do not delay statin treatment. Take a lipid sample on admission and about 3 months after the start of treatment. **[2008, amended 2014]**

Primary prevention for people with type 1 diabetes

1.3.23 Consider statin treatment for the primary prevention of CVD in all adults with type 1 diabetes. **[new 2014]**

1.3.24 Offer statin treatment for the primary prevention of CVD to adults with type 1 diabetes who:

- are older than 40 years **or**
- have had diabetes for more than 10 years **or**
- have established nephropathy **or**
- have other CVD risk factors. **[new 2014]**

1.3.25 Start treatment for adults with type 1 diabetes with atorvastatin 20 mg. [new 2014]

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[3] At the time of publication (July 2014), atorvastatin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

Primary prevention for people with type 2 diabetes

1.3.26 Offer atorvastatin 20 mg for the primary prevention of CVD to people with type 2 diabetes who have a 10% or greater 10-year risk of developing CVD. Estimate the level of risk using the QRISK2 assessment tool. **[new 2014]**

People with CKD

1.3.27 Offer atorvastatin 20 mg for the primary or secondary prevention of CVD to people with CKD[4].

- Increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved (see recommendation 1.3.28) and eGFR is 30 ml/min/1.73 m^2 or more.
- Agree the use of higher doses with a renal specialist if eGFR is less than 30 ml/min/1.73 m^2. **[new 2014]**

Follow-up of people started on statin treatment

1.3.28 Measure total cholesterol, HDL cholesterol and non-HDL cholesterol in all people who have been started on high-intensity statin treatment (both primary and secondary prevention, including atorvastatin 20 mg for primary prevention) at 3 months of treatment and aim for a greater than 40% reduction in non-HDL cholesterol. If a greater than 40% reduction in non-HDL cholesterol is not achieved:

- discuss adherence and timing of dose
- optimise adherence to diet and lifestyle measures
- consider increasing the dose if started on less than atorvastatin 80 mg and the person is judged to be at higher risk because of comorbidities, risk score or using clinical judgement. **[new 2014]**

1.3.29 Provide annual medication reviews for people taking statins.

- Use these reviews to discuss medicines adherence and lifestyle modification and address CVD risk factors.
- Consider an annual non-fasting blood test for non-HDL cholesterol to inform the discussion. **[new 2014]**

1.3.30 Discuss with people who are stable on a low- or middle-intensity statin the likely benefits and potential risks of changing to a high-intensity statin when they have a medication review and agree with the person whether a change is needed. **[new 2014]**
For information about implementing this recommendation, see implementation: getting started

Surveillance decision

This review question should be updated.

4-year surveillance summary

Uptake of statin treatment

A retrospective cohort study(151) (n=183,565) found that a large proportion of UK individuals with ASCVD and high-risk non-ASCVD received statin treatment during the year of NICE CG181 release. When extrapolated to the national level, a very high proportion of patients with ASCVD and high-risk non-ASCVD individuals would require increased statin titration or initiation to achieve full concordance with NICE CG181. Data were obtained from general practice via the Health Improvement Network database.

[4] See the NICE guideline on chronic kidney disease for CKD classification. People on renal replacement therapy are outside the scope of this guideline.

Rosuvastatin

An RCT(152) (n=12,705) evaluated the long-term effects of rosuvastatin at a dose of 10 mg per day (without dose adjustment or lipid targets) among persons of various ethnic backgrounds on six continents who did not have CVD and were at intermediate risk. Treatment with rosuvastatin resulted in a significantly lower risk of cardiovascular events than placebo.

High intensity statins

A post hoc analysis(153) (n=1039) of an RCT compared the long-term antiatherosclerotic efficacy of high-intensity statins (rosuvastatin 40 mg or atorvastatin 80 mg) in patients with ACS when compared with stable disease. Long-term high-intensity statin therapy caused greater plaque regression and comparable major adverse cardiovascular events rates in ACS when compared with non-ACS patients.

A post hoc analysis of an RCT(154) (n=8888) found that in post-MI patients, high-dose atorvastatin (80 mg/day) was superior to moderate-dose simvastatin (20-40 mg/day) in preventing peripheral arterial disease. Atorvastatin treatment significantly reduced overall cardiovascular and coronary events, and coronary revascularisation in these patients.

A post hoc analysis(155) (n=23,508) of 3 RCTs found that high-dose versus usual-dose statin therapy (atorvastatin or simvastatin) or placebo did not impact the incidence of aortic valve stenosis (AVS) among patients without known AVS.

A secondary analysis(156) of an RCT (n=10 001) found that in patients with treatment resistant hypertension, intensive lipid lowering with atorvastatin 80 mg was associated with a significant reduction in cardiovascular events, when compared with atorvastatin 10 mg.

An RCT(157) (n=10,251) compared the effects of combinations of standard and intensive treatment of glycaemia and either blood pressure or lipids. In the lipid trial, the general pattern of results showed no evidence of benefit of intensive regimens (whether single or combined) compared with combined standard lipid and glycaemia treatment. The mortality was significantly higher in the standard lipid/intensive glycaemia group compared with the standard lipid/standard glycaemia group. In the ACCORD lipid trial, neither intensive lipid nor glycaemia treatment produced an overall benefit, but intensive glycaemia treatment increased mortality.

A secondary analysis(158) of an RCT (n=1,503) examined the association between baseline levels of oxidised phospholipids on apolipoprotein B-100 (OxPL-apoB) and major cardiovascular events (MACE), defined as death from CHD, nonfatal MI, resuscitation after cardiac arrest, and fatal/nonfatal stroke, as well as the effect of statin therapy on OxPL-apoB levels and MACE. Elevated OxPL-apoB levels predicted secondary MACE in patients with stable CHD, but the risk was reduced to a non-significant level by atorvastatin 80 mg, compared to atorvastatin 10 mg.

An IPD meta-analysis(159) (37 studies n=32,258) assessed the extent to which high-intensity statins (rosuvastatin 20-40 mg and atorvastatin 40-80 mg) reduced LDL cholesterol in each of four statin benefit groups. The groups were 1) ASCVD; 2) LDL-C >190 mg/dl; 3) diabetes; or 4) a 10-year ASCVD risk >7.5%. Reductions in LDL-C with rosuvastatin 20 and 40 mg were greater than with atorvastatin 40 mg, overall and in each statin benefit group, and with rosuvastatin 40 mg were greater than with atorvastatin 80 mg overall and in three of the four benefit groups.

A post hoc analysis(160) (n=1461) of an RCT compared the usual care (UC) of CVD prevention with a multifactorial intensive care (IC) approach aiming at achieving target values for the main CV risk factors in type 2 diabetes according to a step-wise treat-to-target approach. The proportion of patients on target for LDL-C was increased significantly more with IC than UC. However, the majority of patients failed to achieve the proposed target. IC was associated with a significantly greater increase in statin prescription and lower withdrawal from treatment than UC. The multifactorial intensive care intervention was not clearly defined in the abstract.

Target based high intensity statins

An IPD meta-analysis(161) (n=38,153) aimed to evaluate: 1) the inter-individual variability of reductions in LDL-C, non-HDL-C, or apoB levels achieved with statin therapy; 2) the proportion of patients not reaching guideline-recommended lipid levels on high-dose statin therapy; and 3) the association between very low levels of atherogenic lipoproteins achieved with statin therapy and cardiovascular disease risk. The results indicated that reductions of LDL-C, non-HDL-C, and apoB levels achieved with statin therapy displayed large inter-

individual variation. Among trial participants treated with high-dose statin therapy, over 40% did not reach an LDL-C target <70 mg/dl. Patients who achieved very low LDL-C levels had a lower risk for major CVD events than those achieving moderately low levels.

A systematic review(162) aimed to appraise the clinical and genetic evidence that low-density lipoproteins (LDLs) cause atherosclerotic CVD. evidence from the genetic studies, prospective epidemiologic cohort studies, Mendelian randomisation studies, and RCTs, indicated that LDL is not merely a biomarker of increased risk but a causal factor in the pathophysiology of ASCVD. The findings also suggested that the lower the LDL-C level attained by targeting LDL receptors, the greater the clinical benefit accrued.

General effectiveness of statins

A systematic review(163) (49 studies n=312,175) evaluated the association between lowering LDL-C and relative cardiovascular risk reduction across different statin and non-statin therapies (including diet, bile acid sequestrants, ileal bypass, and ezetimibe). The use of statin and non-statin therapies that act via upregulation of LDL receptor expression to reduce LDL-C were associated with similar relative risks of major vascular events per change in LDL-C. Lower achieved LDL-C levels were associated with lower rates of major coronary events.

A systematic review(164) of systematic reviews (35 reviews) compared the efficacy and safety of various drug treatments, including statins, for fatal and nonfatal ASCVD outcomes in primary ASCVD prevention. Compared with placebo, statins significantly reduced the risk for ASCVD and did not increase overall risk for adverse effects.

A systematic review(165) (19 studies, n=71,344) examined the effectiveness of statins vs placebo, fixed-dose vs titrated statins, and higher- vs lower-intensity statins in adults without prior cardiovascular events. Statin therapy was associated with decreased risk of all-cause mortality, cardiovascular mortality, stroke, MI and composite cardiovascular outcomes. Relative benefits appeared consistent in demographic and clinical subgroups, including populations without marked hyperlipidaemia. Absolute benefits were higher in subgroups at higher baseline risk. Statins were not associated with increased risk of serious adverse events.

Long term effectiveness

A network meta-analysis(166) (88 studies) evaluated the efficacy and safety of long-term treatment of statins for CHD. Efficacy outcomes included changes in blood lipids, risk of CHD mortality and all-cause mortality. Network meta-analysis showed that:

- Levels of blood lipids decreased during statin treatment.
- A high dose of atorvastatin was the most effective treatment reducing blood lipids.
- Fluvastatin, atorvastatin and lovastatin were found to be more effective treatments for the reduction of CHD mortality.
- Atorvastatin, fluvastatin and pitavastatin were found to be the more effective treatments for reducing all-cause mortality.
- Statins were significantly more effective than the control in reducing the risk of CHD mortality and all-cause mortality.
- Compared with placebo, statins increased the incidence risk of muscle disease and kidney disease.

A post-hoc analysis(167) (n=9014) of an RCT assessed the long-term effects of treatment with statin therapy on all-cause mortality, cause-specific mortality, and cancer incidence from extended follow-up over 10 years. During extended follow-up, 85% assigned pravastatin and 84% assigned placebo took statin therapy. Patients who were assigned to pravastatin maintained a significantly lower risk of death from CHD, from CVD and from any cause, compared to placebo.

A post hoc analysis(168) (n=6595) of an RCT found that statin treatment for 5 years (pravastatin 40 mg once daily or placebo for an average of 4.9 years) was associated with improved survival and a substantial reduction in CVD outcomes over a 20-year follow up period.

A post hoc analysis(169) (n=175) of an RCT found that long-term intensive lipid therapy over 25 years significantly reduced total and cardiovascular mortality, compared with usual care. Intensive treatment comprised lovastatin (40 mg/d), niacin (2.5 g/d), and colestipol (20 g/d) from 1989 to 2004, followed by double therapy with simvastatin (40-80 mg/d) and niacin from 2005 to 2006 and by triple therapy of ezetimibe 10 mg and simvastatin (40 to 80 mg/d) plus niacin during 2007 to 2012.

A secondary analysis(170) (n=5803) of an RCT estimated the absolute treatment effect of statin

therapy on major adverse cardiovascular events for individual patients aged over 70 years old. Individual absolute risk reductions (ARRs) for MACE in 5 and 10 years were estimated by subtracting on-treatment from off-treatment risk. Individual ARRs were higher in elderly patients with vascular disease than in patients without vascular disease. Results indicated that treating all patients was more beneficial than prediction-based treatment for secondary prevention of MACE. For primary prevention of MACE, the results indicated potential value of the prediction model to identify those patients who benefit meaningfully from statin therapy.

Gender differences

An IPD meta-analysis(171) (22 studies statin therapy versus control n=134, 537 and five studies of more-intensive versus less-intensive statin therapy n=39,612) compared the effects of statin therapy between women and men. Allocation to a statin had similar absolute effects on 1 year lipid concentrations in both men and women. The proportional reductions per 1.0 mmol/L reduction in LDL cholesterol in major vascular events were similar overall for women and men and also for those women and men at less than 10% predicted 5 year absolute cardiovascular risk.

Combined treatment

An RCT(172) (n=12,705) found that the combination of rosuvastatin (10 mg per day), candesartan (16 mg per day), and hydrochlorothiazide (12.5 mg per day) was associated with a significantly lower rate of cardiovascular events than dual placebo among persons at intermediate risk who did not have CVD.

A systematic review(173) (36 studies) compared the clinical benefits, adherence, and harms of lower-intensity statin combination therapy with those of higher-intensity statin monotherapy among adults at high risk for CVD. Low-intensity statin plus bile acid sequestrant decreased LDL cholesterol level more than mid-intensity monotherapy among high-risk hyperlipidaemic patients. Mid-intensity statin plus ezetimibe decreased LDL cholesterol level more than high-intensity monotherapy among patients with ASCVD and diabetes mellitus, respectively. Evidence was insufficient to evaluate LDL cholesterol for fibrates, niacin, and omega-3 fatty acids. Evidence was insufficient for long-term clinical outcomes, adherence, and harms for all regimens. It should be noted that the statistical significance of the results was not reported in the abstract.

Prognostic Biomarkers

Homocysteine

A post hoc analysis(174) (n=3522) of an RCT found that in older persons aged 70-82 at risk of CVD, those with high homocysteine were at highest risk for fatal and nonfatal CHD. With pravastatin treatment, this group had the highest absolute risk reduction and the lowest number needed to treat to prevent fatal and nonfatal CHD.

Genetic variants

A secondary analysis(175) of an RCT (n=5244) investigated the interaction between genetic variants and pravastatin or placebo therapy on the incidence of CVD. Results indicated that genetic variation was not significantly associated with a clinically meaningful event reduction by pravastatin treatment.

Patients with chronic kidney disease (CKD)

A secondary analysis(176) of an RCT (n=9500) examined the relation between intrastudy change in estimated glomerular filtration rate (eGFR) from baseline and the risk of major cardiovascular events. Stabilisation or increase in eGFR in atorvastatin-treated patients with CHD was associated with a reduced rate of major cardiovascular events. Statin-treated CHD patients with progressive renal impairment were at high risk for future cardiovascular events.

A systematic review(177) (6 studies n=8834) assessed lipid-lowering therapies for CVD primary prevention in CKD. Results showed that statins significantly reduced the risk of CVD in stages 1-3 CKD compared with placebo. Specific statins were not reported in the abstract.

Heart failure

A systematic review(178) (17 trials n=132,538) aimed to establish whether statins reduce major heart failure events. Statins reduced the numbers of patients experiencing non-fatal heart failure hospitalisation and the composite heart failure outcome but not heart failure death. The effect of statins on first non-fatal heart failure hospitalisation was similar whether this was preceded by MI or not.

An IPD meta-analysis(179) (n=9585) pooled data from two large trials (CORONA and GISSI-HF) of heart failure patients not on statin therapy randomised to rosuvastatin 10 mg daily or placebo, in order to improve power to detect

statistically significant differences in atherothrombotic events. Results indicated that rosuvastatin significantly decreased risk for myocardial infarction (MI) among participants with ischaemic aetiology of heart failure. There were no significant differences between rosuvastatin and placebo in risks for stroke or death from other causes.

Topic expert feedback

Target based high intensity statins

Topic experts noted that a review of recommendation 1.3.28, for using high-intensity statins to achieve a percentage reduction rather than an absolute lipid target level, should also be undertaken because of concerns relating to under-treatment and compliance. A formal literature search was considered necessary to reveal outcomes since CG181 was published.

Further feedback indicated that the recommended approach to achieve a percentage reduction has not been adopted universally and many in both primary and secondary care are still treating to an absolute target in both primary and secondary prevention.

Moreover, this could conflict with a large number of on-going and new initiatives in which a target level of cholesterol is an important outcome measure, audit point and reimbursement factor.

Topic expert feedback indicated that a large RCT(152) (n=12,705), which is included in the evidence summary, adds to the data for the use of rosuvastatin, which is likely to be one of the most popular agents when it goes off patent in 2018. However, the majority of experts agreed that the population was not fully representative of the NHS, due to the ethnically diverse sample recruited from 21 countries, and the minority of white people included.

Heart Failure

Topic expert feedback indicated that specific recommendations are needed for lipid modification in people with mild and severe heart failure. It was stated that this area was not reviewed in NICE CG181 or in the chronic update of heart failure (NICE guideline CG108). It was stated that this gap should be addressed by including both New York Heart Association classification (NYHA) 1-2 heart failure and NYHA-3 and higher, the latter being the prime focus of NICE CG108.

Treatment patterns

A study(151) was cited relating to treatment patterns following publication of CG181. This is included in the evidence summary.

Further topic expert feedback indicated that GPs indicated that they have other priorities and primary prevention is too onerous. Looking at uptake for statins according to prescribing data from openprescribing.net, there was not considered to have been a big change in overall prescribing patterns since the guideline was published.

Service delivery

Topic experts noted that the impact of new structures for healthcare service delivery, including clinical networks and sustainability and transformation plans, should be considered in any restructuring of the guideline recommendations.

Given increasing focus on patients with multiple long term conditions, it was felt that the guideline should also take account of these groups.

A cross-reference to the NHS England five year forward view strategy for the NHS, in the context of prevention, and the contribution of the guideline to this wider health policy was advised by topic experts.

Licensing

Topic experts noted that rosuvastatin will become available off patent in December 2017. And that this could potentially influence the wording of the existing guidance on atorvastatin. A new cost-effectiveness analysis was considered necessary, which could conceivably result in a lower 10 year CVD risk threshold for intervention. Expert advice confirmed that generic versions of rosuvastatin are in development but that the acquisition cost is unknown and may vary over time.

Combined treatment

Topic expert feedback indicated that the new RCT evidence supporting the use of combination rosuvastatin, candesartan and hydrochlorothiazide is unlikely to impact on CG181 because this regimen is in line with current practice, and that the blood pressure control elements (candesartan and hydrochlorothiazide) are not directly relevant to CG181.

Impact statement

High intensity statins

NICE CG181 advises that when a decision is made to prescribe a statin, a statin of high intensity and low acquisition cost should be used. In developing the guideline, the committee were unable to judge if rosuvastatin 10 mg, 20 mg or 40 mg would be more effective than atorvastatin 80 mg in reducing cardiovascular events. Given the considerably higher cost of using rosuvastatin at that time, it would have needed to be considerably more effective than atorvastatin for there to be a possibility that its use could be cost effective. In the absence of trial evidence of greater effectiveness the guideline committee were therefore unable to recommend the use of rosuvastatin.

However, the new evidence from an IPD meta-analysis and a large RCT supporting rosuvastatin at doses of 10-40 mg, which constitute high intensity doses, has a potential impact on recommendation 1.3.18 due to the imminent expiry of the rosuvastatin patent and the drug's future availability in a generic form. There is a potential need to update the health economic model to review cost effectiveness in the light of changing acquisition costs.

Topic expert feedback indicating the need to review recommendation 1.3.28, for using high-intensity statins to achieve a percentage reduction rather than an absolute lipid target level, is supported by new IPD meta-analysis evidence. This indicates large inter-individual variation in lipid level reductions achieved from statins and that the lower the LDL-C level attained by statins, the greater the clinical benefit accrued. There is a potential impact on this recommendation.

Effectiveness of statins

The collective evidence and topic expert feedback indicates that statins overall are effective in reducing lipid levels and consequently risk of CVD, CHD and all-cause mortality. Evidence also indicates that the treatment effects are maintained over long term periods. This is consistent with the guideline recommendations.

The new systematic review evidence supporting the use of intensive atorvastatin as the most effective treatment for the reduction of blood lipids is consistent with CG181 recommendations, although recommendation 1.3.18 could be impacted by the expiry of the patent for rosuvastatin and the changing acquisition costs.

Statins in Subgroups

Diabetes

The new evidence, based on RCT data, supports a multifactorial intensive care intervention for reducing CV risk factors in type 2 diabetes. The multifactorial intervention was not clearly defined in the abstract and is therefore unlikely to impact on recommendation 1.3.26, which advises offering intensive atorvastatin 20 mg for the primary prevention of CVD to people with type 2 diabetes who have a 10% or greater 10‑year risk of developing CVD.

However, there is a potential sequential impact on recommendations 1.3.23 and 1.3.24 following the potential impact on recommendation 1.1.9 to use QRISK3 for assessing CVD risk in people with type 1 diabetes (see 181-02).

Heart Failure

New evidence and topic expert feedback indicates that statins, particularly rosuvastatin, are effective in reducing the risk of heart failure hospitalisation and MI, but not heart failure death, in people with heart failure. There is a potential impact to include specific recommendations on the use of statins for people with all NYHA classifications of heart failure. The distinctions between treatments for NYHA1-2 and NYHA3 and higher heart failure should be considered in developing the recommendations.

Renal

The new systematic review and RCT evidence on statins for lipid lowering in patients with CKD supports the use of intensive atorvastatin and indicates that those with pre-existing CHD and CKD are at particularly high risk. This is consistent with recommendation 1.3.27, which advises a starting dose of 20 mg atorvastatin for primary and secondary prevention, and increasing the dose depending on the patient's eGFR.

However, there is a potential sequential impact on recommendation 1.3.27 from the potential impact on recommendation 1.1.11 to use QRISK3 for assessing CVD risk in people with CKD (see 181-02).

Combined treatment

The new RCT evidence supporting the use of combination rosuvastatin, candesartan and

hydrochlorothiazide is unlikely to impact on CG181 because topic expert feedback indicated that this combined regimen is in line with current practice and that the blood pressure control elements (candesartan and hydrochlorothiazide) are not directly relevant to CG181. The new systematic review evidence supporting the use of lower-intensity statin combination therapy is unlikely to impact on CG181, because of inadequate data and insufficient evidence for long-term clinical outcomes.

Evidence on combined intensive treatment with lovastatin, niacin, colestipol, followed by simvastatin and niacin, followed by ezetimibe and simvastatin plus niacin is unlikely to impact because the evidence was based on a small sample size and further research may be needed to substantiate the findings.

Treatment patterns

The new evidence and topic expert feedback indicates the limited impact of the guideline on prescribing patterns, due to the major related issues of adherence to statin therapy and adverse effects (both feared and actual). This is unlikely to impact on the guideline recommendations directly but will be passed on to the NICE implementation team for consideration.

Service delivery

Topic expert feedback indicating the need to include the impact of new structures for healthcare service delivery, including clinical networks and sustainability and transformation plans, on restructuring of the guideline recommendations. However, no new evidence was cited and as CG181 does not include recommendations specific to service delivery, there is unlikely to be an impact directly on the guideline.

Pravastatin

The new cost utility evidence indicating the long term effectiveness of pravastatin specifically is unlikely to impact on recommendations, which advise the use of high intensity statin at a low acquisition cost, based on head to head and cost effectiveness analyses. The new evidence on pravastatin is based on trial data included in the CG181 evidence review, in which atorvastatin was found to be the most cost effective treatment. The guideline committee noted there was outcome evidence for pravastatin at low doses – mostly 10 mg. The committee confirmed that patients should be on a statin even at low dose in preference to any other lipid-lowering drug and patients should be informed that they will benefit even at lower doses and intensities. The new evidence is consistent with this.

Older people

CG181 advises (1.3.19) that for people 85 years or older, atorvastatin 20 mg should be considered as statins may be of benefit in reducing the risk of non‑fatal MI, but to be aware of factors that may make treatment inappropriate. The new evidence based on RCT data indicates that statin treatment may be more beneficial in patients over 70 years with vascular disease than in those without vascular disease. It also indicates that for primary prevention of CVD, there is potential value of using a prediction model to identify patients who would benefit most. For secondary prevention, treating all patients may be more beneficial than prediction based treatment. This is unlikely to impact due to the individually specific factors that require consideration in elderly patients. The guideline committee stated that consideration of risk and benefits and factors such as polypharmacy, comorbidity, frailty and life expectancy are particularly important in older age groups. The new evidence indicating that homocysteine levels in older people may inform risk assessment and treatment is also consistent with this position.

Multimorbidity

Topic expert feedback highlighted the need for the guideline to take account of patients with multiple long term conditions. A cross referral may be required to NICE guideline NG56 Multimorbidity: clinical assessment and management (September 2016). Specifically, recommendation 1.1.2 is relevant to CG181:

Be aware that the management of risk factors for future disease can be a major treatment burden for people with multimorbidity and should be carefully considered when optimising care.

Additional relevant recommendations include 1.1.4. 1.5.1. 1.5.2, 1.6.2 and 1.6.13–1.6.15.

Gender differences

CG181 does not make specific gender-based recommendations and the new evidence is consistent with this, indicating similar benefits of statins between men and women and no requirement to differentiate recommendations by gender.

Genetic variants

The new evidence indicating that genetic variants does not impact on statin effectiveness is consistent with CG181 recommendations, which do not advise treatment according to genetic variation.

New evidence identified that may change current recommendations.

181-012 Who is at risk of adverse effects from statin treatment? (Are some subgroups at different risk of adverse events?)

Recommendations derived from this review question

Advice and monitoring for adverse effects

1.3.31 Advise people who are being treated with a statin:

- that other drugs, some foods (for example, grapefruit juice) and some supplements may interfere with statins **and**
- to always consult the patient information leaflet, a pharmacist or prescriber for advice when starting other drugs or thinking about taking supplements. **[new 2014]**

1.3.32 Remind the person to restart the statin if they stopped taking it because of drug interactions or to treat intercurrent illnesses. **[new 2014]**

1.3.33 Before offering a statin, ask the person if they have had persistent generalised unexplained muscle pain, whether associated or not with previous lipid-lowering therapy. If they have, measure creatine kinase levels.

- If creatine kinase levels are more than 5 times the upper limit of normal, re-measure creatine kinase after 7 days. If creatine kinase levels are still 5 times the upper limit of normal, do not start statin treatment.
- If creatine kinase levels are raised but less than 5 times the upper limit of normal, start statin treatment at a lower dose. **[new 2014]**

1.3.34 Advise people who are being treated with a statin to seek medical advice if they develop muscle symptoms (pain, tenderness or weakness). If this occurs, measure creatine kinase. **[2008]**

1.3.35 If people report muscle pain or weakness while taking a statin, explore other possible causes of muscle pain or weakness and raised creatine kinase if they have previously tolerated statin therapy for more than 3 months. **[new 2014]**

1.3.36 Do not measure creatine kinase levels in asymptomatic people who are being treated with a statin. **[2008]**

1.3.37 Measure baseline liver transaminase enzymes (alanine aminotransferase or aspartate aminotransferase) before starting a statin. Measure liver transaminase within 3 months of starting treatment and at 12 months, but not again unless clinically indicated. **[2008]**

1.3.38 Do not routinely exclude from statin therapy people who have liver transaminase levels that are raised but are less than 3 times the upper limit of normal. **[2008]**

1.3.39 Do not stop statins because of an increase in blood glucose level or HbA_{1c}. (See the recommendations on assessing for risk of diabetes mellitus in preventing type 2 diabetes [NICE guideline PH38].) **[new 2014]**

1.3.40 Statins are contraindicated in pregnancy:

- Advise women of childbearing potential of the potential teratogenic risk of statins and to stop taking them if pregnancy is a possibility.

- Advise women planning pregnancy to stop taking statins 3 months before they attempt to conceive and to not restart them until breastfeeding is finished. **[new 2014]**

Intolerance of statins

1.3.41 If a person is not able to tolerate a high-intensity statin aim to treat with the maximum tolerated dose. **[new 2014]**

1.3.42 Tell the person that any statin at any dose reduces CVD risk. If someone reports adverse effects when taking high-intensity statin discuss the following possible strategies with them:

- stopping the statin and trying again when the symptoms have resolved to check if the symptoms are related to the statin
- reducing the dose within the same intensity group
- changing the statin to a lower intensity group. **[new 2014]**

1.3.43 Seek specialist advice about options for treating people at high risk of CVD such as those with CKD, type 1 diabetes, type 2 diabetes or genetic dyslipidaemias, and those with CVD, who are intolerant to 3 different statins. Advice can be sought for example, by telephone, virtual clinic or referral. **[new 2014].**

Surveillance decision

This review question should not be updated.

4-year surveillance summary

Statin intolerance

A cohort study(180) (n=105,329) evaluated the risk for recurrent MI, CHD events, and all-cause mortality in patients with statin intolerance and in those with high adherence to statin therapy. Statin intolerance was associated with a significantly increased risk for recurrent MI and CHD events but not all-cause mortality. The median follow up period was 1.9 to 2.3 years. Statin intolerance was defined as down-titrating statins and initiating ezetimibe therapy, switching from statins to ezetimibe monotherapy, having International Classification of Diseases diagnostic codes for rhabdomyolysis or an antihyperlipidaemic adverse event, followed by statin down-titration or discontinuation, or switching between 3 or more types of statins within 1 year after initiation.

A NICE Medicines evidence commentary was identified which focused on an analysis(181) of the double-blind and open-label phases of an RCT (n=10,180): Statin adverse effects: study suggests people are more likely to experience muscle aches and pains if they are expecting them.

During the double-blind phase, the annual rate of muscle-related adverse effects was similar and not statistically significantly different in the atorvastatin and placebo groups. This was also the case for erectile dysfunction and cognitive impairment, although that was reported rarely. Sleep disturbance was reported statistically significantly less often among atorvastatin-users than participants randomised to placebo.

By contrast, in the open-label phase, the annual rate of muscle-related adverse effects was statistically significantly higher among atorvastatin users than non-users, although in both groups the rate was lower than during the double-blind phase. Rates of erectile dysfunction and sleep disturbance were also lower than in the double-blind phase, and there was no longer a statistically significant difference between groups for sleep disturbance. Rates of cognitive impairment were broadly similar to the double-blind phase and again reported rarely.

Diabetes

A secondary analysis(182) of an RCT (n= 2,739) examined the effect of atorvastatin on glycaemia progression in type 2 diabetes and whether glycaemia effects reduce the prevention of CVD with atorvastatin. The effect of atorvastatin 10 mg on glycaemia progression among those with diabetes was statistically significant but very small, was not significantly different between sexes, did not increase with duration of statin and did not have an impact on the magnitude of CVD risk reduction with atorvastatin.

A secondary analysis (183) (n=8272) of a cohort study evaluated the risk of new-onset diabetes associated with statin exposure in a cohort of Australian women over 80 years old. Risk of new-onset diabetes increased with increasing dose of statin.

High intensity statins

A systematic review(184) (7 studies, n=62,204) assessed the association between higher dose of various statins and risk of intracerebral haemorrhage (ICH) among patients with CVD. A high dose of statins was defined as atorvastatin 80 mg, simvastatin 80 mg, pravastatin 40 mg, rosuvastatin 20 mg per day. A significant risk of ICH was observed in patients receiving a higher dose of statin, compared to those receiving placebo. There was no difference in all-cause mortality between the two groups. The length of follow up was not reported in the abstract.

A systematic review(185) (17 studies, n=21,910) evaluated the tolerability and adverse events of atorvastatin 80 mg/day for the primary and secondary prevention of CVD. Pooled analyses showed that atorvastatin 80 mg/day was less tolerable and increased the risk of transaminase elevation compared with controls. No significant difference was observed between the two groups in terms of the incidence of creatine kinase elevation, myalgia, and rhabdomyolysis.

Fracture risk

A secondary analysis of an RCT(186) (n=17, 802) found that among adults with elevated biomarker high-sensitivity C-reactive protein hs-CRP level enrolled in a large trial of rosuvastatin therapy for CVD, statin therapy did not significantly affect the risk of fracture. Higher baseline hs-CRP level was not associated with an increased risk of incident fracture.

Age related macular degeneration (AMD)

A cohort study(187) (n=3791) found that statin use was not statistically significantly associated with progression to late AMD. Furthermore, subgroup analyses of persons with or without late AMD at baseline and the various components of late AMD also showed no statistically significant association of statin use with progression to AMD.

Topic expert feedback

Statin intolerance

Topic experts noted that statin intolerant patients are now recognised as a group at increased CVD risk. A clearer definition of statin intolerance and guidance on optimal management was considered necessary to support appropriate application of alternative therapies in such patients. Two studies were cited, of which one was included in the evidence summary(180) and the other excluded as an ineligible study design.

Genetic testing

Genetic testing is becoming much cheaper, but this largely impacts on familial hypercholesterolaemia, which falls outside the current CG181 remit. However, the 'fallout from screening' will have much wider ramifications, such as the 'new' category of polygenic hypercholesterolaemia and the increasing numbers with a genetic diagnosis for statin intolerance.

Impact statement

Statin intolerance

New evidence and expert feedback indicates that patients with statin intolerance are now recognised as a group at increased CVD risk, and that there is a need to set out a clearer definition of statin intolerance. The guideline committee decided that statin intolerance should be defined clinically as the inability to tolerate 3 different statins. The evidence reviews for CG181 did not find clear benefit for other drugs so the guideline committee were not able to recommend alternatives to statins. Instead the recommended approach was to seek specialist advice about other possible treatment options. However, there is a potential need for CG181 to cross refer to the following technology appraisals, covering alternative treatments, in the event of statin intolerance:

TA385 Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia;

TA393 Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (June 2016)

TA394 Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (June 2016)

A large ongoing trial, ODYSSEY Outcomes, was also highlighted by topic experts and is likely to publish in the next 12 months. The trial

is evaluating efficacy and safety of alirocumab, in patients with well-documented statin intolerance and moderate to very high cardiovascular risk. This will be monitored for publication by the NICE Surveillance and Technology Appraisal teams.

Muscle symptoms

New evidence suggesting that people are more likely to experience muscle aches and pains from statin treatment if they are expecting them is consistent with CG181 recommendations 1.3.33-1.3.35 which set out appropriate action to advise patients to seek medical advice and to investigate other causes of muscle symptoms. Careful explanation of possible side effects, in a balanced way that does not negatively frame the information, was considered essential by topic experts. Decision aids, such as the ones produced by NICE, were considered of value in helping people come to informed decisions about the pros and cons of treatment. These decision aids complement the guideline, and no impact is anticipated.

Fracture risk

The new evidence indicating no significant risk of fracture as a result of statin therapy is consistent with the guideline recommendations, which do not stipulate fracture as a potential adverse effect.

AMD

The new evidence indicating no significant risk of AMD progression as a result of statin therapy is consistent with the guideline recommendations, which do not stipulate this as a potential adverse effect.

Diabetes

New evidence indicating the minimal impact of atorvastatin on glycaemia progression in patients with type 2 diabetes is consistent with CG181 recommendations, which does not stipulate any potential adverse effects of atorvastatin specifically in type 2 diabetes.

New evidence indicating that the risk of new-onset diabetes may increase in women over 80 years old with increasing dose of statin is based on a single country specific cohort and is unlikely to impact on the guideline recommendations until further data from larger cohorts becomes available.

Genetic testing

Topic expert feedback indicating the potential value of genetic testing is unlikely to impact on the guideline recommendations because no evidence was identified to support this. New evidence will be monitored in this area for consideration in a future surveillance review of the guideline.

New evidence is unlikely to change guideline recommendations.

181-013 What is the clinical and cost effectiveness of interventions to improve adherence to statin therapy for adults without established CVD (primary prevention) and with established CVD (secondary prevention)?

Recommendations derived from this review question

1.3.44 Do not offer coenzyme Q10 or vitamin D to increase adherence to statin treatment. [**new 2014**]

Surveillance decision

This review question should not be updated.

4-year surveillance summary

Test messaging

An RCT(188) (n=303) found that in patients taking blood pressure or lipid-lowering treatment for the prevention of CVD, text messaging improved medication adherence compared with no text messaging. Texts were sent daily for 2 weeks, alternate days for 2 weeks and weekly thereafter for 22 weeks (6 months overall), using an automated computer programme.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

Text messaging

New evidence indicates the value of text messaging in improving adherence to statin therapy. However, the evidence was derived from a single RCT of limited sample size and is unlikely to impact on the guideline until further evidence becomes available to substantiate the findings.

New evidence is unlikely to change guideline recommendations.

181-014 What is the clinical and cost effectiveness of fibrates versus placebo or statins for adults without established CVD (primary prevention) and with established CVD (secondary prevention)?

Recommendations derived from this review question

Fibrates for the prevention of CVD

1.3.45 Do not routinely offer fibrates for the prevention of CVD to any of the following:

- people who are being treated for primary prevention
- people who are being treated for secondary prevention
- people with CKD
- people with type 1 diabetes
- people with type 2 diabetes. **[new 2014]**

Surveillance decision

This review question should not be updated.

4-year surveillance summary

A follow up study(189) (n=3090) of an RCT found that after 20 years of follow up, patients treated with bezafibrate 400 mg/day experienced a small but significant reduction in the adjusted risk of mortality, compared to placebo. This effect was more prominent among patients with baseline hypertriglyceridemia.

A Cochrane systematic review(190) (six trials n=16,135) aimed to evaluate the clinical benefits and harms of fibrates versus placebo or usual care or fibrates plus other lipid-modifying drugs versus other lipid-modifying drugs alone for the primary prevention of CVD. Patients treated with fibrates had a reduced risk for the combined primary outcome of CVD death, non-fatal MI, or non-fatal stroke compared to patients on placebo. The 2 trials that evaluated fibrates in the background of statins showed no benefits in preventing cardiovascular events.

A Cochrane systematic review(191) (13 trials n=16,112) assessed the efficacy and safety of

fibrates for the prevention of serious vascular events in people with previous CVD, including coronary heart disease and stroke. The meta-analysis (including all fibrate trials) showed evidence for a protective effect of fibrates primarily compared to placebo for the primary composite outcome of non-fatal stroke, non-fatal MI, and vascular death. However, it should be noted that the beneficial effect relies on the inclusion of clofibrate data, a drug that was discontinued in 2002 due to its unacceptably large adverse effects.

A systematic review(192) (10 studies in total, 6 studies on fibrates) assessed the effects of therapies, including fibrates, targeting triglycerides and triglyceride-rich lipoprotein cholesterol on CVD event risk in people with elevated triglycerides or elevated triglycerides paired with low HDL-C. For the pre-specified primary CVD or CHD end point used in each trial, the summary relative risk estimate was significant for both people with elevated triglycerides and particularly for people with elevated triglycerides and low-HDL-C. The results remained statistically significant when each individual trial was removed. The results were not reported specifically for fibrates, however.

Topic expert feedback

Topic expert feedback highlighted the need to be clear that recommendations for people with familial hypercholesterolaemia may be different, and an amendment may be required to cross refer from CG181 (recommendation 1.3.45) to NICE's guideline on familial hypercholesterolaemia (NICE guideline CG71).

Impact statement

The collective new evidence indicates that fibrate monotherapy, but not in combination with statins, may have a protective effect against CVD in primary and secondary prevention. However, in developing CG181 the guideline committee considered that recommendations for fibrates were being made in the context of extensive evidence for the benefit of statins for primary and secondary prevention and that in this context the limited evidence for benefits from fibrate trials did not support their widespread use. The guideline committee decided that fibrate monotherapy should not be offered routinely. The evidence from combination of fibrate with statin found no benefit from addition of fibrate. Therefore the guideline committee considered fibrates in combination with statins should not be recommended. The new evidence identified through surveillance is consistent with this advice. However, topic expert feedback highlighted the need to be clear that recommendations for familial hypercholesterolaemia may be different, and an amendment may be required to cross refer from CG181 (recommendation 1.3.45) to NICE's guideline on familial hypercholesterolaemia (NICE guideline CG71).

New evidence is unlikely to change guideline recommendations.

181-015 What is the clinical and cost effectiveness of nicotinic acids versus placebo or statins for adults without established CVD (primary prevention) and with established CVD (secondary prevention)?

Recommendations derived from this review question

Nicotinic acid for preventing CVD

1.3.46 Do not offer nicotinic acid (niacin) for the prevention of CVD to any of the following:

- people who are being treated for primary prevention
- people who are being treated for secondary prevention
- people with CKD

- people with type 1 diabetes
- people with type 2 diabetes. **[new 2014]**

Surveillance decision

This review question should not be updated.

4-year surveillance summary

An RCT(193) (n=25,673) assessed the clinical efficacy and safety of niacin versus placebo over a median of 3.9 years of follow up. Among patients with atherosclerotic vascular disease, the addition of extended-release niacin-laropiprant to statin-based LDL cholesterol-lowering therapy did not significantly reduce the risk of major vascular events but did increase the risk of serious adverse events.

A further systematic review(194) (13 studies n= 35,206) found that niacin therapy did not lead to significant reductions in total or cause-specific mortality or recurrent cardiovascular events among people with or at risk of atherosclerotic CVD.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

New systematic review and RCT evidence does not support the use of niacin therapy in primary or secondary prevention of CVD. This is consistent with CG181 recommendation 1.3.46 which advises against the use of nicotinic acid (niacin) for the prevention of CVD.

However, topic expert feedback highlighted the need to be clear that recommendations for familial hypercholesterolaemia may be different, and an amendment may be required to cross refer from CG181 (recommendation 1.3.46) to NICE's guideline on familial hypercholesterolaemia (NICE guideline CG71).

New evidence is unlikely to change guideline recommendations.

181-016 What is the clinical and cost effectiveness of bile acid sequestrants (anion exchange resins) versus placebo or statins for adults without established CVD (primary prevention) and with established CVD (secondary prevention)?

Recommendations derived from this review question

1.3.47 Do not offer a bile acid sequestrant (anion exchange resin) for the prevention of CVD to any of the following:

- people who are being treated for primary prevention
- people who are being treated for secondary prevention
- people with CKD
- people with type 1 diabetes
- people with type 2 diabetes. **[new 2014]**

Surveillance decision

This review question should not be updated.

4-year surveillance summary

A systematic review(163) (49 studies n=312175) evaluated the association between lowering LDL-C and relative cardiovascular risk reduction across different statin and non-statin therapies (including diet, bile acid sequestrants, ileal bypass, and ezetimibe). The use of statin and non-statin therapies that act via upregulation of LDL receptor expression to reduce LDL-C were associated with similar relative risks of major vascular events per change in LDL-C. Lower achieved LDL-C levels were associated with lower rates of major coronary events. The specific effect of bile acid was not reported in the abstract, however.

Topic expert feedback

Topic expert feedback highlighted the need to be clear that recommendations for people with familial hypercholesterolaemia may be different, and an amendment may be required to cross refer from CG181 (recommendation 1.3.47) to NICE's guideline on familial hypercholesterolaemia (NICE guideline CG71).

Impact statement

New systematic review evidence indicates that bile acid sequestrants, amongst other therapies that act via upregulation of LDL receptor expression to reduce LDL-C, may be effective.

In developing CG181, the guideline committee noted that bile acid sequestrants have been considered a treatment option if a patient cannot tolerate a statin. However, the committee experience was of low adherence to bile acid sequestrants due to their high rate of gastrointestinal side effects. The committee also noted that bile acid sequestrants can cause numerous drug interactions through their effects on the absorption of lipophilic compounds. Given the lack of evidence for efficacy and side effect and interaction profile, the guideline committee did not consider bile acid sequestrants could be considered as an option for prevention of CVD. The new evidence is therefore unlikely to impact on recommendations that advise against the use of bile acid sequestrants.

However, topic expert feedback highlighted the need to be clear that recommendations for familial hypercholesterolaemia may be different, and an amendment may be required to cross refer from CG181 (recommendation 1.3.47) to NICE's guideline on familial hypercholesterolaemia (NICE guideline CG71).

New evidence is unlikely to change guideline recommendations.

181-017 What is the clinical and cost effectiveness of omega-3 fatty acids versus placebo or statins for adults without established CVD (primary prevention) and with established CVD (secondary prevention)?

Recommendations derived from this review question

1.3.48 Do not offer omega-3 fatty acid compounds for the prevention of CVD to any of the following:

- people who are being treated for primary prevention
- people who are being treated for secondary prevention
- people with CKD
- people with type 1 diabetes
- people with type 2 diabetes. **[new 2014]**

1.3.49 Tell people that there is no evidence that omega-3 fatty acid compounds help to prevent CVD. **[new 2014]**

Combination therapy for preventing CVD

1.3.50 Do not offer the combination of a bile acid sequestrant (anion exchange resin), fibrate, nicotinic acid or omega-3 fatty acid compound with a statin for the primary or secondary prevention of CVD. **[new 2014]**

Surveillance decision

This review question should not be updated.

4-year surveillance summary

A total of 3 systematic reviews(195–197) (34 studies, n=unreported; 14 studies, n=32,656; 5 studies, n=396) examined the effects of Omega-3 Fatty Acids on primary and secondary CVD prevention. The findings indicated that:

- Omega-3 Fatty Acids may be associated with reducing primary CHD risk, with a greater benefit observed among higher-risk populations. However, among RCTs, the reduction in CHD risk was not statistically significant overall.
- Omega-3 PUFAs in patients with CHD was not associated with a protective effect for secondary prevention of major cardiovascular events, but showed a small significant reduction in death from cardiac causes, sudden cardiac death and death from all causes.
- There is insufficient evidence to suggest a beneficial effect of omega-3 PUFA supplementation in adults with peripheral arterial disease with regard to cardiovascular events and other serious clinical outcomes.

Omega-6

A systematic review(110) (4 studies, n=660) aimed to determine the effectiveness of increasing or decreasing omega 6 (Linoleic acid (LA), Gamma-linolenic acid (GLA), Dihomo-gamma-linolenic acid (DGLA), Arachidonic acid (AA), or any combination) intake in place of saturated or monounsaturated fats or carbohydrates for the primary prevention of CVD. No studies were identified that examined the effects of either increased or decreased omega 6 on the primary outcome CVD clinical endpoints and there was insufficient evidence to show an effect of increased or decreased omega 6 intake on CVD risk factors including blood lipids.

Topic expert feedback

Topic expert feedback indicated that new evidence on omega-3 fatty acids was insufficient to impact on the guideline recommendations, but that the ongoing REDUCE-IT trial, covering Icosapent ethyl in combination with statins, should be monitored for publication and potential impact.

Impact statement

The new systematic review evidence indicating a possible benefit of omega-3 fatty acids in primary prevention of CHD is unlikely to impact on the guideline, due to unknown sample sizes of included studies, and the non-significant risk reduction in the included RCTs. Topic expert feedback also reinforces this interpretation.

The systematic review evidence indicating no benefit of omega-3 fatty acids for the secondary prevention of CVD is consistent with guideline recommendation 1.3.48, which advise against this intervention for primary and secondary prevention.

The results of the REDUCE-IT trial will be monitored for publication and potential future impact on the guideline.

New evidence is unlikely to change guideline recommendations.

181-018 Ezetimibe for primary and secondary prevention of CVD

Recommendations derived from this review question

1.3.51 People with primary hypercholesterolaemia should be considered for ezetimibe treatment in line with ezetimibe for the treatment of primary (heterozygous-familial and non-familial)

hypercholesterolaemia (NICE technology appraisal guidance 132). **[2008]** Surveillance decision

Surveillance decision

This review question should not be updated.

4-year surveillance summary

Ezetimibe in combination with statins

A total of 5 systematic reviews(163,198–201) and 4 RCTs(202–205) were identified on adjunctive ezetimibe in combination with statins for the primary and secondary prevention of CVD. The recommendations in this area are covered by the technology appraisal TA385 Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (February 2016).

This information will be passed onto the TA team for consideration when the topic undergoes the review proposal process.

Topic expert feedback

Topic experts noted that ezetimibe is off patent and was covered by TA385. It was felt that incorporation of TA385 into CG181 could enable prescribers to make an informed choice about alternative treatment options.

Topic experts also noted widespread confusion in primary care over the separate TA385 guidance on ezetimibe and familial hypercholesterolaemia, although some degree of synthesis was acknowledged via NICE Key therapeutic topic KTT3 Lipid-modifying drugs.

Impact statement

The new evidence on ezetimibe in combination with statins for the primary and secondary prevention of CVD is covered by recommendations in the technology appraisal TA385 Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (February 2016). This technology appraisal replaced the previous technology appraisal TA132 ezetimibe for the treatment of primary (heterozygous-familial and non-familial) and an amendment to recommendation 1.3.51 may be needed to update this cross referral to the new guidance. The potential impact of the patent expiry of ezetimibe on TA385 will be considered by the NICE Technology Appraisals team.

New evidence is unlikely to change guideline recommendations.

Areas not currently covered in the guideline

NQ – 01 Monoclonal antibodies for the primary and secondary prevention of CVD

This review question was not addressed by the guideline.

New evidence has subsequently been identified and considered for possible addition to the guideline as a new question.

Surveillance decision

This review question should not be added.

4-year surveillance summary

A systematic review(206) (9 studies, n=12,081) aimed to determine the ability of PCSK9 blood levels to predict risk of future cardiovascular events. A small significant association was observed between PCSK9 levels and increased risk of total cardiovascular events. When pooled estimates were derived independently for low- and high-CV risk populations, baseline PCSK9 levels predicted total cardiovascular events only in apparently healthy subjects and not in populations with established CVD or renal disease.

Alirocumab

A total of 1 systematic review(207) and 4 RCTs(208–211) were identified on alirocumab for treating primary hypercholesterolaemia. The recommendations in this area are covered by the technology appraisal TA393 Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (June 2016)

This information will be passed onto the TA team for consideration when the topic undergoes the review proposal process.

A large ongoing trial, ODYSSEY Outcomes, was highlighted by topic experts and is likely to publish in the next 12 months. The trial is evaluating efficacy and safety of alirocumab, a fully human proprotein convertase subtilisin/kexin type 9 monoclonal antibody, in patients with well-documented statin intolerance and moderate to very high cardiovascular risk. This will be monitored by the NICE Surveillance and Technology Appraisal teams.

Evolocumab

A total of 3 RCTs(212–214) were identified on evolocumab for treating primary hypercholesterolaemia. The recommendations in this area are covered by the technology appraisal TA394 Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (June 2016)

This information will be passed onto the TA team for consideration when the topic undergoes the review proposal process.

Topic expert feedback

PCSK9 inhibitors

Topic experts noted that, since publication of CG181, two PCSK9 inhibitors, alirocumab, and evolocumab have been launched. The NICE technology appraisals have also been published recommending alirocumab (NICE TA393) and evolocumab (NICE TA394) for specific groups of patients with inadequate control of non-HDL-cholesterol/LDL-cholesterol on maximum tolerated statin therapy with baseline pre-treatment LDL-Cholesterol and cardiovascular risk determining eligibility. These interventions and risk assessments are within the scope of NICE CG181 and it was advised that these should be incorporated into the guideline recommendations as part of an update. Further recently published evidence was cited(213) and is included in the evidence summary.

Topic experts also noted widespread confusion in primary care over the separate technology appraisals, although some degree of synthesis was acknowledged via NICE Key therapeutic topic KTT3 Lipid-modifying drugs.

Impact statement

New systematic review evidence suggests an association between PCSK9 levels and increased risk of total cardiovascular events, specifically in people without established CVD. This indicates the potential value of PCSK9 inhibitors (monoclonal antibodies) in prevention of CVD and is captured by the following technology appraisals:

TA393 Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (June 2016)

TA394 Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (June 2016)

There is a potential need for CG181 to incorporate or cross refer to these technology appraisals in the section on lipid modification therapy for the primary and secondary prevention of CVD. The technology appraisals are already included in the related NICE Pathway.

New evidence is unlikely to change guideline recommendations.

Editorial and factual corrections identified during surveillance

During surveillance editorial or factual corrections were identified.

- An editorial correction is needed to amend recommendation 1.2.1, to remove the wording that advises limiting the intake of dietary cholesterol to less than 300 mg/day. New evidence and expert feedback indicates that advice given on dietary cholesterol in recommendation 1.2.1, which cross refers to NHS Choices, and the current advice provided by NHS Choices is inconsistent. NHS Choices does not recommend any restriction on dietary cholesterol intake in its advice on lowering cholesterol, which is consistent with new evidence indicating that dietary cholesterol, including egg consumption, may not have an adverse impact on CVD risk.
- Recommendation 1.2.10 cross refers to four commonly used methods to increase physical activity (NICE guideline PH2). **[2008]**. This has been replaced by:
  - Walking and cycling (2012) PH41
  - Physical activity: brief advice for adults in primary care (2013) PH44
  - Exercise referral schemes to promote physical activity (2014) PH54

  An editorial correction is required to reflect this.
- Recommendations 1.1.20, 1.2.12 and 1.3.13 cross refer to obesity (NICE guideline CG43). [2008]. The clinical management of obesity is now covered by Obesity: identification, assessment and management (2014) CG189. An editorial correction is required to reflect this.
- Topic expert feedback indicates that recommendation 1.2.13 requires updating. It advises awareness that men should not regularly drink more than 3–4 units a day and women should not regularly drink more than 2–3 units a day. This is inconsistent with the advice from NHS Choices, which the recommendation cross refers to. An editorial correction is required to align the recommendation with the current NHS advice.
- Topic expert feedback highlighted the need to be clear that recommendations on fibrates, nicotinic acid and bile acid sequestrants for people with familial hypercholesterolaemia may be different to those for people with non-familial hypercholesterolaemia. An editorial correction is required to cross refer from CG181 recommendations 1.3.45, 1.3.46 and 1.3.47 to NICE's guideline on familial hypercholesterolaemia (NICE guideline CG71).
- The existing cross referral from recommendation 1.3.7 to NICE's guideline on familial hypercholesterolaemia (NICE guideline CG71) needs to be amended to reflect the updated recommendations 1.1.1 and 1.1.2. An editorial correction is required to reflect this.
- CG181 cross refers to TA132 Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. An editorial correction is required to recommendation 1.3.51, to incorporate or cross refer to the recommendations from the new guidance TA385 Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (February 2016).
- An editorial correction is needed in section 1.3: Lipid modification therapy for the primary and secondary prevention of CVD to incorporate or cross refer to the recommendations from the following technology appraisals on monocolonal antibodies:
  - TA393 Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (June 2016)
  - TA394 Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (June 2016)

Research recommendations

Prioritised research recommendations

At 4-year and 8-year surveillance reviews of guidelines published after 2011, we assess progress made against prioritised research recommendations. We may then propose to remove research recommendations from the NICE version of the guideline and the NICE database for research recommendations. The research recommendations will remain in the full versions of the guideline. See NICE's research recommendations process and methods guide 2015 for more information.

These research recommendations were deemed priority areas for research by the Guideline Committee; therefore, at this 4-year surveillance review time point a decision will be taken on whether to retain the research recommendations or stand them down.

We applied the following approach:

- New evidence relevant to the research recommendation was found and an update of the related review question is planned.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database. If needed, a new research recommendation may be made as part of the update process.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.
  - The research recommendation will be retained because there is evidence of research activity in this area.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because evidence supports current recommendations.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database because further research is unlikely to impact on the guideline.
- Ongoing research relevant to the research recommendation was found.
  - The research recommendation will be retained and evidence from the ongoing research will be considered when results are published.
- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
  - The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.
- The research recommendation would be answered by a study design that was not included in the search (usually systematic reviews or randomised controlled trials).
  - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.
- The new research recommendation was made during a recent update of the guideline.
  - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

RR – 01 What is the effectiveness of age alone and other routinely available risk factors compared with the formal structured multifactorial risk assessment to identify people at high risk of developing CVD?

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.

Surveillance decision

The research recommendation will be retained because there is evidence of research activity in this area.

RR – 02 What is the improvement in the cost-effectiveness metrics for statin therapy in reducing CVD that can be obtained when using a complete individual patient-based outcomes meta-analysis data set compared with using published outcomes data?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.

RR – 03 What is the effectiveness of statin therapy in older people?

New evidence relevant to the research recommendation was found and an update of the related review question is planned.

A secondary analysis(160) (n=5,803) of an RCT estimated the absolute treatment effect of statin therapy on major adverse cardiovascular events (MACE) for individual patients aged over 70 years old. Individual absolute risk reductions (ARRs) for MACE in 5 and 10 years were estimated by subtracting on-treatment from off-treatment risk. Individual ARRs were higher in elderly patients with vascular disease than in patients without vascular disease. Results indicated that treating all patients was more beneficial than prediction-based treatment for secondary prevention of MACE. For primary prevention of MACE, the results indicated potential value of the prediction model to identify those patients who benefit meaningfully from statin therapy.

The new evidence based on RCT data indicates that statin treatment may be more beneficial in patients over 70 years with vascular disease than in those without vascular disease. It also indicates that for primary prevention of CVD, there is potential value of using a prediction model to identify patients who would benefit most. For secondary prevention, treating all patients may be more beneficial than prediction based treatment. This is unlikely to impact due to the individually specific factors that require consideration in elderly patients. The guideline committee stated that consideration of risk and benefits and factors such as polypharmacy, comorbidity, frailty and life expectancy are particularly important in older age groups.

Surveillance decision

This research recommendation will be retained and if needed, a new research recommendation may be made as part of the update process.

RR – 04 What is the effectiveness of statins and/or other LDL-cholesterol-lowering treatment in people with type 1 diabetes?

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.

Surveillance decision

This research recommendation will be retained and if needed, a new research recommendation may be made as part of the update process.

RR – 05 What is the clinical effectiveness and rate of adverse events of statin therapy using atorvastatin 20 mg per day compared with atorvastatin 40 mg per day and atorvastatin 80 mg per day in people without established CVD?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.

Other research recommendations

The following research recommendations were not deemed as priority areas for research by the guideline committee.

RR – 06 What is the effectiveness of fibrate therapy in patients with mixed hyperlipidaemia?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

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