

# SIGN 149 • Risk estimation and the prevention of cardiovascular disease

*A national clinical guideline*

*June 2017*

## KEY TO EVIDENCE STATEMENTS AND RECOMMENDATIONS

### LEVELS OF EVIDENCE

1 <sup>++</sup>	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1 <sup>+</sup>	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1 <sup>-</sup>	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
	High-quality systematic reviews of case-control or cohort studies
2 <sup>++</sup>	High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2 <sup>+</sup>	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2 <sup>-</sup>	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

### RECOMMENDATIONS

Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the 'strength' of the recommendation).

The 'strength' of a recommendation takes into account the quality (level) of the evidence. Although higher-quality evidence is more likely to be associated with strong recommendations than lower-quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation.

Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland; applicability of published evidence to the target population; consistency of the body of evidence, and the balance of benefits and harms of the options.

**R** For '**strong**' recommendations on interventions that '**should**' be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more good than harm. For '**strong**' recommendations on interventions that '**should not**' be used, the guideline development group is confident that, for the vast **majority** of people, the intervention (or interventions) will do more harm than good.

**R** For '**conditional**' recommendations on interventions that should be '**considered**', the guideline development group is confident that the intervention will do more good than harm for most patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.

### GOOD-PRACTICE POINTS

✓ Recommended best practice based on the clinical experience of the guideline development group.



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Scottish Intercollegiate Guidelines Network

# **Risk estimation and the prevention of cardiovascular disease**

A national clinical guideline



July 2017

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# 1 Introduction

## 1.1 THE NEED FOR A GUIDELINE

Cardiovascular disease (CVD) is an umbrella term that describes a range of conditions caused by blood clots (thrombosis) or build up of fatty deposits inside an artery that cause the artery to harden and narrow (atherosclerosis). The main underlying causes of CVD are coronary heart disease (CHD), stroke, peripheral arterial disease (PAD) and aortic disease.

In 2015, 15% of adults aged 16 and over had any CVD condition, which represents an estimated 670,000 people living with cardiovascular disease in Scotland. Both incidence and prevalence of CVD are higher amongst men, the elderly and in deprived areas of Scotland.<sup>1</sup> Cardiovascular disease caused more than a quarter of all deaths in Scotland in 2015.<sup>2</sup>

Of particular relevance to Scotland are the effects of socioeconomic status on the risk of developing CVD. The incidence and mortality rates from acute myocardial infarction in those aged under 65 are higher in deprived areas than in more affluent areas.<sup>3-6</sup>

Cardiovascular disease has a multifactorial aetiology with a number of potentially modifiable risk factors. The established Framingham risk factors of age, sex, cigarette smoking, blood pressure, total cholesterol and high-density lipoprotein (HDL) cholesterol have proved consistent risk factors in every population studied. In addition, this guideline considers and reports on physical activity and sedentary behaviour. Some ethnic groups may show differences in population baseline risk.<sup>7</sup> Scotland's ethnic population is growing: at the 2011 census around 4% of the country's 5.3 million people were from minority ethnic backgrounds, double the proportion from the previous census in 2001.<sup>8</sup>

Recent estimates show that disease incidence rates are falling and, although the reasons for this decline are complex, improvements in the management of risk factors, in particular, a reduction in smoking rates, are significant factors. Between 2005/6 and 2015/6 the age-standardised incidence rate for CVD fell by 13% in men and nearly 16% in women, driven by a significant fall in CHD incidence and a smaller decline in stroke rates.<sup>6,9</sup> (ISD Scotland. Personal communication, 13 March 2017).

Recognising CVD as a continuum challenges the traditional concepts of primary and secondary prevention, with healthcare professionals adopting a 'high-risk' approach to prevention (one which involves the clinical identification of individuals in that portion of the population at highest risk over a defined time period and their intensive treatment through lifestyle or pharmacological means).<sup>10</sup> In fact, most cases of CVD occur in the large number of individuals at lower levels of absolute risk.<sup>11</sup> High-risk approaches have been facilitated both by the availability of scoring systems to estimate absolute risk (rather than the traditional use of single risk factors) and by the advent of several treatments, principally statins and antihypertensives, which produce marked and apparently independent reductions in CVD risk in people at high risk.<sup>12</sup>

The guideline has attempted to devise effective strategies for the reduction of CVD that take a combined approach using both 'high-risk' and population approaches.

### 1.1.1 UPDATING THE EVIDENCE

This guideline updates SIGN 97: Risk estimation and the prevention of cardiovascular disease to reflect the most recent evidence.

Where no new evidence was identified to support an update, text and recommendations are reproduced verbatim from SIGN 97. The original supporting evidence was not re-appraised by the current guideline development group (GDG).

## 1.2 REMIT OF THE GUIDELINE

### 1.2.1 OVERALL OBJECTIVES

This guideline deals with the management of cardiovascular risk, both primary prevention, defined as the potential for intervention prior to the disease presenting through a specified event (any incident linked to critical disruption of blood flow that may cause damage to the heart, brain or peripheral tissues), and secondary prevention, defined as the potential for intervention after an event has occurred. The guideline development group has tried to consider CVD as a continuum from the preclinical to the end-stage disease, potentially offering different opportunities to intervene, both prior to, and after an event, so creating the potential to alter the outcome of the disease process. The guideline development group believes that it is more relevant to consider an individual in terms of whether they have a low or high risk of cardiovascular events rather than in terms of primary or secondary prevention.

The guideline provides recommendations on estimation of cardiovascular risk and interventions to reduce this risk in people with and without established CVD. The guideline does not make specific recommendations for the management of people with chronic heart failure, acute coronary syndrome, stable angina or cardiac arrhythmias as these are contained within other SIGN guidelines.<sup>13-16</sup> Cardiac rehabilitation is the subject of a further SIGN guideline.<sup>17</sup>

### 1.2.2 TARGET USERS OF THE GUIDELINE

This guideline will be of interest to healthcare professionals involved in the management of patients with cardiovascular disease including cardiologists, dietitians, general practitioners, lipidologists, pharmacists, physiotherapists, practice nurses, psychologists and public health staff, as well as patients, carers, voluntary organisations and policy makers.

### 1.2.3 PATIENT VERSION

A patient version of this guideline is available from the SIGN website, [www.sign.ac.uk](http://www.sign.ac.uk)

### 1.2.4 SUMMARY OF UPDATES TO THE GUIDELINE, BY SECTION

1.1	The need for a guideline	Updated
1.1.1	Updating the evidence	New
1.2.1	Overall objectives	Minor update
1.2.2	Target users of the guideline	New
1.2.4	Summary of updates to the guideline, by section	New
1.3.1	Definitions (risk estimation)	Updated
1.3.2	Risk scores	Updated
1.4	Statement of intent	Minor update
1.4.1	Influence of financial and other interests	New
1.4.2	Prescribing of licensed medicines outwith their marketing authorisation	New
1.4.3	Health technology assessment advice for NHSScotland	Updated
2	Key recommendations	New
3.1	Risk factors	Updated
3.2	The concept of risk and why it matters	Minor update
3.3	Risk scoring systems	Completely revised
3.4	What is meant by high risk?	Completely revised
4.1	Assessing risk	Updated
4.2	Recording risk factor information	Updated
4.3	Using risk assessment tools	Updated
4.4	How to determine cardiovascular risk	Updated

5.1.1	Total and saturated fat	Updated
5.1.2	Omega-3 supplementation	Updated
5.3	Fruit and vegetable intake	Minor update
5.4.2	Folate supplementation	Completely revised
5.4.3	Stanol esters and plant sterols	Updated
5.5	Dietary patterns	New
5.6	Giving dietary advice	Minor update
5.7	Weight reduction and cardiovascular risk	Completely revised
5.8	Metabolic syndrome	Updated
6.1	Definitions (physical activity)	Updated
6.2.1	Physical inactivity as an independent risk factor	Minor update
6.2.2	Levels of physical activity	Minor update
6.2.3	Vigorous and high-intensity physical activity	New
6.2.4	Risks of sedentary behaviour	New
6.2.5	Effects of physical activity on other key risk factors	Minor update
7.1.1	Active smoking	Minor update
7.2.1	The general population (smoking cessation interventions)	Updated
7.2.2	Electronic cigarettes	New
7.2.3	Special populations	Updated
8.1	Alcohol and cardiovascular risk	Updated
8.1.1	Effects of alcohol consumption levels on cardiovascular disease mortality and morbidity	Updated
8.1.2	Methods of modifying alcohol consumption	Minor update
9.1	Antiplatelet agents for people with established cardiovascular disease	Minor update
9.2	Antiplatelet agents for people without cardiovascular disease	Completely revised
9.3	Antiplatelet agents for people with diabetes	Completely revised
9.4	Antiplatelet agents for people with hypertension	Completely revised
9.5	Antiplatelet agents for people with chronic kidney disease	New
10.1	The role of total and low-density lipoprotein cholesterol in cardiovascular disease	Minor update
10.2	Measuring lipid levels	Updated
10.3	Lowering cholesterol to reduce cardiovascular risk	Updated
10.4.1	The effects of statins on LDL cholesterol	Completely revised
10.4.2	The effects of statins on cardiovascular end points	New
10.4.3	Statin therapy for individuals without cardiovascular disease	Updated
10.4.4	Statin therapy for individuals with established cardiovascular disease	Completely revised
10.4.5	Safety of statin therapy	Updated
10.4.6	Reported intolerance to statin therapy	New
10.4.7	Benefits and harms of statin therapy	New
10.5.1	People with diabetes	Updated
10.5.2	Familial hypercholesterolaemia	Updated
10.5.4	Older people	Updated
10.5.5	Sex	New
10.5.6	Chronic kidney disease	New
10.6.1	Bile acid sequestrants	Minor update
10.6.2	Ezetimibe	Updated

10.6.3	Fibrates	Updated
10.6.4	Nicotinic acid	Updated
10.6.5	PCSK9 inhibitors	New
10.7	Management of combined dyslipidaemia	Updated
11.1	Blood pressure thresholds for intervention with drug therapy	Updated
11.1.1	Blood pressure thresholds for individuals with symptomatic cardiovascular disease	Completely revised
11.1.2	Blood pressure thresholds for individuals without symptomatic cardiovascular disease	Completely revised
11.1.3	Blood pressure thresholds for specific groups at high cardiovascular risk	New
11.2	Target values for blood pressure lowering	Updated
11.2.1	Type 2 diabetes	New
11.2.2	Chronic kidney disease	New
11.2.3	Dialysis	New
11.2.4	Conclusions (target values for blood pressure lowering)	New
11.3	Selection of antihypertensive therapy	Minor update
11.3.1	The British Hypertension Society algorithm	Updated
12.1	The impact of psychological wellbeing on cardiovascular risk	Updated
12.2.1	Psychological interventions	Updated
12.2.2	Pharmacological interventions for depression	New
13	Provision of information	Updated
14	Implementing the guideline	Updated

### 1.3 RISK ESTIMATION

For many health professionals the calculation of absolute cardiovascular risk is the starting point for the development of CVD prevention strategies.

#### 1.3.1 DEFINITIONS

Absolute risk is also known as total risk or global risk. This risk is defined as the percentage chance of an individual having a CVD event over a given period of time, for example a ten-year risk of 20%. The specific factors used to estimate absolute risk in the ASSIGN (Assessing cardiovascular risk using SIGN guidelines to ASSIGN preventive treatment) score are age, sex, smoking, systolic blood pressure, total cholesterol, HDL cholesterol, family history of premature CVD, diagnosis of diabetes, diagnosis of rheumatoid arthritis and deprivation (*see section 3.3 for further information on ASSIGN*). While these are the most significant risk factors which predict cardiovascular risk, other risk calculators include a wide range of other factors including antihypertensive treatment, atrial fibrillation, chronic kidney disease, ethnicity and body mass index. Relative risk refers to the risk of someone who has risk factors having a CVD event compared with an individual of the same age and sex without risk factors.

In a similar way, results from randomised intervention trials may be presented as absolute or relative changes to the outcomes of interest, depending on whether the result from participants within the trial who received the intervention is subtracted from the result of those who do not receive the intervention (absolute effect) or divided by it (relative effect). Although the relative effects of a treatment is the same regardless of baseline risk, patients with a lower baseline risk will have a lower absolute chance of benefiting and a lower residual risk. Patients with a greater baseline risk will have a greater absolute chance of benefiting but also a greater residual risk. While absolute event rates can be useful to communicate the impact of a treatment to patients, trial selection may influence the apparent rates due to differences in baseline risk in the populations, and so the potential benefits or hazards when the trial results are applied in current practice may be different.

### 1.3.2 RISK SCORES

Risk scores cannot perfectly predict absolute risk. They are extremely useful in assessing or estimating risk and in prioritising treatment on an equitable basis.

In Scotland, absolute CVD risk is usually calculated from electronic decision support tools based on the ASSIGN algorithm (*see section 3.3*).

## 1.4 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results.

The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at through a process of shared decision making with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be documented in the patient's medical records at the time the relevant decision is taken.

### 1.4.1 INFLUENCE OF FINANCIAL AND OTHER INTERESTS

It has been recognised that financial interests in, or close working relationships with, pharmaceutical companies may have an influence on the interpretation of evidence from clinical studies.

It is not possible to completely eliminate any possible bias from this source, nor even to quantify the degree of bias with any certainty. SIGN requires that all those involved in the work of guideline development should declare all financial interests, whether direct or indirect, annually for as long as they are actively working with the organisation. By being explicit about the influences to which contributors are subjected, SIGN acknowledges the risk of bias and makes it possible for guideline users or reviewers to assess for themselves how likely it is that the conclusions and guideline recommendations are based on a biased interpretation of the evidence.

Signed copies of declaration of interests forms are retained by the SIGN Executive and a register of interests is available in the supporting material section for this guideline at [www.sign.ac.uk](http://www.sign.ac.uk)

### 1.4.2 PRESCRIBING OF LICENSED MEDICINES OUTWITH THEIR MARKETING AUTHORISATION

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (MA) also known as product licence. This is known as 'off-label' use.

Medicines may be prescribed 'off label' in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration via a different route
- for administration of a different dose
- for a different patient population.

An unlicensed medicine is a medicine which does not have MA for medicinal use in humans.

Generally 'off-label' prescribing of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the marketing authorisation. Such use should be supported by appropriate evidence and experience.<sup>18</sup>

"Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability".<sup>18</sup>

The General Medical Council recommends that when prescribing a medicine 'off label', doctors should:

- be satisfied that such use would better serve the patient's needs than an authorised alternative (if one exists)
- be satisfied that there is sufficient evidence/experience of using the medicines to show its safety and efficacy, seeking the necessary information from appropriate sources
- record in the patient's clinical notes the medicine prescribed and, when not following common practice, the reasons for the choice
- take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine.

Non-medical prescribers should ensure that they are familiar with the legislative framework and their own professional prescribing standards.

Prior to any prescribing, the licensing status of a medication should be checked in the summary of product characteristics ([www.medicines.org.uk](http://www.medicines.org.uk)). The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers.<sup>19</sup>

#### 1.4.3 HEALTH TECHNOLOGY ASSESSMENT ADVICE FOR NHSSCOTLAND

Specialist teams within Healthcare Improvement Scotland issue a range of advice that focuses on the safe and effective use of medicines and technologies in NHSScotland.

The Scottish Medicines Consortium (SMC) provides advice to NHS boards and their Area Drug and Therapeutics Committees about the status of all newly-licensed medicines and new indications for established products. NHSScotland should take account of this advice and ensure that medicines accepted for use are made available to meet clinical need where appropriate.

In addition, Healthcare Improvement Scotland reviews Multiple Technology Appraisals (MTAs) produced by the National Institute for Health and Care Excellence (NICE) and provides advice about their applicability in NHSScotland. If Healthcare Improvement Scotland advises that MTA guidance is applicable in Scotland, NHSScotland should take account of this and ensure that recommended medicines and treatment are made available to meet clinical need where appropriate.

NICE MTAs deemed valid for NHSScotland supersede extant SMC advice as they are generally underpinned by a larger and more recent evidence base.

SMC advice and NICE MTA guidance relevant to this guideline are summarised in section 14.4.

## 2 Key recommendations

The following recommendations were highlighted by the GDG as the key clinical recommendations that should be prioritised for implementation.

### 2.1 ESTIMATING CARDIOVASCULAR RISK

- R** Individuals with the following risk factors should be considered at high risk of cardiovascular events:
- established cardiovascular disease, or
  - stage 3 or higher chronic kidney disease or micro- or macroalbuminuria, or
  - familial hypercholesterolaemia, or
  - who are over the age of 40 and have diabetes, or
  - who are under the age of 40 and have diabetes, and
    - at least 20 years duration of disease, or
    - target organ damage (eg proteinuria, micro- or macroalbuminuria, proliferative retinopathy or autonomic neuropathy), or
    - significantly elevated cardiovascular risk factors.

### 2.2 DIET

- R** Patients, and individuals at risk of cardiovascular disease, who are overweight or obese, should be targeted with interventions designed to reduce weight by at least 3 kg, and to maintain this reduction.

### 2.3 PHYSICAL ACTIVITY

- R** Physical activity of at least moderate intensity (eg breathing faster than normal) is recommended for the whole population (unless contraindicated by an individual's condition).

### 2.4 SMOKING

- R** All people who smoke should be advised to stop and offered support to help facilitate this in order to minimise cardiovascular and general health risks.

### 2.5 ANTIPLATELET THERAPY

- R** Aspirin is not recommended for primary prevention of cardiovascular disease.

### 2.6 LIPID LOWERING

- R** Adults who are assessed as being at high cardiovascular risk, but with no established CVD, should be offered treatment with atorvastatin 20 mg/day following an informed discussion of risks and benefits between the individual and their responsible clinician. In those already taking an alternative regimen due to reported intolerance with atorvastatin, there is no need to change their current regimen.

## 3 Cardiovascular risk

### 3.1 RISK FACTORS

The INTERHEART study assessed the importance of risk factors for coronary artery disease worldwide.<sup>20</sup> Nine measured and potentially modifiable risk factors accounted for more than 90% of the proportion of the risk for acute myocardial infarction. Smoking, history of hypertension or diabetes, waist:hip ratio, dietary pattern, physical activity, alcohol consumption, blood apolipoproteins and psychosocial factors were identified as the key risk factors. The effect of these risk factors was consistent in men and women across different geographic regions and by ethnic group. The British Regional Heart Study also found that smoking, blood pressure and cholesterol accounted for 90% of attributable risk of CHD.<sup>21</sup>

Worldwide, the three most important modifiable and causal cardiovascular risk factors are smoking, hypertension and abnormal lipids. Further risk factors which are modifiable and causal include obesity, diabetes, poor diet, alcohol intake, and physical activity. Psychosocial factors may contribute directly and indirectly to cardiovascular risk. Age, sex, ethnicity and genetics, although not modifiable, also contribute to risk in a multiplicative way. Cardiovascular risk factors do not differ widely across populations (although their relative contributions to risk may).<sup>22</sup> Taken together, all risk factors contribute to absolute cardiovascular risk which is directly modifiable both by lifestyle interventions and pharmacological treatment.

### 3.2 THE CONCEPT OF RISK AND WHY IT MATTERS

Most cardiovascular deaths will occur in individuals at moderate risk as they constitute the largest group. High-risk individuals will have the most to gain from risk factor modification and historically are given the highest priority in clinical practice.<sup>23</sup>

When estimating risk total CVD outcomes, rather than CHD end points, should be used to encompass stroke prevention as well as CHD prevention. Stroke deaths are underestimated using traditional CHD end points.<sup>7</sup> Not all current risk-prediction systems accurately predict the different risk profiles that exist in different ethnic groupings and cultures. For example, a risk score derived from white European cohorts may substantially overpredict the risk in a Chinese population.<sup>24</sup> CVD risk prediction based on absolute risk is now advocated for treatment decisions for lipid-lowering therapy, antihypertensives and, in people with atrial fibrillation, for warfarin.

#### 3.2.1 PREDICTING RISK

Intervention studies have shown that while relative risk reduction may remain broadly constant, absolute risk reduction varies considerably because it is a function of the initial level of baseline risk (*see section 1.3.1*). Consider the example in Table 1 of a man with a baseline risk of a cardiovascular event of 10% over ten years who takes effective preventive treatment and lifestyle measures. His risk falls by a third, a relative risk reduction of 33.3%, while his absolute risk is reduced to 6.7%, an absolute risk reduction (ARR) of 3.3%. If another man with a higher baseline absolute risk of 30% takes the same effective treatments his risk also falls by about a third to 20%. However, his absolute risk reduction is 10%. Relative risk reductions in CHD events in the statin trials appear similar regardless of baseline risk and baseline cholesterol.<sup>25</sup> This would support the concept that the best way to target patients is to calculate absolute risk.

Table 1: Example illustrating absolute and relative risk reductions

Baseline ten-year absolute risk of CVD	Relative risk reduction	Post-treatment ten-year absolute risk of CVD	Absolute risk reduction
10%	33%	6.7%	3.3%
30%	33%	20%	10%

Overprediction of CVD risk means that people with less to gain potentially become patients and are exposed to the risks of lifelong pharmacological treatment. Underprediction means that people with much to gain may not be offered preventive treatment. The best way to target patients for risk reducing interventions is to estimate absolute risk.

### 3.3 RISK SCORING SYSTEMS

The concept of risk scoring for CVD is now well established worldwide in high- and middle-income countries, based and extended from the original Framingham risk score in the US.<sup>26,27</sup> Since 2007, the ASSIGN score has been used in Scotland to identify individuals at highest risk of CVD. ASSIGN was tailored to the Scottish population by inclusion of social deprivation and family history of premature CVD as additional CVD risk modifiers. In so doing, when implemented, ASSIGN was world leading and its approach helped classify more people with a positive family history and who are socially deprived as being at high risk. When used in Scotland it attenuated a large social gradient in future CVD sufferers not identified for preventive treatment by the Framingham cardiovascular score.<sup>28</sup> It therefore improved social equity, although overall discrimination of future events was not greatly improved.<sup>29</sup> Since then, other risk scores have copied this approach and implemented social factors into their risk score as well as other important risk modifiers which meaningfully improve risk prediction. Most notably, the Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3) risk score, based on the QRISK2 algorithm developed for use in England and Wales, now includes a measure of social class as well as family history of premature CVD.<sup>30</sup> It has also added blood pressure treatment, rheumatoid arthritis, and presence of atrial fibrillation as risk modifiers, together with ethnicity, diabetes and chronic kidney disease. Importantly, it has introduced additional metrics such as an estimate of years to be gained from preventive treatments based on when lipid lowering, blood pressure treatment or smoking cessation is started, as well as heart age and other useful outputs which may improve patient understanding of their risks and therefore their motivation and adherence to treatment.

Whilst ASSIGN was innovative in 2007, there is now scope to improve its performance and presentation in light of more recent developments in risk scoring.

### 3.4 WHAT IS MEANT BY HIGH RISK?

In addition to more comprehensive scoring systems with greater functionality, the greatest change to risk scoring is defining the level of risk of CVD deemed high enough to merit intervention. Currently in Scotland, high risk is defined as asymptomatic individuals without established CVD (or other conditions which confer automatically high cardiovascular risk) who are estimated to be at 20% or greater risk of a cardiovascular event over the next 10 years.

In 2014, based on economic modelling, NICE recommended that the risk threshold for statin initiation be reduced to a blanket 10% threshold so that all individuals with more than a 1 in 10 chance of having a heart attack or stroke in the next 10 years are considered at high risk and offered statin therapy.<sup>31</sup> Whilst this approach identifies the proportion of the population which is cost effective to treat, it is less clear how the additional workload within primary care to implement this policy is accounted for. Similarly, the societal ramifications of this new threshold effectively placing almost all people in England and Wales above 65 years of age at high risk of CVD were not explored. There is a strong age gradient in CVD events; hence the vast majority of older people are classified as being at high risk. In Scotland, almost 95% of individuals are at 10% or greater risk of a cardiovascular event within ten years by the age of 60–64. Implementing this threshold in Scotland would increase the total number eligible for preventive treatment by around 70% to over 1.3 million.

There is increasing recognition that the age at which statin therapy is commenced may dictate a patient's capacity to benefit in terms of life years gained. Essentially, the later one starts treatment, the lower the capacity to gain extra life years, and vice-versa. This effect is partly explained by competing risks so that in older individuals, the chances of dying from a cause other than CVD increases. For example, in the PROSPER trial, where the average participant was 75 years of age when pravastatin was commenced, an average of 3.2 years of therapy provided long-term protection against CHD events and CHD mortality but did not increase life expectancy, possibly due to competing mortality with deaths from other causes.<sup>32</sup> Such an effect should

be contrasted with the long-term results from the WOSCOPS trial which found that five years of pravastatin treatment in 45 to 64-year old Scottish men maintained improved survival resulting from decreased mortality from cardiovascular causes and an ongoing reduction in cardiovascular hospital admissions over 20 years.<sup>33</sup>

The focus on short-term risk has been driven by a number of factors. Firstly, this strategy identifies individuals most likely to benefit from drug therapy in the short term, thereby maximising the cost effectiveness of (sometimes expensive) medications. Additionally, most trials of CVD risk-factor intervention are of short duration with limited data regarding the long-term effects of pharmacological therapy. Consequently, it can be argued that short-term risk assessment translates more directly than long-term risk assessment into clinical interactions and decision making. However, given that age is heavily weighted in most risk calculators, modest elevations in risk factors have little effect on short-term risk among men aged <45 and women aged <65 years.<sup>34</sup>

The current short-term emphasis of risk estimation aims to help reduce the risk of individuals experiencing a CVD event. However, this approach also focuses attention on individuals who, most likely, already have advanced atherosclerosis. The complications of atherosclerosis occur most commonly in individuals aged >50, but the pathophysiological processes begin in childhood and mainly result from the effects of modifiable risk factors; cholesterol, blood pressure, and smoking as well as their lifestyle determinants, including poor diet and physical inactivity.<sup>35</sup>

A pooled survival analysis of several large observational studies of individuals free from CVD showed that even though approximately 40% of individuals with optimal risk factor levels at age 55 eventually had a CVD event by age 95 years, their age at onset of total CVD was an average of 8 to 14 years later than individuals with at least two major risk factors. Maintenance of optimal risk factors through ages 45–65 may not guarantee a life free from total CVD, but it increases the probability that more years will be lived free of CVD.<sup>36</sup> Therefore, there is significant scope for widespread benefits at a population level if prevention efforts and risk factor modification could begin before the age of 50 and the widespread development of atherosclerosis.

These findings are particularly important for individuals who, by virtue of clinical features associated with increased vascular burden (for example hypertension or hypercholesterolaemia), are likely to be at greater risk of cardiovascular events measured across their lifetime, compared with individuals without such factors, but by virtue of younger age, or absence of other risk factors do not reach the short-term (ten-year) threshold for preventive treatment.

In view of concerns about lowering the risk threshold and in order to explore options to normalise the effects of age on short-term risk, the GDG has considered alternatives to a fixed 10% CVD risk threshold. These include a measure of capacity to benefit (through life expectancy metrics) or adopting differential thresholds at different ages, with lower treatment thresholds at younger ages and higher thresholds at higher ages. The latter approach would tend to identify younger individuals at higher trajectories of risk. It would also mean that not all elderly individuals are necessarily recommended for preventive therapy. This approach was introduced in Norway in 2009 and arguments have recently been made in support of age-differentiated risk thresholds, noting that this approach can improve the sensitivity and specificity of statin guidelines.<sup>37,38</sup>

Additional work is necessary to assess these alternatives. It is clear that any new approach needs evaluation and must be backed up with economic analysis, be fully implemented into an online risk scoring system (updating the ASSIGN risk score, as necessary), and be acceptable and liked by patients and doctors. This work is outwith the scope of this guideline. Consequently, the current ASSIGN CVD risk scoring system remains in place and the 20% treatment threshold unchanged. This guideline will be updated when a new algorithm for risk scoring and new thresholds are available.

## 4 Estimating cardiovascular risk

### 4.1 ASSESSING RISK

Treatment decisions are based on the likelihood that an individual will have a cardiovascular event over a given period of time. Assessment of absolute cardiovascular risk is the starting point for discussions between healthcare professionals and patients who are potentially at significant risk of a cardiovascular event. The prevention of cardiovascular events is the goal of treatment.

This guideline uses many of the risk assessment strategies outlined in JBS3.<sup>30</sup>

The following individuals should be offered an assessment of cardiovascular risk at least every five years:

- all adults aged 40 years or above, and
- individuals at any age with a first-degree relative who has premature atherosclerotic CVD or familial dyslipidaemia.

The following groups of people should be assumed to be at high risk and do *NOT* require risk assessment with a scoring system:

- people with established cardiovascular disease (including previous myocardial infarction, acute coronary syndrome, revascularisation, stroke, transient ischaemic attack, aortic aneurism, peripheral arterial disease or those with significant plaque on coronary angiography or carotid ultrasound)
- people with stage 3 or higher chronic kidney disease (CKD), or micro- or macroalbuminuria
- people with familial hypercholesterolaemia
- people with diabetes over the age of 40 years
- people with diabetes under the age of 40 years with
  - a long duration of diabetes (20 years), or
  - micro- or macroalbuminuria, or
  - proliferative retinopathy or autonomic neuropathy, or
  - significant other risk factors in the view of the healthcare professional.

### 4.2 RECORDING RISK FACTOR INFORMATION

Cardiovascular risk is the product of the effect of several risk factors. Individual risk factors can cluster together in significant patterns and tend to have a multiplicative effect on an individual's total cardiovascular risk.<sup>39</sup> Measuring any single risk factor will usually not adequately estimate total cardiovascular risk.

#### 4.2.1 TAKING A CLINICAL HISTORY

The following items of information should be collected routinely when assessing cardiovascular risk.<sup>30</sup>

*Table 2: Items to include in a clinical history for cardiovascular risk assessment*

Risk factor	Rationale for measurement
age	Cardiovascular risk increases with age.
sex	Other factors being equal, men are at higher risk of a cardiovascular event.
lifetime smoking habit (and number of cigarettes smoked per day)	Categorising an individual's smoking status as current smoker or non-smoker is insufficient for the calculation of accurate CVD risk. A current smoker may have less lifetime exposure to tobacco and less associated cardiovascular damage than an ex-smoker. The CVD risk of an ex-smoker is likely to be intermediate between a current smoker and a lifelong non-smoker.
family history of cardiovascular disease	In people with a family history of clinically-proven cardiovascular disease (angina, myocardial infarction, transient ischaemic attack, or ischaemic stroke) in a first-degree relative (parent, sibling) before the age of 60 years, the risk of a coronary event is approximately doubled. <sup>40</sup>
ethnicity	Rates of cardiovascular disease vary considerably between ethnic groups which may reflect increased susceptibility and differential exposure to risk factors ( <i>see section 4.3</i> ).
socioeconomic status	For given levels of other risk factors, populations which are more deprived have a higher CVD risk. ASSIGN uses the Scottish Index of Multiple Deprivation calculated via linkage to postcode of residence to measure socioeconomic status.

Regular physical activity has both preventive and therapeutic effects on many chronic conditions such as CHD and stroke.<sup>41</sup> Although not included as a risk factor in the ASSIGN algorithm, discussing levels of activity can help to prioritise intervention in those who are not meeting current targets (*see section 6.2*).

Healthcare professionals should also be aware of potential psychosocial issues during CVD risk assessment as these have the potential to modify management decisions (*see section 12*).

#### 4.2.2 CLINICAL MEASUREMENTS

The following should be measured when assessing cardiovascular risk.<sup>30</sup>

*Table 3: Factors that should be measured for cardiovascular risk assessment*

Risk factor	Rationale for measurement
blood pressure	Systolic blood pressure should be measured according to the NICE/British Hypertension Society (BHS) guideline. <sup>42</sup> The mean systolic pressure measured over two separate occasions should be used to calculate risk. In individuals taking antihypertensive medication the most recently recorded pretreatment value should be adopted.
weight and body mass index	Individuals with a body mass index (BMI) >30 kg/m <sup>2</sup> have a 40-fold increased risk of developing diabetes and a two to three-fold increased risk of CHD <sup>43,44</sup> and stroke compared with individuals with a normal BMI (≤25 kg/m <sup>2</sup> ). <sup>45</sup> Although not included as a risk factor in ASSIGN, these data may be used to inform lifestyle interventions and monitor risk reduction.
cholesterol	Total cholesterol (TC), HDL cholesterol and triglyceride should be measured in a laboratory from a random (non-fasting) sample of blood. A fasting sample with calculated LDL cholesterol is needed when a diagnosis of familial hypercholesterolaemia (FH) is being considered ( <i>see section 10.5.2</i> ). The accuracy of measuring HDL cholesterol in the context of high triglyceride levels may be compromised. Intercurrent illness may also affect circulating lipid levels.
diabetes	Diabetes confers, on average, twice of the risk of cardiovascular events compared with those without the disease. Furthermore, risks escalate with duration of diabetes so that lifetime risks are high, especially in those who develop diabetes at a younger age. Consequently, risk estimation is not recommended for individuals with diabetes and many will be directly eligible for preventive treatment ( <i>see section 4.1</i> ).  For individuals without a diagnosis of diabetes but with risk factors (for example, obesity, hypertension, dyslipidaemia, family history of diabetes or specific ethnicities) a range of validated tools may be used to screen for the presence of diabetes (glycated haemoglobin (HbA1c), fasting plasma glucose measurement or oral glucose tolerance testing). <sup>46</sup> Glycated haemoglobin is not suitable for the diagnosis of type 1 diabetes or diabetes in pregnant women. <sup>47</sup>
rheumatoid arthritis	Individuals with rheumatoid arthritis (RA) are at significantly increased risk of cardiovascular events. <sup>48,49</sup> People with RA, within the QRESEARCH database, had an elevated CVD risk independent of other risk factors, with adjusted hazard ratios (HR) of 1.50 (95% confidence interval (CI) 1.39 to 1.61) in women and 1.38 (95% CI 1.25 to 1.52) in men, respectively. <sup>50</sup>
renal function	Individuals with CKD are at significantly increased risk of cardiovascular events. <sup>51,52</sup> To aid the differential diagnosis of CKD, renal function should be estimated from glomerular filtration rate (eGFR). An eGFR <60 ml/min/1.73 m <sup>2</sup> is indicative of stage 3 CKD and such individuals do not require risk estimation but should have aggressive interventions to reduce their risk of cardiovascular events. Albuminuria at any level above the normal threshold of 30 mg/g confers cardiovascular risk and warrants preventive treatment. <sup>52</sup>

### 4.3 USING RISK ASSESSMENT TOOLS

The ASSIGN cardiovascular risk assessment tool allows clinicians to estimate ten-year risk of CVD events in asymptomatic individuals with no clinical evidence of cardiovascular disease. The calculation of risk will be via a computer-based desktop tool. Computer programs give a more precise estimate of risk than charts, presenting risk as a continuous variable rather than a threshold, such as  $\geq 20\%$ .<sup>53</sup>

True CVD risk will be higher in the following groups than the results indicated by risk estimation tools which do not include these in prediction algorithms:

- those with atrial fibrillation
- those from specific minority ethnic groups (eg, Indian, Pakistani, Bangladeshi or other Asian, see *Table 4*)
- women with premature menopause.

In some ethnic minorities, risk tools under- and overestimate CVD risk, because they have not been validated in these populations. For example, in people originating from the south Asian subcontinent it is safest to assume that the CVD risk is higher than predicted from most scoring tools. Adjusted hazard ratios for cardiovascular disease have been calculated in ethnic groups within the cohort study underpinning the QRISK2 tool (see *Table 4 and section 3.3*).<sup>50</sup> The ASSIGN risk tool incorporates family history as a risk factor which may account for some of the excess CVD risk of individuals from some ethnic minorities.

*Table 4: Adjusted hazard ratios (95% CI) for cardiovascular disease in subgroups of the derivation cohort of QRISK2*

Ethnic group	Women	Men
White/not recorded	1	1
Indian	1.43 (1.24 to 1.65)	1.45 (1.29 to 1.63)
Pakistani	1.80 (1.5 to 2.17)	1.97 (1.70 to 2.29)
Bangladeshi	1.35 (1.06 to 1.72)	1.67 (1.40 to 2.01)
Other Asian	1.15 (0.86 to 1.54)	1.37 (1.09 to 1.72)
Black Caribbean	1.08 (0.94 to 1.24)	0.62 (0.53 to 0.73)
Black African	0.58 (0.42 to 0.82)	0.63 (0.47 to 0.85)
Chinese	0.69 (0.44 to 1.10)	0.51 (0.32 to 0.83)

### 4.4 HOW TO DETERMINE CARDIOVASCULAR RISK

**R** Individuals with the following risk factors should be considered at high risk of cardiovascular events:

- established cardiovascular disease, or
- stage 3 or higher chronic kidney disease or micro- or macroalbuminuria, or
- familial hypercholesterolaemia, or
- who are over the age of 40 and have diabetes, or
- who are under the age of 40 and have diabetes, and
  - at least 20 years duration of disease, or
  - target organ damage (eg proteinuria, micro- or macroalbuminuria, proliferative retinopathy or autonomic neuropathy), or
  - significantly elevated cardiovascular risk factors.

**R** Asymptomatic individuals should be considered at high risk if they are assessed as having a  $\geq 20\%$  risk of a first cardiovascular event within ten years.

**R** Cardiovascular risk assessment should be offered at least once every five years in adults over the age of 40 years with no history of cardiovascular disease, familial hypercholesterolaemia, CKD or diabetes and who are not being treated to reduce blood pressure or lipids.

- R** Individuals at high cardiovascular risk should be supported to make lifestyle changes and be offered drug therapy, to reduce their absolute risk.
- ✓ Consider an annual review to discuss lifestyle modification, medicines adherence and address CVD risk factors. Frequency of review may be adapted to the individual.
  - ✓ Other risk factors not included in the CVD risk prediction should be taken into account when assessing and managing a person's overall CVD risk. These may include: ethnicity, body mass index, atrial fibrillation, psychological wellbeing and physical inactivity.

Some individuals will have extreme values of single risk factors. Although absolute risk takes several risk factors into account, possession of such a 'lighthouse' risk may mandate intervention.<sup>54</sup> Single risk factors in this range include total cholesterol  $\geq 8$  mmol/l (see section 10.5.2) or elevated blood pressure (systolic pressure  $\geq 160$  mm Hg or diastolic pressure  $\geq 100$  mm Hg, or lesser degrees of hypertension with associated target organ damage (see section 11).<sup>55,56</sup> In these cases, whilst treatment is aimed at the single elevated risk factor, the reduction of global risk is the ultimate goal. Management of other risk factors is also important, especially where the key risk factor proves refractory.

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## 5 Diet

Environmental factors, including diet, play an important role in the development of CHD. The diet of any individual is related to other lifestyle factors (smoking, exercise, etc). Randomised controlled trials of diet are able to eliminate such bias but are more difficult to conduct than those of drugs or supplements. National reporting has indicated little progress in meeting the Scottish dietary goals over the period 2001 to 2012.<sup>57</sup>

### 5.1 ALTERING DIETARY FAT INTAKE

#### 5.1.1 TOTAL AND SATURATED FAT

A Cochrane review of 48 trials of at least six months duration examined the effect of reduction of total and saturated fat in the diet on reducing serum cholesterol levels and on total and cardiovascular mortality and morbidity.<sup>58</sup> Saturated fat reduction (through total dietary fat reduction and/or replacement of saturated with unsaturated dietary fat) may be protective of cardiovascular events overall, reducing them by 14% (risk ratio (RR) 0.86, 95% CI 0.77 to 0.96, 24 comparisons, 65,614 participants). However, there were no clear effects of dietary fat changes on total mortality (RR 0.98, 95% CI 0.93 to 1.04, 71,790 participants) or cardiovascular mortality (RR 0.94, 95% CI 0.85 to 1.04, 65,978 participants).

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The dietary reference value for saturated fat in the UK, which represents the maximum contribution that saturated fat should make to the population average intake for those aged five years and over, is 11%.<sup>59</sup> The average healthy man and woman require around 2,500 calories and 2,000 calories respectively to maintain their weight, although estimates for individuals may vary depending on age, metabolism and levels of physical activity. The recommended maximum intake of saturated fat translates to around 30 g/day for men and 20 g/day in women.

**R** | Diets low in saturated fats should be recommended to all for the reduction of cardiovascular risk.

- ✓ |
- The average man should aim to consume no more than 30 g of saturated fat per day.
  - The average woman should aim to consume no more than 20 g of saturated fat per day.

#### 5.1.2 OMEGA-3 SUPPLEMENTATION

There is no clear evidence that increased consumption of omega-3 fats, suggested as the protective element of oily fish consumption, reduces CVD when consumed as supplements. In a meta-analysis of RCTs examining the effects of omega-3 fatty acid for sudden cardiac death (SCD) prevention in patients with cardiovascular disease, benefits were only observed in patients receiving suboptimal medical management. In patients treated according to guidelines, omega-3 fatty acids did not reduce the risk ratio of SCD (RR 0.96, 95% CI 0.84 to 1.10).<sup>60</sup> The impact of statins, aspirin, angiotensin converting enzyme (ACE) inhibitors and antiplatelet agents (reflecting current medical management) removed any benefit from the omega-3 fatty acid supplements.

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In a meta-analysis of trials in adults with or at high risk of CVD, no clear effect from omega-3 fatty acids was reported on composite cardiovascular outcomes (RR 0.96, 95% CI 0.90 to 1.03), total mortality (RR 0.95, 95% CI 0.86 to 1.04), non-vascular mortality (RR 0.97, 95% CI 0.84 to 1.11), coronary events (RR 0.86, 95% CI, 0.67 to 1.11) or revascularisation (RR 0.95, 95% CI 0.89 to 1.00). There was also no evidence of benefit for cerebrovascular events (RR 1.03, 95% CI 0.92 to 1.16) or arrhythmia (RR 0.99, 95% CI 0.85 to 1.16). Omega-3 fatty acids did protect against vascular death (RR 0.86, 95% CI 0.75 to 0.99) but not sudden death (RR 1.00, 95% CI 0.75 to 1.33) which reflects the effects from omega-3 oils in those with CVD without current medical management. Adverse events were more common in those taking omega-3 fatty acids than placebo (RR 1.18, 95% CI 1.02 to 1.37), and were mainly gastrointestinal.<sup>61</sup>

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Current dietary guidelines suggest consumption of two 140 g portions of fish per week, one of which should be an oily fish.<sup>62</sup>

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**R** | **Omega-3 fatty acid supplements should not be offered for reduction of CVD risk.**

✓ | As fish consumption may help to reduce intake of (saturated) fat from meat, and may have a role in reducing fatal CHD with low risk of adverse effects, individuals should be advised to follow Government dietary guidelines to consume two 140 g portions of fish per week, one of which should be an oily fish.

## 5.2 REDUCING DIETARY SALT

A meta-analysis of 28 trials on the effect of moderate salt reduction on blood pressure demonstrated that a modest reduction in salt intake for four or more weeks has a significant effect on blood pressure in both hypertensive and normotensive individuals. The pooled estimates of blood pressure fall were 4.96/2.73 ± 0.40/0.24 mm Hg in hypertensive patients ( $p < 0.05$ ).<sup>63</sup>

A Cochrane review of salt restriction for the prevention of CHD cited too few cardiovascular events in the trials, of at least six months duration, to make a clear conclusion. It did report a small but significant reduction in systolic blood pressure in participants who had followed a salt-restricted diet and reductions were greater in subgroups with hypertension.<sup>64</sup> Another Cochrane review of advice to reduce salt intake lasting at least six months also reported small but significant benefits to blood pressure. Long-term maintenance of low-sodium diets was difficult for individuals, even with considerable advice, support and encouragement.<sup>65</sup>

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The Food Standards Agency has recommended that adults should consume no more than 6 g of salt per day (approximately equivalent to one teaspoonful).<sup>66</sup>

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**R** | **People with hypertension should be advised to reduce their salt intake as much as possible to lower blood pressure.**

✓ | All individuals should aim to consume less than 6 g of salt per day.

## 5.3 FRUIT AND VEGETABLE INTAKE

Diets with at least 400 g of fruit and vegetables (equivalent to five portions) per day are recommended in Scotland.<sup>58</sup> Two systematic reviews of cohort studies examined the benefits of fruit and vegetable consumption for the reduction of CHD risk. There is evidence from one review supporting increased vegetable (RR 0.77) and fruit (RR 0.86) intake to reduce CHD event rates,<sup>67</sup> and a 15% reduction in relative risk of CHD for those consuming high levels of fruit and vegetables compared with those consuming low levels (equivalent to a fourfold increase in fruit and doubling of vegetables) in another.<sup>68</sup>

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**R** | **Increased fruit and vegetable consumption is recommended for the entire population to reduce cardiovascular risk.**

## 5.4 EFFECT OF SPECIFIC MINOR DIETARY COMPONENTS

### 5.4.1 ANTIOXIDANT VITAMIN SUPPLEMENTATION

Several systematic reviews of RCTs were identified that investigated the association between vitamin supplementation and prevention of CHD. One systematic review of 84 RCTs found that neither supplements of vitamin E alone nor given with other agents yielded a statistically significant beneficial or adverse pooled relative risk for all-cause mortality, cardiovascular mortality, fatal or non-fatal myocardial infarction or reduction in blood lipids.<sup>69</sup> Another meta-analysis of RCTs of vitamin supplementation identified a lack of any statistically significant or clinically important effects of vitamin E on cardiovascular disease.<sup>70</sup>

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A meta-analysis examining the effect of vitamin E dose on all-cause mortality identified that high-dose ( $\geq 400$  international units per day) vitamin E increased all-cause mortality by 39 per 10,000 individuals treated (95% CI 3 to 74 per 10,000;  $p < 0.035$ ). Low-dose trials did not significantly reduce all-cause mortality.<sup>71</sup>

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The US Preventive Services Task Force guideline investigated evidence on the role of antioxidant supplementation in reducing the incidence of or progression to CHD. The guideline found little evidence that any single vitamin supplementation (vitamin A, vitamin C, vitamin E,  $\beta$ -carotene), combined antioxidants or multivitamins had a benefit on primary or secondary prevention.<sup>72</sup>

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**R** | **Antioxidant vitamin supplementation is not recommended for the prevention or treatment of coronary heart disease.**

#### 5.4.2 FOLATE SUPPLEMENTATION

A Cochrane review of 12 RCTs of at least one year follow up in 47,429 participants at risk of, or with, established CVD found no effect of homocysteine-lowering interventions (vitamins B6, B9 or B12, alone or in any combination) compared with placebo, on non-fatal or fatal myocardial infarction (MI) (RR 1.02, 95% CI 0.95 to 1.10), stroke (RR 0.91, 95% CI 0.82 to 1.00), death by any cause (RR 1.01, 95% CI 0.96 to 1.07) or serious adverse events (cancer) (RR 1.06, 95% CI 0.98 to 1.13).<sup>73</sup>

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A systematic review and meta-analysis of 16 RCTs of folic acid supplementation compared with placebo found no effect of supplementation on major cardiovascular events (RR 0.98, 95% CI 0.93 to 1.04), stroke (RR 0.89, 95% CI 0.78 to 1.01), MI (RR 1.00, 95% CI 0.93 to 1.07), or deaths from any cause (RR 1.00, 95% CI 0.96 to 1.05). Moreover, folic acid as compared with placebo also had no effect on the following secondary outcomes: risk of revascularisation (RR 1.05, 95% CI 0.95 to 1.16), acute coronary syndrome (RR 1.06, 95% CI 0.97 to 1.15), cancer (RR 1.08, 95% CI 0.98 to 1.21), vascular death (RR 0.94, 95% CI 0.88 to 1.02), or non-vascular death (RR 1.06, 95% CI 0.97 to 1.15).<sup>74</sup>

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**R** | **Homocysteine-lowering interventions (folate or B-vitamin supplementation) are not recommended for the prevention or treatment of cardiovascular disease.**

#### 5.4.3 STANOL ESTERS AND PLANT STEROLS

Stanol esters and plant sterols are present in small amounts in normal diets, and can be supplemented using dietary products, such as certain margarines and yoghurt drinks. Two systematic reviews provide evidence that they can reduce low-density lipoprotein (LDL) cholesterol.<sup>75,76</sup> In the larger review which included 41 RCTs, 2 g per day supplements of stanol esters and plant sterols led to a 10% reduction in LDL cholesterol.<sup>75</sup> There was no benefit from further dosage increases. In a cross-over RCT carried out in Colombia, subjects with a BMI <25 kg/m<sup>2</sup> demonstrated a larger total cholesterol reduction during treatment with 8 g plant stanol esters per day compared with placebo than those with BMI  $\geq$ 25 kg/m<sup>2</sup> (18.5 mg/dl, 8.6% v 12.6 mg/dl, 5.8%). LDL reduction showed the opposite trend where falls were smaller in those with lower BMI (11.3 mg/dl, 9.6% in those with BMI <25 kg/m<sup>2</sup>) and (12.8 mg/dl, 11.0% in those with BMI  $\geq$ 25 kg/m<sup>2</sup>).<sup>77</sup>

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There is no evidence on whether these reductions in cholesterol persist into the longer term and whether they translate to reduction in CVD events. There is an absence of long-term data (more than five years) on their safety.

#### 5.4.4 NUTS

There is limited evidence from two RCTs that consuming certain nuts may improve lipid profiles, reducing serum cholesterol by up to 0.4 mmol/l.<sup>78,79</sup> The trials were small with short-term follow up only, and involved consuming large amounts of unsalted nuts, which may be unrealistic for the general population in Scotland: Twenty per cent of the calorie intake was derived from nuts (averaging about 75 g/day). The effects of nut consumption in the context of a Mediterranean diet is discussed in section 5.5.

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There is insufficient evidence to support a recommendation.

#### 5.4.5 SOYA INTAKE

Soya-based foods are an important constituent in many vegetarian diets and have been investigated for possible beneficial effects on lipid profiles. Two small randomised trials, have suggested that substitution of moderate to large amounts of soya-based foods into the diet may have a small impact in lipid profiles.<sup>80,81</sup> Consuming 50 g of soya protein a day (in the form of burgers) was reported to reduce total cholesterol by 0.4 mmol/l.

There is insufficient evidence to support a recommendation.

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### 5.5 DIETARY PATTERNS

Mediterranean diets are generally characterised as having moderate fat intake (where the main sources of added fat are olive oil and unsalted nuts), being rich in vegetables and fruits and low in red meat (with poultry and fish replacing beef and lamb). There is no universal definition nevertheless there is a wide range of diets described as Mediterranean or having features of Mediterranean diets. Some interventions induced weight loss, making the impact of dietary changes alone difficult to estimate.

A Cochrane review of RCTs which randomised participants to at least three months of advice to follow a Mediterranean-style dietary pattern or provision of dietary factors relevant to a Mediterranean diet compared with no or minimal intervention included 52,044 adult participants from the general population with or without CVD. Overall, modest lowering of total cholesterol (-0.16 mmol/l, 95% CI -0.26 to -0.06) and LDL cholesterol (-0.07 mmol/l, 95% CI -0.13 to -0.01) were observed with the interventions. Clinical events were reported in only one trial. The Women's Health Initiative of 48,835 postmenopausal women, while not described as a Mediterranean diet incorporated increased fruit and vegetable and cereal intake. No statistically significant effects from the intervention were seen on fatal and non-fatal end points at eight years.<sup>82</sup>

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A meta-analysis of six RCTs (n=3,650) comparing Mediterranean diet patterns with low-fat diets (≤30% energy from fat) with two years follow up in overweight or obese adults at high risk of CVD reported greater reductions in weight (2.2 kg, 95% CI 3.9 to 0.6) systolic (1.7 mm Hg, 95% CI 3.3 to 0.05) and diastolic blood pressure (1.5 mm Hg, 95% CI 2.1 to 0.8) and total cholesterol 0.19 mmol/l (95% CI 0.26 to 0.11) with Mediterranean diet patterns, but there was no usual diet comparator and the greater weight loss in the Mediterranean diet patterns means that it is unclear whether the risk factor changes were mediated by weight loss or the Mediterranean diet patterns themselves.<sup>83</sup>

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A more recent RCT (PREDIMED) randomised 7,447 individuals aged 50–80 who were at high risk of CVD to one of two Mediterranean diet pattern (Med) arms, either with additional unsalted nuts (around 30 g per day) (n=2,554) or additional extra virgin olive oil (EVOO) (around 30 g per day consumed) (n=2,543) or to a control low-fat diet (n=2,450). Advice was energy unrestricted and mean baseline BMI ranged from 29.7–30.2 kg/m<sup>2</sup>. Median follow up was 4.8 years. A primary end-point event (MI, stroke and death from CVD) occurred in 288 participants in total across all arms. Multivariable-adjusted hazard ratios were 0.72 (95% CI 0.54 to 0.96) and 0.70 (95% CI 0.54 to 0.92) for the Med diet with additional nuts and EVOO, respectively, compared with the control group. Total mortality was not different between Med diet groups and control. Subgroup analysis by BMI category suggested that the greatest benefit may occur in overweight and obese individuals (HR 0.51, 95% CI 0.37 to 0.71) compared with those at normal weight (HR 1.04, 95% CI 0.71 to 1.54) or underweight (HR 0.69, 95% CI 0.29 to 1.67). Weight change is not reported.<sup>84</sup>

1<sup>++</sup>

A prospective cohort analysis of the PREDIMED study, where the exposure was olive oil, divided participants into energy-adjusted tertiles of their self-reported total olive oil and EVOO consumption prior to intervention. Those in the highest tertile of total olive oil and EVOO consumption had an estimated 35% (HR 0.65, 95% CI 0.47 to 0.89) and 39% (HR 0.61, 95% CI 0.44 to 0.85) reduction in cardiovascular events (ARR 1% and 1.9%, respectively). Higher total olive oil consumption was associated with a 48% relative reduction in risk of cardiovascular mortality (HR 0.52, 95% CI 0.29 to 0.93, ARR 0.4%). These associations suggest that greater consumption of olive oil was associated with reduced mortality risk, making olive oil a key element of the Mediterranean diet pattern.<sup>85</sup>

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Altering glycaemic index of the diet is another approach to changing dietary pattern. A systematic review and meta-analysis of RCTs comparing low and high glycaemic index diets reported that studies of at least 20 weeks' duration, but some in excess of one year, showed no significant effects on total or LDL cholesterol.<sup>86</sup> 1<sup>++</sup>

Given that individuals with established CVD are at increased absolute cardiovascular risk compared with individuals without CVD but estimated to be at high risk and with similar characteristics, the recommendation for Mediterranean diet can be extrapolated to this group.

**R** | **Adopting a Mediterranean diet pattern supplemented with 30 g extra virgin olive oil or unsalted nuts per day is recommended for adults at high risk of CVD or with established CVD.**

The Eatwell Guide defines the UK Government's advice on healthy eating and is a visual representation of how different foods contribute towards a healthy balanced diet (see Annex 2). Its recommendations support the components of a Mediterranean diet pattern.

✓ | Use the Eatwell Guide to help individuals make informed choices around the selection of dietary components and their optimal proportions which conform to Mediterranean diet patterns and support restricting saturated fat, sugars and salt intake.

## 5.6 GIVING DIETARY ADVICE

Randomised trials have shown that dietary advice can have effects on self-reported dietary intake as well as objective risk factors. Most evidence on beneficial effects is for patients with cardiovascular disease rather than those estimated to be at higher risk. These effects reduce with time,<sup>87</sup> although, in one study a measurable effect persisted for six to nine years.<sup>88</sup>

### 5.6.1 WHO SHOULD GIVE DIETARY ADVICE?

In one systematic review dietitians were better than doctors at lowering cholesterol through dietary advice alone, but there were no significant differences between dietitians and nurses or self-help resources.<sup>89</sup> 1<sup>++</sup>

### 5.6.2 HOW SHOULD DIETARY ADVICE BE GIVEN?

A variety of methods has been attempted varying from brief advice to comprehensive multifactorial lifestyle interventions. In one RCT, up to two hours of counselling achieved greater effects than 10 minutes of counselling, but the differences were small.<sup>90</sup> In another RCT, 14 group sessions (90 minutes each) during one year increased self-reported fruit and vegetable intake and reduced self-reported fat intake, but without significant changes to lipid profiles.<sup>91</sup> One RCT found that telephone coaching led to a 10% reduction in total and LDL cholesterol.<sup>92</sup> The intervention involved five telephone calls over 24 weeks and included assessment to establish knowledge, explanation, assertiveness training, goal setting, and reassessment. Length of telephone calls varied, but median times were 20 minutes for the first call and 10 minutes for subsequent calls. 1<sup>++</sup>  
1<sup>+</sup>

✓ | Interventions to improve diet should be based on educational competencies (improved knowledge, relevance, individualisation, feedback, reinforcement and facilitation).

## 5.7 WEIGHT REDUCTION AND CARDIOVASCULAR RISK

Four systematic reviews of lifestyle intervention (diet and/or physical activity) to reduce weight which evaluated effects on blood pressure were identified.<sup>93-96</sup> Interventions which reduced weight by 3–11 kg were moderately effective in reducing blood pressure, with reductions in systolic blood pressure (SBP) of around 1 mm Hg per kg weight lost. 2<sup>+</sup>

Three systematic reviews evaluated the effects on blood lipids of moderate weight loss through lifestyle intervention.<sup>93-95</sup> 1<sup>+</sup>  
1<sup>++</sup>

Weight loss of at least 3 kg led to reductions in LDL cholesterol of approximately 0.2–0.3 mmol/l. There were insufficient data to determine the effects of lifestyle-mediated weight loss on morbidity or mortality outcomes.

One systematic review comparing the effects of bariatric surgery with non-surgical interventions in RCT or cohort studies reported a substantially (~50%) lower risk of CVD events and mortality with surgery.<sup>97</sup> Another systematic review of RCTs comparing bariatric surgery (>25 kg weight loss) with non-surgical interventions reported greater diabetes remission with surgery, both in a complete case analysis (relative risk 22.1, 95% CI 3.2 to 154.3), and in a conservative analysis assuming diabetes remission in all non-surgically-treated individuals with missing data (relative risk 5.3, 95% CI 1.8 to 15.8).<sup>98</sup> Thus, the data suggest that substantial (surgically-induced) weight loss may reduce morbidity and mortality.

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1++

**R** Patients, and individuals at risk of cardiovascular disease, who are overweight or obese, should be targeted with interventions designed to reduce weight by at least 3 kg, and to maintain this reduction.

✓ Patients' weight should be measured annually.

## 5.8 METABOLIC SYNDROME

The metabolic syndrome is characterised by insulin resistance and visceral obesity and is associated with hypertension, impaired glucose handling, lipid abnormalities and a variety of more subtle metabolic anomalies.

Previously, metabolic syndrome criteria were proposed as a way to simultaneously predict diabetes and cardiovascular risk. However, the fact that people with metabolic syndrome are at increased risk of cardiovascular disease events or diabetes does not mean that the construct is useful for risk prediction in itself or compared with other approaches. Evidence now indicates that metabolic syndrome performs relatively poorly for risk prediction compared with established risk predictors for each condition in clinical practice, highlighting that these established risk predictors and not metabolic syndrome should be used for this purpose.<sup>99</sup>

3

Importantly, relevant information can be easily collected at the same time for the prediction of both conditions, with measurement of HbA1c in non-fasting individuals thought to be at elevated risk of diabetes, at the same time that lipids are checked.

## 6 Physical activity

Regular activity has both preventive and therapeutic effects on many chronic conditions such as CHD, stroke, cancer, musculoskeletal disorders, obesity, diabetes and mental-health problems.<sup>41</sup>

### 6.1 DEFINITIONS

Physical activity has been defined as any bodily movement that results in energy expenditure.<sup>100</sup> Physical activity can be categorised as occupational (physical activity at work), leisure time (non-occupational physical activity), exercise (physical activity that is structured and done for a specific reason) and active living (for example non-recreational walking, housework and gardening). Physical activity is commonly described as having four dimensions: duration (for example minutes, hours), frequency (for example times per week or month), intensity (for example rate of energy expenditure) and type (for example walking, gardening, swimming).<sup>101</sup> For most people, the easiest and most acceptable forms of physical activity are those that can be incorporated into everyday life. Examples include walking or cycling.<sup>41</sup> Exercise intensity can be defined (or monitored) using a number of indices including percentage of maximal heart rate ( $HR_{max}$ ), percentage of maximal oxygen uptake ( $VO_{2max}$ ), rate of energy expenditure (reported in metabolic equivalents (METs), or multiples of resting metabolic rate), self-reported rating of perceived exertion (RPE) or talk test.

Table 5: Classification of absolute and relative exercise intensity

Intensity	Relative intensity			Absolute intensity	
	$HR_{max}$ (%)	$VO_{2max}$ (%)	RPE	METs	Talk Test
Very light to light	<57–63	<37–45	9–11	1.5<3	Conversation uninhibited
Moderate	64–76	46–63	12–13	3<6	Conversation possible
Vigorous	77–95	64–90	14–17	6<9	Conversation harder but possible
High to maximum	≥96	≥91	≥18	≥9	Conversation difficult to impossible

Table adapted with permission from Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al; American College of Sports Medicine. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc.* 2011;43(7):1334-59.

The table refers to the general population. Examples of activities undertaken at each intensity, can be found in Annex 3.

Sedentary behaviour is defined as non-sleeping activities in a sitting or reclining posture with energy expenditure  $\leq 1.5$  METs.<sup>102</sup>

### 6.2 PHYSICAL ACTIVITY AND CARDIOVASCULAR RISK

#### 6.2.1 PHYSICAL INACTIVITY AS AN INDEPENDENT RISK FACTOR

Ten observational studies that examined the association of physical activity with CVD, after controlling for other key risk factors, were identified. All studies (or specific elements of the studies) confirmed an inverse relationship between physical activity and the risk of a coronary event.<sup>20,103-111</sup>

Effect sizes ranged from non-significant relationships for specific types of activity (for example active commuting; hazard ratio for cardiovascular mortality=1.08, 95% CI 0.95 to 1.23)<sup>104</sup> to highly significant associations (for example men who ran for an hour or more per week had a 42% risk reduction, RR 0.58, 95% CI 0.44 to 0.77, ARR 0.3%) compared with men who did not run ( $p < 0.001$ ).<sup>111</sup> One well-conducted case-control study reported a multivariate odds ratio (OR) of 0.51 (95% CI 0.29 to 0.90) when comparing low levels of occupational physical activity against higher levels.<sup>103</sup> Similar results were reported for leisure time activity. This suggests that physical activity can reduce the risk of a coronary event, when all other major risk factors are controlled for, by as much as a half.

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There is also evidence that reduced cardiorespiratory fitness (ie the ability of the body to use oxygen to do physical work), which is improved by increasing physical activity, is a risk factor for CVD.<sup>112,113</sup>

## 6.2.2 LEVELS OF PHYSICAL ACTIVITY

The types of activity, durations, frequencies and intensities included in the ten studies varied greatly. This lack of consistency makes it difficult to draw conclusions in relation to the exact type, quantity and quality of activity required for a benefit.

The evidence indicates that activities of moderate intensity are protective. For example, INTERHEART, one of the largest case-control studies of its kind, reported a reduced incidence of myocardial infarction from activities that included walking, cycling or gardening (OR 0.86, 95% CI 0.76 to 0.97).<sup>20</sup> In another study that compared distance walked per day, those who walked less than 0.25 miles per day had double the risk of CHD mortality or morbidity of those who walked more than 1.5 miles per day (RR 2.3, 95% CI 1.3 to 4.1) which represented an increase in the absolute risk of incidence of CHD of 2.6% across two to four years of follow up.<sup>105</sup>

2<sup>++</sup>

The evidence also suggests a dose-response relationship for both intensity and duration. For example, a study of postmenopausal women showed that women in increasing quintiles of energy expenditure measured in METS had adjusted relative risks of total CVD of 1.00, 0.89, 0.81, 0.78 and 0.72, respectively ( $p$  for trend  $< 0.001$ ).<sup>109</sup> The reduction in absolute risk of CVD between the lowest and highest quintiles of physical activity was 0.5%. Similar trends exist for duration of exercise.<sup>106</sup>

2<sup>+</sup>

The type of activity appears to be relatively unimportant. For example, one good-quality study reported comparable effects for both occupational and leisure time activity.<sup>103</sup>

2<sup>++</sup>

Activity may not need to be continuous to be of benefit. One study reported that after accounting for total energy expended on physical activity and potential confounders, duration of activity did not have an independent effect on CHD risk ( $p$  trend=0.25); that is, longer sessions of exercise did not have a different effect on risk compared with shorter sessions, as long as the total energy expended was similar.<sup>108</sup>

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## 6.2.3 VIGOROUS AND HIGH-INTENSITY PHYSICAL ACTIVITY

One systematic review and four RCTs were identified comparing the effects of vigorous- and high-intensity physical activity with moderate-intensity physical activity on cardiovascular disease risk factors and cardiorespiratory fitness ( $VO_{2max}$ ).<sup>114-118</sup> These consistently reported greater improvements in  $VO_{2max}$  with vigorous- and high-intensity exercise. There was mixed evidence on whether vigorous- or high-intensity physical activity resulted in greater improvements on CVD risk factors, with one study showing greater blood pressure reductions with high-intensity compared with moderate-intensity physical activity in patients with hypertension.<sup>117</sup> Another reported clinically marginal but statistically significant greater benefits in reducing HbA1c, triglycerides and total cholesterol, but not in other risk factors or CHD risk scores for vigorous- compared with moderate-intensity physical activity in patients with type 2 diabetes.<sup>114</sup> Other studies reported no differences between physical activity intensity groups for blood pressure and lipid changes in patients with heart failure, or after revascularisation.<sup>115,116,118</sup>

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In a systematic review of exercise-based rehabilitation in patients with heart failure, withdrawal of exercising patients from studies decreased with increasing exercise intensity. The relative risk for the composite end point of death or hospitalisation was 0.86 (95% CI 0.79 to 0.94,  $p = 0.001$ ) in patients undertaking a vigorous-intensity physical-activity intervention compared with control groups.<sup>115</sup>

1<sup>+</sup>

The potential risks of adverse events associated with vigorous- and high-intensity exercise have been evaluated in a number of studies, all of which reported that risks were extremely low. In an RCT of 303 patients with type 2 diabetes, no significant difference in adverse events between moderate- and vigorous-intensity physical-activity interventions over 12 months was reported.<sup>114</sup> In a systematic review of patients with heart failure no deaths were directly attributable to exercise in 123,479 patient hours of training (including 7,223 hours of high-intensity and 84,655 hours of vigorous-intensity physical activity).<sup>115</sup>

1+

In patients undergoing cardiac rehabilitation, rates of cardiac events were low for both moderate- and high-intensity exercise (1 per 129,456 training hours for moderate-intensity exercise and 1 per 23,182 hours for high-intensity exercise).<sup>119</sup>

In a meta-analysis of observational studies of vigorous physical activity in the general population the absolute risk increase associated with an hour of additional physical activity per week was 2 to 3 per 10,000 person years for MI and 1 per 10,000 person years for SCD.<sup>120</sup> This risk was reduced in those undertaking habitual physical activity (by 47% for each additional physical activity session per week for MI and 30% for each additional session per week for SCD). Thus, the benefits of physical activity (*see sections 6.2.1 and 6.2.2*) far outweigh the risks of an adverse event and vigorous-intensity physical activity can be regarded as safe.

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#### 6.2.4 RISKS OF SEDENTARY BEHAVIOUR

A systematic review of prospective observational studies suggested that high levels of total sedentary behaviour are associated with higher risk of CVD and mortality.<sup>121</sup> The relative risk of being in the highest compared with lowest population groups of sedentary behaviour was 2.47 (95% CI 1.44 to 4.24) for CVD, 1.90 (95% CI 1.36 to 2.66) for CVD mortality and 1.49 (95% CI 1.14 to 2.03) for all-cause mortality. Many, but not all, of the studies included in this meta-analysis adjusted for physical activity or energy expenditure, suggesting that high levels of sedentary behaviour may be associated with additional CVD risk at any level of physical activity. However, a recent meta-analysis suggests that undertaking very high levels of physical activity (more than one hour per day of moderate to vigorous physical activity) eliminates the association between excess sitting and CVD risk.<sup>122</sup>

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Evidence for the risks associated with occupational sitting is less consistent, with about half of studies suggesting greater risk of CVD and two thirds of studies suggesting greater risk of all-cause mortality associated with high levels of sitting.<sup>123</sup>

2+

Due to the observational nature of these data causality between sedentary behaviour and CVD or mortality cannot be definitively ascribed. Nevertheless, there are data which associate adverse changes to cardiometabolic risk factors with short-term imposition of sedentary behaviour, suggesting a potential mechanistic link between sedentary behaviour and CVD risk.<sup>124</sup>

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Although definitive evidence from long-term RCTs of benefits of reducing sedentary behaviour is lacking, given that the harms associated with reducing sedentary behaviour are negligible, it would be prudent to provide general advice to minimise periods of prolonged sitting in line with current UK physical activity guidance.<sup>41</sup>

**R** Physical activity of at least moderate intensity (eg breathing faster than normal) is recommended for the whole population (unless contraindicated by an individual's condition).

**R** Physical activity may include occupational and/or leisure-time activity and should incorporate accumulated bouts of moderate-intensity activities such as brisk walking.

**R** Those who are moderately active and are able to increase their activity should be encouraged to do so. Activity can be increased through a combination of changes to intensity, duration or frequency.

- R** | Those who are already moderately active without contraindication can safely be encouraged to undertake vigorous-intensity exercise to achieve additional benefits.
- R** | Individuals should be advised to minimise the amount of time spent being sedentary (sitting) over extended periods.
- ✓ | All patients, irrespective of health, fitness or activity level, should be encouraged to increase activity levels gradually.

The evidence reviewed and corresponding recommendations are in general agreement with nationally recognised recommendations that state all adults should:<sup>41</sup>

- aim to be active daily. Over a week, activity should add up to at least 150 minutes (2.5 hours) of moderate-intensity activity in bouts of 10 minutes or more, or 75 minutes of vigorous-intensity activity.
- undertake physical activity to improve muscle strength (such as weight training, carrying heavy load, heavy gardening, push ups or sit ups) on at least two days a week.

4

Older adults (aged 65 years and older) at risk of falls should incorporate physical activity to improve balance and co-ordination on at least two days a week.

All children and young people should engage in moderate- to vigorous-intensity physical activity for at least 60 minutes and up to several hours every day.

National guidance is available on the most effective way to promote physical activity.<sup>125,126</sup>

## 6.2.5 EFFECTS OF PHYSICAL ACTIVITY ON OTHER KEY RISK FACTORS

Several meta-analyses provide evidence for a significant effect on CHD risk factors from exercise.

One meta-analysis combined the results of 28 RCTs of mainly healthy white adults.<sup>127</sup> Despite a large degree of variability, endurance exercise training had a favourable influence overall on the blood lipid profile relative to future risk of CHD. The most commonly observed lipid change in all weight categories in relation to endurance training was a significant ( $p < 0.05$ ) increase in HDL cholesterol. Reductions in LDL cholesterol (-5.0%,  $p < 0.05$ ), triglycerides (-3.7%,  $p < 0.05$ ), and total cholesterol (-1%, not significant) were observed less frequently (independent of dietary interventions). There was a marked inconsistency in response of blood lipids. Twenty-four of 51 studies showed an increase in HDL cholesterol but the range over all studies was from -5.8% to +25%. It was not possible to establish a dose-response relationship between duration, intensity or frequency of exercise and blood lipid response.

1+

A further meta-analysis of 54 trials showed that previously sedentary adults could decrease systolic blood pressure by 3.8 mm Hg (95% CI 2.7 to 5.0 mm Hg,  $p < 0.001$ ) with regular aerobic exercise.<sup>128</sup> Exercise lowered blood pressure in people who were normotensive or hypertensive; overweight or of normal weight; and black, white, or Asian. The blood pressure reductions tended to be less marked in trials with longer follow-up periods, most likely because adherence to the intervention programme decreased over time. All forms of exercise studied appeared to be effective in reducing blood pressure. There was no relation between the frequency or intensity of the exercise and the clinical result.

1+

## 7 Smoking

### 7.1 TOBACCO EXPOSURE AND CARDIOVASCULAR RISK

This section summarises the evidence describing the relationship between tobacco exposure and cardiovascular health and focuses on cessation interventions for the vulnerable population subgroup of people with depression. No relevant evidence was identified for interventions in ethnic subgroups.

#### 7.1.1 ACTIVE SMOKING

Tobacco smoking is strongly and dose-dependently associated with all cardiovascular events, including CHD, stroke, PAD and cardiovascular death.<sup>129,130</sup> Smoking cessation reduces these risks substantially, although the decrease is dependent on the duration of cessation.<sup>131,132</sup> Men who smoke are three times more likely to die aged 45–64 and twice as likely to die aged 65–84 than non-smokers.<sup>129</sup> Studies done in women during the 1950s and 1960s reported relative risks for total mortality ranging from 1.3 to 1.4. Smokers in the Nurses' Health Study were at nearly 1.9 times the risk compared with people who have never smoked.<sup>133</sup> In the Million Women's Study, those smoking at baseline had a mortality rate ratio of 2.76 (95% CI 2.71 to 2.81) compared with never smokers after 12 years. There was an average lifespan difference between the two groups of 11 years.<sup>134</sup>

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The additional risk of cardiovascular disease conferred by smoking is mediated by the number of cigarettes smoked. A large case-control study noted the strong relationship between risk of MI and number of cigarettes smoked, with individuals who smoked over 40 cigarettes per day having almost ten times the relative risk of MI as non-smokers (OR 9.16, 99% CI 6.18 to 13.58).<sup>20</sup>

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The proportion of adults (aged 16 and over) who smoke in Scotland has been falling consistently in recent years. In 2003, 28% of adults in Scotland smoked compared with 21% in 2015. Over the same period, the proportion of all adults who have never smoked, or have never smoked regularly, increased from 50% to 55%. Among all smokers aged 16 and over, there was also a significant fall over time in the mean number of cigarettes smoked per day from a mean of 16.7 per day in 1995 to 12.6 in 2015.<sup>1</sup>

The prevalence of regular (at least weekly) smoking among 13 year olds has decreased since 1994 from 11% to 2% among boys and from 10% to 2% among girls. Among 15 year old children, the prevalence of regular smoking has decreased from 30% in 1996 to 7% in 2015 in both boys and girls. Smoking prevalence is currently at its lowest rates since records began in 1982.<sup>135</sup> There is evidence that young people can become addicted to tobacco very quickly<sup>136</sup> and many want to stop smoking.<sup>137</sup>

✓ Priority should be given to identifying and supporting young people to help them stop smoking.

The prevalence of smoking is highest amongst those on low incomes. Amongst some groups smoking rates as high as 75% have been reported.<sup>138</sup> Regular smokers are less likely than non-smokers to live in the least deprived areas.<sup>135,139</sup>

✓ Priority should be given to developing programmes and targeting smokers on low incomes to stop smoking, recognising the particular difficulties experienced by this group of smokers.

A prospective cohort study of over 120,000 males suggested that smoking cigars increases risk of early death from CHD.<sup>140</sup> The association between cigar smoking and death from CHD was stronger among younger men and current rather than former smokers, as is observed with cigarette smoking. No increased risk was observed among current cigar smokers aged 75 or older, or for former cigar smokers of any age. For men younger than 75 who were current cigar smokers at baseline, the adjusted rate ratio for CHD mortality was 1.30 (95% CI 1.05 to 1.62).

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A case-control study, involving 587 individuals who smoked cigarettes with differing known tar yields and 2,685 controls, indicated that smoking higher-yield cigarettes is associated with an increased risk of MI. The study revealed a dose-response relationship between total tar consumption per day and MI.<sup>141</sup> The odds ratios for individuals smoking medium- and high- compared with low-tar-yield cigarettes were 1.86 (95% CI 1.21 to 2.87) and 2.21 (95% CI 1.47 to 3.34), respectively.

2+

**R** | **All people who smoke should be advised to stop and offered support to help facilitate this in order to minimise cardiovascular and general health risks.**

## 7.1.2 PASSIVE SMOKE EXPOSURE

Several systematic reviews and observational studies provide evidence that exposure to environmental tobacco smoke (ETS) is associated with CVD events. In 2015, 12% of children in Scotland lived in accommodation in which someone smoked inside (down from 19% in 2012 and 16% in 2013 and 2014). However, a lower proportion (6%) of children were reported to be exposed to second-hand smoke in their home (down from 12% in 2012).<sup>1</sup>

One systematic review calculated that environmental exposure to tobacco smoke causes an increase in relative risk of CHD of around 25%. It is of similar magnitude to the effects of exposure to ETS on lung cancer, but the number of excess deaths from heart disease compared with lung cancer will be far greater in non-smokers due to the higher prevalence of CHD.

Individuals who have never smoked have an estimated 30% increased relative risk of CHD if they live with a smoker ( $p < 0.001$ ). The excess risk from smoking one cigarette per day is 39%, similar to the risk in a non-smoker living with a smoker. Reversal of the effect would reduce the risk of CHD by about as much as taking aspirin or by what many people could achieve through dietary change.<sup>130</sup> Other systematic reviews highlight the increased risk of CHD events through exposure to ETS in the workplace<sup>142</sup> and at home.<sup>143</sup>

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2+

Two observational studies indicated that non-smokers exposed to cigarette smoke had an increased risk of acute coronary syndrome of 51% (OR 1.51, 95% CI 1.21 to 2.99) compared with non-smokers not exposed to smoke.<sup>144,145</sup>

2++

2+

Another case-control study examined the relationship between ETS and MI, in the workplace and at home.<sup>146</sup> The odds ratio for MI was 1.58 (95% CI 0.97 to 2.56) for an average daily passive exposure to the smoke from 20 cigarettes per day or more at home. Combined exposure at home and work showed an increasing odds ratio for MI, up to 1.55 (95% CI 1.02 to 2.34) in the highest category of weighted duration, that is, more than 90 hour-years of exposure (1 hour-year=365 hours, or one hour per day for one year). In addition, more recent exposure appeared to convey a higher risk. This study confirms an increased risk of MI from exposure to ETS and suggests that intensity of spousal exposure, combined exposure from home and work, and time since last exposure are important.

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**R** | **Exposure to passive smoking increases cardiovascular risk and should be minimised.**

## 7.2 SMOKING CESSATION INTERVENTIONS

### 7.2.1 THE GENERAL POPULATION

There are many guidelines and policy documents covering mainstream NHS smoking cessation services and wider primary prevention.<sup>147-150</sup>

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In 2015, 64% of smokers and recent ex-smokers who had ever attempted to quit had used some form of nicotine replacement therapy (NRT) or e-cigarettes, for this purpose in the last three months, with the figure higher for women (69%) than men (64%). The particular items most likely to have been used as part of the quit attempt were nicotine patches (36%) and e-cigarettes (33%). Nicotine gum and nasal sprays/nicotine inhalers were used by 18% and 9% respectively, with other products, such as lozenge/microtab, varenicline and bupropion, being less common.<sup>139</sup>

The main pharmacological interventions that are offered include nicotine replacement therapy (single or combination), varenicline, or bupropion. These can be offered on their own or as part of a programme of group support provided through a smoking cessation service or individual support that is usually provided by a pharmacist. The most common route of referral for people that are ready to attempt stopping smoking is directly to a smoking cessation service in a pharmacy, where these are available.

The choice of products in any smoking cessation regimen is determined by patient preference and smoking habits (for example number smoked per day or time of first cigarette). The mainstay of treatment for combination nicotine replacement therapy is usually a patch which releases nicotine over a 16- or 24-hour period, combined with an immediate-release form of nicotine (spray, mist, lozenge etc) to help cope with cravings and withdrawal symptoms that are experienced while using the patch. Varenicline is an alternative form of treatment usually offered as a pill that acts as a selective nicotine receptor partial agonist. Varenicline binds nicotine receptors and its partial agonist activity is sufficient to alleviate the symptoms of craving and withdrawal; simultaneously varenicline prevents nicotine from binding to receptors and this reduces the reward and reinforcing effects of smoking (antagonist activity). For these reasons varenicline is not used in combination with nicotine replacement therapy and the safety and efficacy of varenicline combined with other nicotine replacement therapy has not been studied. Bupropion is another tablet treatment option which was originally developed as an antidepressant but is now licensed in the UK only for smoking cessation. It works as a nicotine antagonist and its effects on smoking cessation are independent to its antidepressant properties.

One systematic review and two RCTs comparing smoking cessation interventions were identified.

A systematic review of 20 studies concluded that quitting smoking is associated with a 36% reduction in crude relative risk of mortality for patients with CHD who quit compared with those who continued smoking (RR 0.64, 95% CI 0.58 to 0.71).<sup>151</sup> 2<sup>++</sup>

Two RCTs addressed lifestyle advice/training and reported a reduction in smoking in those who went through an educational programme.<sup>87,152</sup> Both studies only included male patients and lacked sufficient power to allow a firm conclusion to be drawn.

In the Oslo Diet and Antismoking Trial, advice to change diet and smoking habits reduced the relative risk of CHD mortality in men with high triacylglycerol concentrations after 23 years follow up. Men with normal triacylglycerol concentrations did not appear to achieve similar long-term benefit from lifestyle intervention.<sup>152</sup> 1<sup>+</sup>

The Vestfold Heartcare Study Group trial investigated whether a comprehensive programme of lifestyle modification could favourably influence dietary and exercise habits in addition to smoking cessation.<sup>87</sup> After following a low-fat diet, regular exercise, smoking cessation and psychological support and education sessions, patients in the lifestyle intervention group reduced the intake of saturated fat, sugar and cholesterol ( $p < 0.001$ ) increased their exercise level ( $p < 0.001$ ) and stopped smoking ( $p < 0.05$ ) compared with the usual care group. Results indicated a relative reduction of 22% in five-year risk of CHD in males (95% CI 9 to 35), however, the study lacked statistical power and should be interpreted with caution. 1<sup>+</sup>

Two Cochrane meta-analyses, which include over 20 RCTs, indicate a large treatment effect from varenicline compared with placebo, bupropion, and single NRT in relation to biochemically-confirmed quit rates up to six months post-treatment, but an equivalent effect to combination NRT.<sup>153,154</sup> Varenicline gives a pooled relative risk for sustained abstinence at six months or longer compared with placebo of 2.27 (95% CI 2.02 to 2.55, 14 trials, 6,166 people). Varenicline also increases the odds of quitting compared with placebo (OR 2.88, 95% CI 2.40 to 3.97). A lower dose of varenicline reduces adverse effects and still gives a relative risk of 2.09 (95% CI 1.56 to 2.78, four trials, 1,272 people) compared with placebo for sustained abstinence at six months or longer. Varenicline offers a 12–15% chance of a successful quit compared with 4–5% with placebo, meaning that approximately 10–12 people needed to be treated with varenicline for each additional successful quit attempt at six months or longer. 1<sup>++</sup>

The SMC reported that a cost-utility analysis from the manufacturer indicated that varenicline results in lower lifetime NHS costs for a cohort of smokers as well as generating more Quality Adjusted Life Years (QALYs), compared with other ways of quitting smoking.<sup>155</sup>

A large meta-analysis, including over 10,000 participants in 39 RCTs has indicated that minor side effects with varenicline are common, affecting around 20% of people.<sup>156</sup> These include nausea, sleep disturbance and insomnia although most people tolerate these and continue with their treatment and the side effects reduce over time. There is no reliable evidence that varenicline is associated with an increased risk of significant adverse neuropsychiatric events.

1<sup>++</sup>

The NHS Health Scotland guideline on smoking cessation recommends that varenicline, single NRT, combination NRT (interventions involving more than one type of nicotine replacement delivery), and bupropion may all be used as treatments depending on patient preferences and other factors.<sup>147</sup> These can be offered alongside behavioural support (individual or group support service) or on their own.

4

One systematic review which compared different forms of NRT concluded that all forms of NRT can help people to stop smoking, almost doubling long-term success rates. The risk ratio for abstinence with any form of NRT compared with control was 1.60 (95% CI 1.53 to 1.68).<sup>157</sup>

1<sup>++</sup>

A systematic review of the effect of antidepressants on smoking cessation showed that bupropion and nortryptiline approximately doubled the odds of a motivated individual stopping smoking.<sup>158</sup> Based on 19 trials of bupropion monotherapy with over 4,000 participants, the pooled OR for smoking cessation was 2.06 (95% CI 1.77 to 2.40). Serious adverse effects using bupropion at the doses indicated for smoking cessation are rare (less than one per 1,000 treated).<sup>159</sup>

1<sup>++</sup>

Nortryptiline is not licensed for use in smoking cessation and is contraindicated in patients with recent myocardial infarction or arrhythmias (particularly heart block).<sup>160</sup>

4

**R** Varenicline or combination nicotine replacement therapy should be offered alone or as part of a smoking cessation programme to augment professional advice and increase long-term abstinence rates.

**R** Bupropion and single nicotine replacement therapy may also be considered as smoking cessation treatments.

## 7.2.2 ELECTRONIC CIGARETTES

In 2015, 7% of adults aged 16 and over currently used electronic cigarettes (e-cigarettes) in Scotland, with a further 11% having previously used them (17% having ever used). These figures were similar for both men and women. E-cigarette use is strongly associated with smoking behaviour, with both current and past use of e-cigarettes much higher among current cigarette smokers than among ex-regular or never regular smokers. In total, 16% of smokers reported currently using e-cigarettes and an additional 36% said they had done so in the past, the equivalent figures for ex-regular smokers were 9% and 7%, respectively.<sup>139</sup>

A Cochrane meta-analysis which included two RCTs and 11 observational studies showed a relative risk of a successful quit attempt of 2.29 for nicotine-containing e-cigarettes over placebo e-cigarettes (95% CI 1.05 to 4.96). The relative risk for reducing tobacco consumption by at least half with nicotine-containing e-cigarettes over placebo e-cigarettes was 1.31 (95% CI 1.02 to 1.68).<sup>161</sup> No statistically significant differences were found between nicotine-containing e-cigarettes and nicotine patch on either of the above measures. No significant adverse events were attributed to e-cigarettes and there was no difference in the likelihood of minor side effects with nicotine-containing e-cigarettes compared with placebo e-cigarettes. These findings are supported by a further RCT.<sup>162</sup>

1<sup>++</sup>

However, some uncertainty persists about the benefits of nicotine-containing e-cigarettes as a smoking cessation intervention on account of significant methodological weaknesses in the studies included in the Cochrane review and the relatively small sample size of the RCT. While the constituents of nicotine-containing e-cigarettes are not known to be harmful to health when ingested as food or drink, there is no reliable health surveillance data available on the long-term impact of inhaling these substances. Nicotine-containing e-cigarettes are not licensed as smoking cessation treatments, while alternative licensed products are available. Furthermore, the use of e-cigarettes is being superseded by electronic nicotine delivery systems (ENDS) which may be more efficient at delivering nicotine to the body although their harms and benefits as a smoking cessation intervention have not been extensively researched.

### 7.2.3 SPECIAL POPULATIONS

#### *Patients with depression*

One meta-analysis<sup>163</sup> and three RCTs<sup>164-166</sup> were identified which considered smoking cessation in individuals with clinical depression.

The meta-analysis considered whether a history of major depression is associated with failure to quit smoking. No differences in either short-term (three months or less) or long-term (six months or more) abstinence rates were observed between smokers who were positive versus negative for history of depression. The authors conclude that a lifetime history of major depression does not appear to be an independent risk factor for cessation failure in smoking cessation treatment. 2<sup>++</sup>

The three RCTs considered different smoking cessation strategies for patients with depression. One trial investigated the effect of nortriptyline hydrochloride and cognitive behavioural therapy (CBT) on smoking treatment outcomes in smokers with a history of major depressive disorders.<sup>165</sup> Nortriptyline produced higher abstinence rates than placebo, independent of depression history and alleviated a negative affect occurring after smoking cessation. Cognitive behavioural therapy was more effective for participants with a history of depression. 1<sup>+</sup>

A smaller trial investigated the effect of sertraline as a cessation aid to patients with clinical depression. The trial showed that sertraline did not add to the efficacy of intensive individual counselling. However, given that the end-of-treatment abstinence rate for the placebo group was much higher than expected, it is unclear whether a ceiling effect of the high level of psychological intervention received by all participants prevented an adequate test of the drug.<sup>164</sup> 1<sup>+</sup>

One small trial examined the efficacy of a mood management intervention for smoking cessation in abstinent alcoholics with a history of major depression.<sup>166</sup> Patients were randomised to either behavioural counselling (BC) alone or counselling with a CBT component. Significantly more smokers in the CBT group had quit smoking by the end of the intervention period (69.2%; 9 of 13) than in BC (31.3%; 5 of 16) ( $p=0.04$ ). The abstinence rates remained unchanged at one month follow up. At three month follow up, differences in smoking abstinence rates were not significant between CBT (46.2%; 6 of 13) and BC (25.0%; 4 of 16) conditions. At 12 month follow up, significantly more participants in CBT were abstinent from smoking (46.2%; 6 of 13) than in BC (12.5%; 2 of 16) ( $p=0.04$ ). 1<sup>-</sup>

Antidepressants have an effect on smoking cessation rates in this group (but are not licensed specifically for this indication). It is not clear whether this effect is mechanistic or related directly to the treatment of depression. There are no significant trials of other pharmacological interventions (eg NRT, bupropion) in this group of patients.

**R** **Smokers with coronary heart disease and comorbid clinical depression should be offered treatment to reduce depressive symptoms and to increase the likelihood of stopping smoking.**

#### *Patients from ethnic minorities*

There have been few statistically reliable nationwide surveys of the prevalence of smoking or effectiveness of cessation interventions among ethnic minorities in Scotland.

Scottish Health Survey data have been combined for ethnic minority groups over a period of four years (2008–2011) to provide information on the health behaviours in this sector of the community.<sup>167</sup> Respondents from Pakistani and 'Asian, other' ethnic groups (people who did not self identify as belonging to Asian Indian, Chinese or Pakistani groups) were significantly less likely to smoke than the national average (prevalence of 13% and 9% respectively compared with 25% among the White British respondents. This is consistent with other UK-wide research indicating that smoking rates in ethnic minority groups tend to be the same or lower than in the general population.<sup>168</sup>

While smoking rates for men and women in the UK on the whole are converging, amongst minority ethnic groups there are still marked gender differences in smoking behaviour. Rates are low, in particular, among south Asian women, however research conducted by Action on Smoking and Health (ASH) Scotland has indicated that smoking is escalating among south Asian girls in Scotland, particularly in young Pakistani women.<sup>169</sup>

ASH Scotland has conducted a mapping exercise to identify smoking cessation projects, services, resources and training courses available to individuals from ethnic subgroups. Although some material was identified which had been specifically targeted to ethnic subgroups (mostly leaflets), generally, mainstream tobacco services were not attracting representative proportions of individuals from ethnic subgroups.<sup>170</sup>

## 8 Alcohol

### 8.1 ALCOHOL AND CARDIOVASCULAR RISK

Excess alcohol consumption is a well-established risk factor for cardiovascular disease, as well as being a causal factor in more than 200 disease and injury conditions. Worldwide, 3.3 million deaths per year result from harmful use of alcohol, representing 5.9% of all deaths.<sup>171</sup>

The effects of alcohol on other long-term conditions, for example, mental health, liver disease and cancer are not considered in this guideline but should be taken into account when providing advice in a clinical setting.

There is considerable confusion over the definition of a standard unit of alcohol. One unit of alcohol in the UK means a beverage containing 8 g or 10 ml of ethanol. The amount of alcohol in units is calculated as: volume of drink (litres) x percentage by volume alcohol.<sup>1</sup> There is a commonly held belief that half a pint of beer, or one glass of wine equate to a unit, but exact strength and volume are critical, as the examples in Table 6 illustrate (*see Annex 4*). Drinks poured at home are often larger than standard pub measures.

Table 6: Volumes of drinks equivalent to one unit of alcohol

Drink	Percentage alcohol	Volume equivalent to one unit
Beer/lager	3.5%	0.5 pint
Beer/lager	5.0%	0.35 pint
Wine	10%	100 ml (one 750 ml bottle = 7.5 units)
Wine	13%	77 ml (one 750 ml bottle = 9.75 units)
Fortified wine/sherry	17.5%	57.1 ml
Spirits	40%	25 ml

✓  Examples of what constitutes a 'drink' or unit of alcohol should be given to the patient.

Most adults in Scotland consume alcohol with men reporting an average of 17.2 units of alcohol per week and women reporting an average of 8.7 units per week. Thirty six per cent of men and 17% of women report drinking at harmful or hazardous levels (defined as more than 14 units of alcohol consumption per week in men and women).<sup>1</sup>

#### 8.1.1 EFFECTS OF ALCOHOL CONSUMPTION LEVELS ON CARDIOVASCULAR DISEASE MORTALITY AND MORBIDITY

Systematic reviews of cohort and case-control studies show a 'J'-shaped relationship between alcohol consumption and cardiovascular risk of mortality and morbidity.<sup>172-177</sup> However, there are social considerations, individual factors and likely unmeasured covariates that act as confounding variables in these studies. 2-  
2++  
2+

A systematic review and meta-analysis of prospective cohort studies showed a lower risk of all-cause mortality for light to moderate drinkers compared with non-drinkers. There was a 'J'-shaped association with the lowest risk associated with consumption of 2.5–14.9 g/day (approximately one to one and a half drinks per day) (RR 0.83, 95% CI 0.80 to 0.86) compared with non-drinkers and an elevated risk for consuming >60 g/day (approximately five or more drinks per day) (RR 1.30, 95% CI 1.22 to 1.38). Risk of cardiovascular mortality was lowered in a dose-dependent relationship ranging from 29% in studies reporting <2.5 g/day alcohol consumption to 15% in studies reporting 30–60 g/day alcohol consumption.<sup>172</sup> 2-

Another systematic review showed that compared with no alcohol intake, low alcohol intake (<15 g/day) was associated with a lower risk of total stroke (RR 0.85, 95% CI 0.75 to 0.95), ischaemic stroke (RR 0.81, 95% CI 0.74 to 0.90) and stroke mortality (RR 0.67, 95% CI 0.53 to 0.85), but no significant association with haemorrhagic stroke (RR 0.96, 95% CI 0.74 to 1.24). Heavy alcohol intake (>30 g/day) was associated with an increased risk of total stroke (RR 1.20, 95% CI 1.01 to 1.43) but it had no significant associations with haemorrhagic stroke, ischaemic stroke or stroke mortality.<sup>173</sup> 2++

Epidemiological studies have reported that alcohol consumption is associated with blood pressure with evidence of a 'J'-shaped curve suggesting cardioprotection at low levels of consumption in women, but not in men.<sup>178</sup> A meta-analysis of 15 RCTs showed that alcohol reduction was associated with a significant and dose-dependent reduction in mean systolic and diastolic blood pressures.<sup>179</sup>

1-

It has been suggested that the apparent cardioprotective effect of alcohol may be accounted for by methodological flaws in the evidence. There may be a bias towards the publication of studies which identify a benefit, suggesting that intakes lower than the maximum reported may be optimal.<sup>146</sup> Abstainers may have higher rates of pre-existing ill health (ie reverse causality), which would result in relatively poorer outcomes in comparative studies with alcohol drinkers.<sup>180</sup>

2++

Mendelian randomisation is used as a tool to try and overcome some of the limitations in existing observational studies, as allocation of genetic variants is random with regard to potential confounders. A recent Mendelian randomisation analysis of 56 epidemiological studies which included a total of 261,991 participants considered carriers of the rs1229984 variant in the alcohol dehydrogenase 1B gene (*ADH1B*), which encodes an enzyme involved in the primary pathway of alcohol metabolism.<sup>181</sup> This gene variant has been associated with reduced consumption of alcohol due to unpleasant side effects.

The analysis reported that carriers of this variant consumed 17.2% fewer units of alcohol per week (95% CI -18.9% to -15.6%), had a lower prevalence of binge drinking and higher abstinence than non-carriers. Carriers also had significantly lower systolic blood pressure (0.88 mm Hg, 95% CI -1.19 to 0.56), odds of hypertension (OR 0.94, 95% CI 0.91 to 0.98), odds of CHD (OR 0.90, 95% CI 0.84 to 0.96), non-HDL cholesterol (-0.03 mmol/l, 95% CI -0.05 to -0.01), and also lower waist circumference and BMI. Carriers had lower odds of ischaemic stroke (OR 0.83, 95% CI 0.72 to 0.95) but no association with combined subtypes of stroke (OR 0.98, 95% CI 0.90 to 1.07) was found. These effects remained the same across all categories of alcohol consumption. When analysis was restricted to non-drinkers there was no association between carriage of the polymorphism and CHD (OR 0.98, 95% CI 0.88 to 1.10). This is consistent with the assumption that the associations ascribed to the *ADH1B* variant are mainly due to alcohol consumption.

3

Evidence is consistent in showing that heavy drinking is associated with the highest risk of CVD and that light to moderate consumption carries a lower risk. However evidence from studies which reduce the limitations of traditional observational data has challenged the view that light to moderate alcohol consumption confers reduced risk of cardiovascular disease compared with abstinence. Individuals with a genetic predisposition to consume less alcohol had a reduced risk of CHD and ischaemic stroke, and lower levels of established and emerging risk factors for cardiovascular disease. These findings suggest that reductions of alcohol consumption, even for light to moderate drinkers, may be beneficial for cardiovascular health.

**R** Patients with or without evidence of cardiovascular disease should be advised to reduce alcohol consumption and that even light to moderate alcohol consumption may increase cardiovascular risk.

✓ When giving advice to patients with coronary heart disease, national health promotion advice should be followed.<sup>182</sup>

- Men and women are advised not to drink regularly more than 14 units per week to keep health risks from drinking alcohol to a low level.
- If you do drink as much as 14 units per week, it is best to spread this evenly over three days or more. If you have one or two heavy drinking sessions, you increase your risks of death from long-term illnesses and from accidents and injuries.
- The risk of developing a range of illnesses (including, for example, cancers of the mouth, throat and breast) increases with any amount you drink on a regular basis.
- If you wish to cut down the amount you're drinking, a good way to help achieve this is to have several drink-free days each week.

## 8.1.2 METHODS OF MODIFYING ALCOHOL CONSUMPTION

Three systematic reviews consider methods of reducing alcohol intake in those whose drinking is considered to be harmful or risky.<sup>183-185</sup> All conclude that brief interventions are the most effective method with increased benefit from multicontact interventions. One review concluded that for benefit an intervention had to include two of the three key elements: feedback, advice and goal setting.<sup>160</sup> Many of the individual studies included in the reviews were not UK-based and some reviews included interventions which may not be deliverable in primary care in the UK (for example electric aversion therapy).

1++  
1+  
2++

Brief interventions may include some of the following: information, feedback and advice on prevalence of drinking, adverse effects of alcohol, drinking cues, drinking diaries, drinking agreement/contract, retrospective self report of drinking alcohol or current alcohol quantities and types of alcohol consumed, injuries, healthcare utilisation, recommended levels of alcohol consumption, education on risks involved in consumption of alcohol, strategies for changing drinking habits, feedback of personal health data.<sup>186,187</sup>

There is a range of suggested timescales for brief interventions from five minutes to 20 minutes, from a single occasion up to five sessions, and vary from face to face to by telephone.

A single RCT of participants with type 2 diabetes and/or hypertension confirmed the benefit of multicontact, brief counselling to reduce alcohol consumption in high-risk individuals (11% absolute reduction in numbers of heavy drinkers in the intervention group).<sup>187</sup>

1++

One review specifically looked at the effectiveness of untargeted screening prior to delivering a brief intervention to modify alcohol consumption.<sup>186</sup> It found that of 1,000 patients 90 screened positive, 25 of whom qualified for a brief intervention. At one year, two or three of these would have reduced their drinking to within the recommended alcohol intake levels.

1+

**R** Brief multicontact interventions should be used to encourage patients to reduce their levels of drinking if their current intake is hazardous to their health.

✓ Universal screening as a case-finding exercise in primary care is not recommended.

## 9 Antiplatelet therapy

### 9.1 ANTIPLATELET AGENTS FOR PEOPLE WITH ESTABLISHED CARDIOVASCULAR DISEASE

The favourable benefit to risk profile of aspirin for patients with established cardiovascular disease is well recognised. In meta-analyses, the Antithrombotic Trialist's (ATT) Collaboration showed clear evidence of a reduction in all-cause mortality, vascular mortality, non-fatal reinfarction of the myocardium, and non-fatal stroke in people with acute coronary syndrome, stroke, transient ischaemic attacks (TIAs), or other vascular disease.<sup>188,189</sup> The trials used aspirin doses of 50–325 mg/day. The meta-analysis provided no evidence of any greater benefit from high-dose aspirin, while adverse effects from aspirin are minimised at lower dosages.

1++

A meta-analysis compared the benefit and gastrointestinal risk of low dose (<325 mg aspirin) use for the secondary prevention of thromboembolic events. It showed that aspirin reduced all-cause mortality by 18%, the number of strokes by 20%, myocardial infarctions by 30%, and other vascular events by 30%. Patients who took aspirin were 2.5 times more likely than those in the placebo group to have gastrointestinal tract bleeding. The number needed to treat (NNT) for aspirin to prevent one death from any cause of mortality was 67, while 100 needed to be treated to detect one non-fatal gastrointestinal tract bleed.<sup>190</sup>

1++

The evidence supports daily doses of aspirin in the range of 75–325 mg for the long-term prevention of serious vascular events in high-risk people, and it is usual practice to prescribe 75 mg daily. Although there is no clinical trial evidence of treatment beyond a few years, there is likely to be ongoing benefit, so it is usual to continue aspirin therapy for life.

**R** Individuals with established atherosclerotic disease should be offered treatment with 75 mg aspirin daily.

The P2Y<sub>12</sub>-receptor antagonist clopidogrel was equivalent to aspirin in prevention of further events in patients with CHD or ischaemic stroke.<sup>191</sup> In a subgroup analysis, clopidogrel appeared to be more effective than aspirin among patients with peripheral vascular disease, although the study was not powered to detect a significant effect in any subgroup. Clopidogrel should be used as monotherapy if aspirin causes side effects.<sup>191</sup>

1+

✓ Clopidogrel should be considered in patients with symptomatic cardiovascular disease who have aspirin hypersensitivity or intolerance or in whom aspirin causes unacceptable side effects.

A P2Y<sub>12</sub>-receptor antagonist is recommended in combination with aspirin in patients with proven troponin-positive acute coronary syndrome for six months following the acute event. Longer durations may be used where the risks of atherothrombotic events outweigh the risk of bleeding. Shorter durations may be used where the risks of bleeding outweigh the risk of atherothrombotic events (*see SIGN guideline number 148 on acute coronary syndrome*).<sup>15</sup>

4

Meta-analysis of two large RCTs with 20,000 patients in each showed that starting daily aspirin (160–300 mg) promptly in patients with suspected acute ischaemic stroke reduced the immediate risk of further stroke or death in hospital and the overall risk of death or dependency.<sup>192</sup> Odds of recurrent ischaemic stroke were reduced by 30% in the group taking aspirin (OR 0.70,  $p < 0.000001$ ; ARR 0.7%). Death without further stroke was reduced by 8% (OR 0.92,  $p = 0.05$ ; ARR 0.4%). In total there was a net decrease of 11% in the overall risk of further stroke or death in hospital (OR 0.89,  $p = 0.001$ ; ARR 0.9%).

1++

One RCT assigned patients to aspirin (30–325 mg daily, median 75 mg) with ( $n = 1,363$ ) or without ( $n = 1,376$ ) dipyridamole (200 mg twice daily) within six months of a transient ischaemic attack or minor stroke of presumed arterial origin.<sup>193</sup> Combination therapy with aspirin and dipyridamole reduced the composite outcome of death from all vascular causes, non-fatal stroke, non-fatal MI or major bleeding complication by 20% (HR 0.80, 95% CI 0.66 to 0.98; ARR 1.0% per year, 95% CI 0.1 to 1.8).

1++

A large RCT followed up individuals aged over 55 who had experienced an ischaemic stroke within less than 90 days before randomisation and allocated them to receive aspirin (25 mg) plus extended-release dipyridamole (200 mg) twice daily (n=10,181) or clopidogrel (75 mg) daily (n=10,151). The mean duration of follow-up was 2.5 years (range, 1.5 to 4.4). There was no significant difference between groups for primary (first recurrence of stroke) or secondary (composite of stroke, myocardial infarction, or death from vascular causes) outcomes. Recurrent stroke occurred in 916 patients (9.0%) receiving aspirin plus dipyridamole and in 898 patients (8.8%) receiving clopidogrel (HR 1.01, 95% CI 0.92 to 1.11). The secondary outcome occurred in 1,333 patients (13.1%) in each group (HR for aspirin/dipyridamole 0.99, 95% CI, 0.92 to 1.07). No statistically significant differences were recorded in safety outcomes between groups, although adverse events leading to permanent discontinuation of the study medication were more common in the group receiving aspirin plus dipyridamole (1,650 patients, 16.4%) compared with the group receiving clopidogrel (1,069 patients, 10.6%). The rate of new or worsening congestive heart failure was significantly lower in the group receiving aspirin plus dipyridamole (144 patients, 1.4%) than in the group receiving clopidogrel (182 patients, 1.8%) (HR 0.78, 95% CI, 0.62 to 0.96).<sup>194</sup>

1++

**R** Individuals with a history of stroke or transient ischaemic attack and who are in sinus rhythm should be considered for treatment with clopidogrel 75 mg daily or combination of low dose aspirin (75–300 mg daily) and dipyridamole (200 mg twice daily) to prevent stroke recurrence and other vascular events.

## 9.2 ANTIPLATELET AGENTS FOR PEOPLE WITHOUT CARDIOVASCULAR DISEASE

A health technology appraisal of nine systematic reviews, which mostly include the same nine major trials, and a meta-analysis of three further RCTs of aspirin for the primary prevention of CVD noted that aspirin doses used varied from 75–500 mg/day, and from 100–325 mg on alternate days, and the rate of cardiovascular events in the control arms differed by a factor of ten between trials.<sup>195</sup> The overview reported results from several meta-analyses across multiple outcomes. All included studies were formally appraised and rated as high quality. Given that most of the included reviews incorporated the same trials, a selection of important results is noted below.

1++

All-cause mortality in those receiving aspirin was marginally reduced by 6% compared with placebo, a result which is only of borderline statistical significance (RR 0.94, 95% CI 0.88 to 1.00). Pooling data from several meta-analyses yielded an absolute risk estimate of 33–46 deaths avoided over ten years per 10,000 patients treated. Individual patient data in the ATT Collaboration, which was also included in this analysis, is consistent with this, with 30 deaths avoided per 10,000 patients treated for 10 years (or a 10-year likelihood of survival increased from 94.7% to 95% with aspirin), although this analysis included only 6 of the 9 RCTs analysed in the other reviews.<sup>196</sup>

Major cardiovascular events (MCE), defined as the composite of non-fatal MI, non-fatal stroke or cardiovascular death, were non-significantly reduced by 14% (OR 0.86, 95% CI -26 to 1%).<sup>197</sup> Assuming a control group risk of 3.25% (random-effects pooled estimate) and OR of 0.86, the NNT to avoid an event was calculated at 226 and would result in 64 fewer events among 10,000 people over 10 years. Other study-level meta-analyses of the same group of RCTs show an odds ratio of 0.90 (95% CI 0.85 to 0.96) for the same composite end point which was statistically significant, yielding an NNT of 253 and 57 fewer events per 10,000 individuals over 10 years.<sup>198</sup> Using a pooled estimate of risk for the control group of 5.84%, 84 such events may be avoided per 10,000 patients treated for 10 years. Individual patient data analysis from the ATT Collaboration showed the pooled yearly event rate ratio to be 0.88 (95% CI 0.82 to 0.94) for the composite end point, and an absolute difference of 70 events avoided for 10,000 persons followed up for 10 years. The same analysis showed a relative risk of 0.82 (95% CI 0.75 to 0.90) for the combined end point of non-fatal MI or CHD death, and the corresponding absolute benefit of 55 events avoided for 10,000 persons over 10 years.<sup>196</sup>

Stroke mortality was increased with aspirin treatment (RR 1.23, 95% CI 0.84 to 1.74) although this was not statistically significant. In the ATT Collaboration analysis, ischaemic strokes were reduced by aspirin (RR 0.86, 95% CI 0.74 to 1.00, p=0.05) while haemorrhagic strokes were increased by 32% (RR 1.32, 95% CI 1.00 to 1.75, p=0.05). Due to both comparisons including confidence limits of 1.0, a null effect cannot be ruled out.<sup>196</sup>

Assessment of the risk of bleeding events is not straightforward due to the differences in definitions of bleeding used in the primary prevention trials, some using major bleeding and others using non-trivial bleeding. In addition there were significant differences in the bleeding risks in the control arms of the studies, as well as variable (and non-dose-related) responses to aspirin. The meta-analyses are consistent in their findings of a statistically significant increase in bleeding. The relative risk for major bleeding with aspirin was 1.62 (95% CI 1.31 to 2.00). The number of extra major bleeds was estimated to be 46–49 per 10,000 individuals followed for 10 years.<sup>198,199</sup> The analysis of the individual patient data by the ATT showed an RR of 1.54 (95% CI 1.30 to 1.82) with aspirin, and an absolute excess of major bleeds of 35 per 10,000 people over 10 years.<sup>196</sup>

Table 7 describes risk ratios for patient-level variables associated with major gastrointestinal or other extracranial bleeds

*Table 7: Rate ratios associated with risk factors for bleeding in people with no known vascular disease in primary prevention trials*

Variable	Major or other extracranial bleed (95% CI)
Age (per decade)	2.15 (1.93 to 2.39)
Male sex	1.99 (1.45 to 2.73)
Diabetes mellitus	1.55 (1.13 to 2.14)
Current smoker	1.56 (1.25 to 1.94)
Mean blood pressure (per 20 mm Hg)	1.32 (1.09 to 1.58)
Cholesterol (per 1 mmol/l)	0.99 (0.90 to 1.08)
Body mass index (per 5 kg/m <sup>2</sup> )	1.24 (1.13 to 1.35)

*Adapted from Sutcliffe P, Connock M, Gurung T, Freeman K, Johnson S, Kandala NB, et al. Aspirin for prophylactic use in the primary prevention of cardiovascular disease and cancer: a systematic review and overview of reviews. Health Technology Assessment (Winchester, England) 2013;17 (43):1-253.*

The number of excess gastrointestinal bleeds over 10 years varied from 68–117 per 10,000 people treated depending on the method of calculation of the risk in the control group.<sup>199</sup> Haemorrhagic strokes were increased with a RR of 1.32 (95% CI 1.00 to 1.75), estimating an excess of these events of eight per 10,000 people treated over 10 years.<sup>196</sup>

A summary of benefits and harms was calculated by aggregating the rate of averted or of incurred events from study-level data and is shown in Table 8.<sup>195</sup>

*Table 8: Events averted or incurred with aspirin use for 10,000 persons with no known vascular disease followed up for 10 years*

Benefits	Harms
36–46 deaths averted	30–49 major bleeds
60–84 MCE averted	68–117 gastrointestinal bleeds
	8–25 haemorrhagic strokes

**R** Aspirin is not recommended for primary prevention of cardiovascular disease.

1<sup>++</sup>

### 9.3 ANTIPLATELET AGENTS FOR PEOPLE WITH DIABETES

A health technology appraisal identified seven meta-analyses which provided data on the benefits and harms of aspirin when taken by individuals with diabetes who are without cardiovascular disease.<sup>195</sup> Aspirin use was associated with no significant reduction in total mortality, cardiac deaths or ischaemic stroke in any of the included meta-analyses. Pooled point estimates for reduction in MCE were all around 10%, however all of the upper confidence limits included the possibility of no improvement, and, in some cases, implied the possibility of greater risk from aspirin. Bleeding risks were variously defined in different meta-analyses, but in each case, the pooled point estimates for these outcomes were strongly in favour of the comparator (RR approximately 2 to 3), but were associated with considerable uncertainty so that effect sizes were statistically insignificant and the 95% lower confidence interval encompassed protection by aspirin.

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Improvement in precision and confidence of treatment in people with diabetes is anticipated with the results of large ongoing RCTs. Until these trials publish, it is vital to consider both the absolute benefits and risks of aspirin on an individual basis, as for non-diabetic patients.

**R** Aspirin is not routinely recommended in people with diabetes who do not have a diagnosis of cardiovascular disease.

### 9.4 ANTIPLATELET AGENTS FOR PEOPLE WITH HYPERTENSION

In contrast to the benefits of antiplatelet therapy with aspirin in those with established cardiovascular disease, there is a paucity of data on the primary prevention of cardiovascular events in individuals with hypertension. A Cochrane review of antiplatelet agents and anticoagulants for patients with hypertension identified four trials, with only a single RCT reporting on total mortality and showing no effect compared with placebo. It also reported a non-significant reduction in cardiovascular events (pooled OR 0.92, 95% CI 0.81 to 1.05; two trials) and stroke (pooled OR 0.94, 95% CI 0.76 to 1.17; two trials), but a statistically significant excess of both major (calculated OR 1.85, 95% CI 1.38 to 2.48, absolute risk increase 0.65%; one trial) and minor non-fatal bleeding (calculated OR 1.80, 95% CI 1.39 to 2.35, absolute risk increase 0.73%; one trial).<sup>200</sup>

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**R** Aspirin is not recommended for primary prevention of cardiovascular disease in patients with hypertension.

### 9.5 ANTIPLATELET AGENTS FOR PEOPLE WITH CHRONIC KIDNEY DISEASE

A systematic review included data on a number of studies of antiplatelet therapy for CKD, but these were almost all conducted in patients with established vascular disease.<sup>201</sup> The only analysis of primary prevention with aspirin in patients with CKD which was specifically identified in this review was derived from a subgroup of the Hypertension Optimal Treatment (HOT) study. The findings were similar to the overall trial in showing a reduction in MI (when silent MI was excluded) but no significant benefit to overall mortality and with a doubling of risk of major haemorrhage compared with placebo.

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There is insufficient evidence to form a recommendation on the use of aspirin for primary prevention of cardiovascular disease in individuals with CKD.

# 10 Lipid lowering

## 10.1 THE ROLE OF TOTAL AND LOW-DENSITY LIPOPROTEIN CHOLESTEROL IN CARDIOVASCULAR DISEASE

The link between cardiovascular risk and variation in blood lipid concentration was shown in a study of over 356,000 men aged 35–57 years who were followed up for six years. The study demonstrated a continuous, graded, strong relationship between serum cholesterol and six-year age-adjusted CHD mortality.<sup>202</sup> This relationship persisted in smokers and non-smokers, people with and without hypertension and was evident irrespective of the presence or absence of vascular disease.<sup>203–205</sup>

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Other epidemiological evidence has shown that populations with higher cholesterol levels experience more atherosclerosis and CHD than populations with lower levels<sup>206</sup> and the higher the level of cholesterol, the greater the risk of a coronary event.<sup>202</sup>

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Low-density lipoprotein cholesterol usually makes up 60–70% of total serum cholesterol and the strong relationship between total cholesterol level and CHD suggests that LDL cholesterol is a powerful risk factor.<sup>207</sup> The role of LDL cholesterol in atherosclerosis is confirmed by studies carried out in individuals with genetic disorders that result in extreme elevations of cholesterol levels, such as FH.<sup>208</sup> These individuals tend to develop premature CHD with evidence of advanced atherosclerosis even in the absence of any other risk factor for coronary disease.

Genetic variants which affect LDL cholesterol provide further evidence of the causal relationship between LDL cholesterol and cardiovascular disease.<sup>209</sup> There is also strong evidence to support the role that not only LDL cholesterol but other triglyceride-rich apolipoprotein B-carrying particles also play a causal role in cardiovascular disease and non-HDL cholesterol (which includes all apo-B-carrying lipoproteins) is a powerful predictor of cardiovascular events (*see section 10.2*).<sup>210</sup>

## 10.2 MEASURING LIPID LEVELS

Most biochemistry laboratories directly measure total cholesterol, HDL cholesterol and triglycerides but not LDL cholesterol. Low-density lipoprotein cholesterol can be calculated indirectly by measuring total cholesterol, HDL cholesterol and triglycerides (TG) from a fasting venous blood sample and applying the Friedewald equation:  $LDL = TC - HDL - (TG/2.2)$  (all in mmol/l) where TG/2.2 approximates to very low-density lipoprotein cholesterol levels.<sup>188</sup> This method is not suitable for individuals with TG levels >4.5 mmol/l. Non-HDL cholesterol is calculated as  $TC - HDL$ .

Given the practical problems of routinely collecting 12-hour fasting samples, non-fasting blood samples are generally collected for estimation of TC and HDL cholesterol and this approach is suitable for cardiovascular risk estimation in the vast majority of individuals. Prediction of cardiovascular events is more accurate when total cholesterol and HDL cholesterol are included (for example, by the TC:HDL ratio, as in the JBS3 and QRISK2 risk calculators, or non-HDL cholesterol, as in ASSIGN) rather than using calculated LDL cholesterol alone.<sup>211</sup> Accurate estimation of LDL cholesterol requires a full lipid profile to be carried out on a fasting venous blood sample as HDL cholesterol and TG levels vary between fasting and non-fasting states. HDL cholesterol is lower by 5% to 10% in the non-fasting state than in the fasting state and TG levels are 20–30% higher. It should, however, be recognised that in specific situations, such as pretreatment investigation of those with total cholesterol >7.5 mmol/l in whom a diagnosis of FH is considered or for LDL cholesterol-based cascade testing in relatives of an individual with FH, fasted blood sampling remains clinically useful. The accuracy of measuring HDL cholesterol in the context of high triglyceride levels may be compromised. Intercurrent illness may also affect circulating lipid levels.

✓ A lipid profile taken to assess cardiovascular risk should include total cholesterol, HDL cholesterol and triglycerides and should not be taken at the time of intercurrent illness.

### 10.3 LOWERING CHOLESTEROL TO REDUCE CARDIOVASCULAR RISK

There is strong evidence from both genetic studies and RCTs of various medicines to support the role of lowering LDL cholesterol to reduce cardiovascular risk. Genetic studies provide evidence that lifelong lower LDL cholesterol results in reductions in cardiovascular events.<sup>25,209</sup> Statin therapy (see section 10.4) has been shown to reduce major atherosclerotic cardiovascular events and the need for arterial revascularisation by about 20–25% per 1 mmol/l reduction in LDL cholesterol in meta-analyses of numerous RCTs, while other approaches to LDL cholesterol lowering such as bile acid sequestrants and ezetimibe have also demonstrated benefit in trials (see sections 10.6.1 and 10.6.2).<sup>212,213</sup>

An extensive systematic review and meta-analysis quantifying the effect of cholesterol lowering on the risk of vascular events in patients with and without CVD emphasised the importance of cholesterol reduction, in itself, rather than treatment modality.<sup>214</sup> Evidence for lipid-lowering drugs other than statins is presented in section 10.6.

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### 10.4 STATIN THERAPY

#### 10.4.1 THE EFFECTS OF STATINS ON LDL CHOLESTEROL

Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) are central to lipid-lowering therapy for the prevention of first and recurrent vascular events. Statins inhibit cholesterol synthesis in the liver, increasing hepatocyte LDL receptor expression and thereby increasing hepatic uptake of LDL cholesterol from the circulation. The primary action of statins is to lower LDL cholesterol with only small effects on HDL cholesterol or triglyceride levels.

A meta-analysis of 164 short-term RCTs of lipid lowering by different statins showed the absolute LDL-cholesterol reduction achieved with different doses of different statins (see Table 9).<sup>214</sup> The reductions in LDL cholesterol are dose dependent and log linear, so that with each doubling of the dose of statin, LDL levels fall by approximately 6%.

Table 9: Absolute reductions (mmol/l) (95% confidence intervals) and percentage reductions in serum LDL cholesterol concentration according to statin and daily dose

Statin	Daily dose (mg)				
	5	10	20	40	80
<b>atorvastatin</b>	1.51 (1.28 to 1.74) 31%	1.79 (1.62 to 1.97) 37%	2.07 (1.90 to 2.25) 43%	2.36 (2.12 to 2.59) 49%	2.64 (2.31 to 2.96) 55%
<b>fluvastatin</b>	0.46 (0.18 to 0.75) 10%	0.74 (0.55 to 0.93) 15%	1.02 (0.90 to 1.13) 21%	1.30 (1.19 to 1.41) 27%	1.58 (1.40 to 1.76) 33%
<b>pravastatin</b>	0.73 (0.54 to 0.92) 15%	0.95 (0.83 to 1.07) 20%	1.17 (1.10 to 1.23) 24%	1.38 (1.31 to 1.46) 29%	1.60 (1.46 to 1.74) 33%
<b>rosuvastatin</b>	1.84 (1.74 to 1.94) 38%	2.08 (1.98 to 2.18) 43%	2.32 (2.20 to 2.44) 48%	2.56 (2.42 to 2.70) 53%	2.80 (2.63 to 2.97) 58%
<b>simvastatin</b>	1.08 (0.93 to 1.22) 23%	1.31 (1.22 to 1.40) 27%	1.54 (1.46 to 1.63) 32%	1.78 (1.66 to 1.90) 37%	2.01 (1.83 to 2.19) 42%

Percentage reductions are independent of pretreatment LDL-cholesterol concentration and are based on an average baseline LDL level of 4.8 mmol/l.

Table reprinted from Law MR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 2003;326 (7404):1423 with permission from BMJ Publishing Group Ltd.

#### 10.4.2 THE EFFECTS OF STATINS ON CARDIOVASCULAR END POINTS

Meta-analyses of individual patient data from randomised, placebo-controlled, double-blinded trials of statins which have included those with and without established vascular disease show a consistent relative reduction in clinical end points across the spectrum of baseline cardiovascular risk.<sup>25</sup> Treatment with various statin regimens yielded a mean difference in LDL cholesterol between the treatment and control groups of 1.07 mmol/l at one year from average baseline LDL cholesterol of 3.7 mmol/l. This was associated with an annual reduction in first major vascular events (non-fatal myocardial infarction, coronary death, stroke or coronary revascularisation) from 3.6% to 2.8%, and an overall weighted average of 21% fewer vascular events per 1 mmol/l reduction in LDL cholesterol over a median of five years with reductions of 27% in non-fatal MI and 20% in coronary deaths

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Various subgroups have been studied in further detail and the results remain consistent. This meta-analysis<sup>25</sup> included subgroup analyses of major CVD events according to sex, age (<65, 65–75, >75 years), systolic (<140, 140–160, >160 mm Hg) and diastolic (<80, 80–90, >90 mm Hg) blood pressure, smoking status, eGFR (<60, 60–90, >90 mL/min/1.73 m<sup>2</sup>) and, importantly, baseline LDL cholesterol (<2.0, 2.0–2.5, 2.5–3.0, 3.0–3.5, >3.5 mmol/l). Relative benefit per mmol/l reduction in LDL cholesterol was similar across all subgroups.

Proportional reductions in cardiovascular events for any given reduction in LDL cholesterol are as large for those at lower risk as populations at higher risk and there is clear evidence for cardiovascular benefit even at event rates of <5% over five years.<sup>215</sup> Individuals at higher levels of absolute risk consequently gain more absolute risk reduction from statin intervention than those at lower levels.

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#### 10.4.3 STATIN THERAPY FOR INDIVIDUALS WITHOUT CARDIOVASCULAR DISEASE

Individual RCTs have established that primary prevention with statins reduces major clinical end points. A meta-analysis of 18 trials, including almost 57,000 individuals, demonstrated the magnitude of the clinical effectiveness of this therapy, mostly in those identified as being at relatively high risk of coronary events due to existing risk factors.<sup>216</sup>

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In individual patient data meta-analysis of 70,025 statin trial participants, first major vascular events were reduced by 25% per 1 mmol/l lower LDL cholesterol, similar to that achieved in those with pre-existing CHD (21% reduction per 1 mmol/l lower LDL cholesterol).<sup>25</sup>

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Given this effect, for an individual the absolute reduction in CVD risk will be dependent on both their baseline cardiovascular risk and their level of LDL cholesterol with those at higher levels accruing greater absolute risk reduction compared with those at lower levels for the same statin regimen. Table 10 demonstrates expected LDL cholesterol and CVD risk reductions (after the first year of treatment) associated with different statins at a range of doses across two sample levels of baseline LDL cholesterol.

Table 10: Absolute LDL-cholesterol reduction (mmol/l) and approximate CVD risk reduction (%) associated with statin therapy at different doses (mg) and baseline LDL cholesterol levels (mmol/l)

Statin/ dose	5		10		20		40		80	
	2	4	2	4	2	4	2	4	2	4
<b>atorvastatin</b>										
LDL-c reduction	0.6	1.2	0.7	1.5	0.9	1.7	1.0	2.0	1.1	2.2
CVD reduction	16%	29%	18%	35%	23%	39%	25%	44%	27%	47%
<b>fluvastatin</b>										
LDL-c reduction	0.2	0.4	0.3	0.6	0.4	0.8	0.5	1.1	0.7	1.3
CVD reduction	6%	11%	8%	16%	11%	22%	13%	27%	18%	31%
<b>pravastatin</b>										
LDL-c reduction	0.3	0.6	0.4	0.8	0.5	1.0	0.6	1.2	0.7	1.3
CVD reduction	8%	16%	11%	22%	13%	25%	16%	29%	18%	31%
<b>rosuvastatin</b>										
LDL-c reduction	0.8	1.5	0.9	1.7	1.0	1.9	1.1	2.1	1.2	2.3
CVD reduction	22%	35%	23%	39%	25%	42%	27%	45%	29%	48%
<b>simvastatin</b>										
LDL-c reduction	0.5	0.9	0.5	1.1	0.6	1.3	0.7	1.5	0.8	1.7
CVD reduction	13%	23%	13%	27%	16%	31%	18%	35%	22%	39%

LDL cholesterol and risk reductions apply from year two of treatment.

Risk reduction calculated as  $1 - 0.75^{\text{LDL-cholesterol reduction in mmol/l}}$  based on the Cholesterol Treatment Trialists' (CTT) Collaboration meta-analyses. Absolute LDL cholesterol reduction based on percentage reductions in Table 9 and baseline LDL cholesterol of either 2 or 4 mmol/l

One meta-analysis presented data on first major cardiovascular events according to strata of CVD risk (specifically five-year CVD event risks of <5, 5–10, 10–20, 20–30 and >30%).<sup>215</sup> Cardiovascular benefit was also demonstrated in those in the lower absolute risk groups. In those with five-year risk <5%, first major CVD events were reduced by 38%, coronary events by 43% and revascularisation by 48% per 1 mmol/l lower LDL cholesterol. Similarly, in those with 5–10% five-year risk, major CVD events were reduced by 31%, coronary events by 39% and revascularisation by 37% per 1 mmol/l lower LDL cholesterol. These two lowest risk groups were combined for analysing stroke events and this provided a similar 24% reduction. It should be noted that the lowest risk group (<5% CVD events over five years) was dominated by the JUPITER trial. As JUPITER was stopped early, it is possible that the CVD benefit in this group is overestimated.

A further meta-analysis used a different definition for low-risk individuals in their study-level analysis of 29 trials with 80,711 participants, namely those with <20% 10-year risk of CVD death or non-fatal MI.<sup>217</sup> Mean 10-year risk of CVD death or non-fatal MI was 6%. Total mortality, non-fatal MI and non-fatal stroke were all reduced by statin therapy with no clear evidence of heterogeneity between higher potency and lower potency statin regimens. Because of the lower event rates in the low-risk group (and hence the lower absolute risk reductions achieved, the number needed to treat to avoid one death was 239, and 153 to avoid a non-fatal MI (compared with NNT 86 and 62, respectively, in meta-analyses of higher-risk groups) over a median of two years. This meta-analysis also compared outcomes of low-potency statins (lovastatin, fluvastatin, pravastatin and simvastatin) with high-potency statins (rosuvastatin and atorvastatin), but did not demonstrate any statistically significant difference in all-cause mortality, fatal or non-fatal MI or stroke between low- and high-potency statins.

Simvastatin and atorvastatin undergo metabolic inactivation by cytochrome P450 (see section 10.4.4) and levels are therefore more likely to be affected by other agents which are metabolised by this pathway, either increasing the risks of toxicity or decreasing their efficacy. Other statins have less potential for drug interactions.

Generic statin interventions are likely to be cost effective at annual levels of vascular disease risk down to 1%.<sup>25</sup>

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The NICE guideline on lipid modification reported that high-intensity statin treatment reduced cardiovascular outcomes to a greater degree than low-intensity statin treatment compared with placebo (cardiovascular mortality – RR 0.73, 95% CI 0.61 to 0.88 v 0.84, 95% CI 0.78 to 0.91, respectively; non-fatal MI – RR 0.46, 95% CI 0.37 to 0.59 v 0.78, 95% CI 0.72 to 0.84, respectively). High-intensity statin treatment using atorvastatin 20 mg is cost effective compared with medium-intensity statin treatment for people who do not have CVD and who have a 10-year QRISK2 cardiovascular risk score above 6.8%. Overall there was no consistent trend for the rates of adverse events and intensity of statin and no increase in myalgia with statin intensity. The NICE guideline development group concluded that high-intensity statins are the most clinically effective option for primary prevention of CVD and are cost effective compared with all other options.<sup>31</sup>

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**R** Adults who are assessed as being at high cardiovascular risk, but with no established CVD, should be offered treatment with atorvastatin 20 mg/day following an informed discussion of risks and benefits between the individual and their responsible clinician. In those already taking an alternative regimen due to reported intolerance with atorvastatin, there is no need to change their current regimen.

- ✓ In individuals without established cardiovascular disease, lifestyle measures to reduce cholesterol levels should be encouraged, irrespective of the need for pharmacological treatment.
- ✓ Secondary causes of dyslipidaemia should be considered and excluded before commencing lipid-lowering drug therapy.

#### 10.4.4 STATIN THERAPY FOR INDIVIDUALS WITH ESTABLISHED CARDIOVASCULAR DISEASE

Individuals with established CVD are at higher risk of future cardiovascular events than those without previous vascular disease. A meta-analysis of data from 170,000 participants in 26 randomised trials of statin therapy showed an annual rate of major vascular events of 1.8% in untreated individuals without previous CVD compared with 5.6% in individuals with established CHD. While CVD event rates are now lower due to secular declines this demonstrates that individuals with CVD are likely to be at significantly higher risk than most individuals without CVD who are estimated to be eligible for preventive treatment by means of formal risk calculation.<sup>25</sup>

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Although the relative reduction in risk of CVD events with statin therapy is approximately constant across all baseline levels of total or LDL cholesterol and cardiovascular risk (per mmol/l reduction in LDL cholesterol), the absolute risk reduction is affected by global cardiovascular risk, with individuals who are at the highest global risk achieving the greatest absolute risk reduction from statins (see Table 1). Individuals who are at high cardiovascular risk, such as those with established symptomatic CVD or those with FH, will gain more benefit from more aggressive lipid lowering than individuals at lower absolute levels of risk.

Multiple major randomised trials have confirmed that statins reduce cardiovascular events in those with established CVD. Relative reductions are similar to those observed in primary-prevention trials. In 87,903 participants with established CHD, major vascular events were reduced by 21% while in 25,920 participants with non-coronary vascular disease, major vascular events were reduced by 19% per 1 mmol/l lower LDL cholesterol in individual participant data analyses.<sup>25</sup>

Based on the relationship between absolute cardiovascular risk and the benefit obtained from LDL-cholesterol reduction, five trials were included in meta-analyses of individual patient data to assess the risks and benefits of more intensive cholesterol-lowering therapy versus standard dosing of statins.<sup>25</sup> All trials were undertaken in patients with coronary disease, three in populations with stable coronary artery disease and two in populations with acute coronary syndrome (ACS), and included 39,612 patients. The mean baseline LDL was 2.5 mmol/l, and the observed annual event rate for major cardiovascular events in the less-intensively treated group varied from 3.8 to 13.1%. Median follow up was 5.1 years. There was a reduction in the absolute annual rate of vascular events from 5.3% with lower-dose statin to 4.5% in the more aggressively treated group, a relative reduction of 15%. The mean difference in LDL-cholesterol levels between the groups at one year was 0.51 mmol/l (or 28% risk reduction per mmol/l lower LDL cholesterol, a figure consistent with the event reductions achieved per mmol/l reduction in placebo- and standard care-controlled trials). There were also significant relative reductions of 19% in revascularisation procedures and 16% in ischaemic stroke.

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Another meta-analysis examined ten trials of intensive- compared with moderate-dose statin treatment.<sup>218</sup> All were secondary-prevention studies, three of which were conducted in patients with ACS. Total mortality and cardiovascular mortality were not significantly reduced overall while, in the ACS trials, mortality was reduced by 25% and cardiovascular deaths by 26%. There was a non-significant 15% reduction in the combined end point of cardiovascular deaths/non-fatal MI in the ACS trials, while the same end point had a highly significant reduction of 10% in the overall analysis of the ten studies. Strokes were reduced by 14% with more-intensive therapy.

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There are no convincing short-term benefits from initiating statins within 14 days of an ACS event, although the benefits of more-intensive therapy in the longer term are clear. To examine short-term benefit, a Cochrane review reported data, at one and four months, from 18 placebo/standard-care-controlled trials (n=14,303) which commenced statins within 14 days of ACS. There was no reduction in all-cause death, MI or stroke though there was an isolated 24% reduction in unstable angina at four months.<sup>219</sup>

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Trials in these meta-analyses used fixed doses of statins (at low dose versus high dose) and cannot directly justify whether statins should be prescribed at the doses used in trials or titrated to achieve LDL targets. However, the size of the proportional reduction in major vascular events is directly related to the absolute LDL-cholesterol reduction achieved (*see Tables 9 and 10*) and suggests that the goal of statin therapy for secondary prevention should be to reduce LDL cholesterol as much as possible without increasing myopathy risk, rather than treating to prespecified targets.

The statins tested in major trials produced broadly similar beneficial outcomes indicating a class, rather than statin-specific effect, with different levels of potency among the different drugs. Statin treatment results in substantial relative reduction in total and LDL cholesterol in all individuals at high risk of any type of major vascular event, irrespective of their pretreatment total or LDL-cholesterol values.

The NICE guideline on lipid modification found that high-intensity statin treatment using atorvastatin 20 mg, 40 mg or 80 mg is cost effective compared with medium-and low-intensity statin treatment and to no treatment for people who already have CVD.<sup>31</sup> While NICE's analysis indicated that atorvastatin 20 mg was the most cost-effective option, this was driven by the assumption of equal efficacy among all high-intensity statins with respect to clinical outcomes, although there is evidence of modest differences in terms of reducing LDL cholesterol levels for different doses (*see Table 9*). However, further threshold analysis showed that atorvastatin 80 mg would be cost effective compared with atorvastatin 20 mg if it was 2% relatively more effective in decreasing CVD events and there was no loss in utility due to greater adverse events. Given the evidence of increased LDL-lowering efficacy associated with atorvastatin 80 mg compared with atorvastatin 20 mg and calculated CVD risk reductions (*see Table 10*) the GDG concluded that the difference in CVD risk reduction between the two regimens was likely to exceed 2% and therefore it may be considered cost effective at a threshold of £20,000 per QALY.

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As simvastatin 80 mg is more expensive than any dose of atorvastatin and there is no evidence for superiority to atorvastatin,<sup>214</sup> and given the evidence of increased risk of myopathy on simvastatin 80 mg,<sup>220</sup> NICE concluded that individuals newly initiated on statin therapy for secondary prevention of CVD should be offered atorvastatin 80 mg.

**R** All patients with established atherosclerotic cardiovascular disease should be offered intensive statin therapy with atorvastatin 80 mg/day following an informed discussion of risks and benefits between the individual and responsible clinician.

✓ Consider a lower dose of atorvastatin in patients at increased risk of adverse effects or drug-drug interactions.

For individuals commenced on statin therapy it would be appropriate to repeat lipid measurements and if there has been a reduction in non-HDL cholesterol of less than 1 mmol/l or 40% to check adherence to medication and lifestyle changes.

## 10.4.5 SAFETY OF STATIN THERAPY

A comprehensive review of all statin trials to date, undertaken by a Task Force of the US National Lipid Association, provides strong support for the safety of statins,<sup>221</sup> which is confirmed by a second meta-analysis.<sup>222</sup> Overall, there was no increased risk of cancer or non-cardiovascular mortality. Raised levels of liver enzymes (aspartate and alanine aminotransferase) to more than three times their upper normal limit occurred in fewer than 1% of participants treated across the dose range of the marketed statins, with the exception of atorvastatin administered at maximal (80 mg) dose and combination statin and ezetimibe therapy (see sections 10.5.2 and 10.6.2). A large-scale meta-analysis of 170,255 patients from 76 placebo/standard-care-controlled trials showed 12% and 30% increases in the reporting of elevated aspartate aminotransferase and alanine aminotransferase respectively.<sup>223</sup> In a meta-analysis of lipid-lowering trials, an absolute increase of 1% was reported for raised transaminases in high- versus moderate-dose statin trials which was largely driven by high-dose atorvastatin. This effect is completely reversible upon withdrawal of treatment.

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Myopathy, with raised levels of creatine kinase to more than ten times the upper normal limit, and rhabdomyolysis (a similar or greater elevation in creatine kinase which leads to renal failure) are very rare. In a meta-analysis of major statin trials with 170,000 participants there were four additional cases of rhabdomyolysis per 10,000 participants in the five trials of more versus less intensive statin therapy (based on 14 cases in 19,829 participants on intensive therapy and six cases in 19,783 participants on less-intensive therapy). All of these cases involved patients taking simvastatin 80 mg daily. In the 21 trials of standard statin therapy versus control there was only one additional case of rhabdomyolysis per 10,000 participants on statins.<sup>25</sup>

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Statins interact with a number of other medications. The risk of myopathy increases when statins are used in combination with gemfibrozil or nicotinic acid (niacin) and these combinations should be avoided.<sup>160</sup> Some statins (particularly atorvastatin and simvastatin) are metabolised by cytochrome P450 3A4 and concomitant use of other potent inhibitors of this enzyme (for example 'azole' anti-fungal agents and human immunosuppressive virus protease inhibitors) may increase plasma levels of these statins and increase the risk of adverse effects, such as myopathy and rhabdomyolysis. The risk of myopathy is also increased when high doses of simvastatin are combined with less potent cytochrome P450 inhibitors, including amiodarone, verapamil, and diltiazem. The consumption of even modest quantities of grapefruit juice can significantly increase exposure to simvastatin, increasing the risk of myopathy. Patients taking atorvastatin should also avoid drinking large quantities of grapefruit juice. These concerns do not apply to fluvastatin, which is metabolised by a different cytochrome P450 enzyme, or to pravastatin and rosuvastatin, which are not substantially metabolised by cytochrome P450.<sup>224</sup>

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Statins should be avoided in:

- patients with active liver disease or persistently abnormal liver function tests (with the important exception of mild non-alcoholic fatty liver disease where statin therapy will often be required and should not be avoided)
- women who are pregnant or likely to be pregnant and in those who are breastfeeding (see section 10.5.3).<sup>160</sup>

Data regarding the risk of haemorrhagic stroke in people on statins are inconclusive. A meta-analysis of 39,612 individuals in five trials reported only 126 first such events.<sup>25</sup> However, by combining results from this meta-analysis with other trials the authors suggested that statins could increase the risk of haemorrhagic stroke, relatively, by 21%. They acknowledge that, although statistically significant, the absolute size of this potential hazard would be about 50 times smaller (perhaps a few extra haemorrhagic strokes annually per 10,000 treated) than the definite absolute benefits (a few hundred occlusive events avoided annually per 10,000 treated) for patients who are at high risk of vascular events. Importantly, ischaemic strokes are far more common than haemorrhagic strokes in Western populations.

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Concerns have been raised about statin treatment increasing the risk of developing diabetes. One meta-analysis reported a new diagnosis of diabetes in 3.8% of statin-treated patients compared with 3.5% on placebo, a significantly increased risk of 9% (17 of 76 trials).<sup>223</sup> A further meta-analysis reported a larger relative increase in risk of 18% in two studies.<sup>216</sup> There is insufficient evidence about any effect of statin therapy on the development of microvascular complications related to diabetes.

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Statins have no effect on non-cardiovascular mortality (RR 0.97, 95% CI 0.92 to 1.03) or on risk of developing cancer (RR 0.99, 99% CI 0.91 to 1.09).<sup>25</sup> A review of data from most of the major randomised trials of statin therapy concluded that lowering LDL cholesterol by 2 mmol/l with statin therapy in 10,000 individuals for five years would cause about five cases of myopathy, 50–100 cases of new-onset diabetes and possibly 5–10 haemorrhagic strokes. However, at the same time statin therapy would prevent 1,000 individuals from suffering a major cardiovascular event in a secondary-prevention population (10% absolute benefit), or 500 individuals in a primary-prevention population at high cardiovascular risk (5% absolute benefit).<sup>225</sup>

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- ✓ Simvastatin 80 mg should not be offered for primary or secondary prevention of CVD due to the risk of myopathy. Any patients currently on this regimen may continue on it if they have been stable for at least one year.
- ✓ Statins should not be prescribed with gemfibrozil.
- ✓ Patients who are using medications that influence cytochrome P450 metabolism should avoid concomitant use of atorvastatin or simvastatin. In such cases, pravastatin or rosuvastatin are acceptable alternative lipid-lowering therapies.
- ✓ Statins should not be offered to:
  - patients with active liver disease or persistently abnormal liver function tests, or
  - women who are pregnant, likely to be pregnant or breastfeeding.

#### 10.4.6 REPORTED INTOLERANCE TO STATIN THERAPY

The evidence from a small number of studies suggests that that the vast majority (70–90%) of patients who report prior statin intolerance (to one or more statins with discontinuation or myopathy or other apparent statin-related side effect) are able to take some form of statin when rechallenged.

In a retrospective analysis of patient records in one observational study, statins were discontinued at least temporarily for 57,292 out of 107,835 patients. Statin-related events were documented for 18,778 (17.4%) patients and 11,124 of these patients discontinued statins at least temporarily. Over the subsequent 12 months 6,579 (59.1%) patients were rechallenged with a statin. Most patients who were rechallenged (92.2%) were still taking a statin 12 months after the statin-related event. Among the 2,721 patients who were rechallenged with the same statin to which they had a statin-related event, 1,295 (47.6%) were on the same statin 12 months later, including 996 (36.6%) on the same or higher dose.<sup>226</sup>

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Another observational, retrospective study of 1,605 patients with self-reported statin intolerance reported that 72.5% of participants who reported intolerance to at least two statins were able to take long-term statin treatment. More patients who were able to comply with long-term statin therapy used rosuvastatin (43%) than any other drug. Intermittent dosing of statin was used by 149 (9.3%) patients and these had significantly smaller LDL-cholesterol reduction compared with the daily dosing group (n=1014, 63.2%) ( $21.3 \pm 4.0\%$  v  $27.7 \pm 1.4\%$ ,  $p < 0.001$ ).<sup>227</sup>

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Minor muscle discomfort is common in people treated with statins, though its incidence varies and the incidence of true statin-related myalgia is disputed.<sup>228,229</sup>

A small RCT recruited 43 patients with documented statin-associated myalgia leading to discontinuation of at least one statin (other than pravastatin) with resolution after discontinuation. Participants were allocated to treatment with either pravastatin or red yeast rice, a lipid-lowering dietary supplement. Of the 22 patients randomised to pravastatin 40 mg/day, only two withdrew from medication owing to myalgia, while one out of 21 discontinued treatment in the group receiving red yeast rice.<sup>230</sup>

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The safety and efficacy of statin therapy was explored in a review which considered the role of different types of evidence and discussed common errors in its interpretation. This review included a meta-analysis of data from 13 major statin trials regarding symptomatic muscle complaints (pain and weakness). The authors concluded that statin therapy may cause such adverse effects in only 50–100 patients per 10,000 treated for 5 years (0.5–1.0% absolute harm) indicating that under double-blind conditions, there is little evidence of any notable excess in muscle symptoms on statin therapy.<sup>225</sup>

**R** Patients who report statin intolerance may be rechallenged, if willing, initially with the same dose of the same statin unless they have significant creatine kinase elevation.

**R** If reported statin intolerance persists, patients should be offered an alternative statin.

✓ Patients started on a statin should be advised to report unexplained muscle pains or other adverse effects promptly, especially if associated with fever or malaise.

#### 10.4.7 BENEFITS AND HARMS OF STATIN THERAPY

Statin therapy reduces the risk of major vascular events by around 25% each year of treatment (after the first year) per 1 mmol/l reduction in LDL cholesterol (see Table 10). Given the potential for some high-potency statins (see Table 9) to reduce LDL cholesterol by 2 mmol/l or more, such treatment could reduce the risk of heart attacks and strokes by around a half among eligible patients. Only five new cases of myopathy would be expected per 10,000 patients treated for five years with a high-potency statin, and these resolve when treatment is stopped. Converting the absolute benefits and risks of statin treatment to numbers needed to treat (NNT) or harm (NNH) shows that many more individuals eligible for preventive therapy with statins need to be treated to result in a single major harm than to prevent a major event (see Table 11). Treating 2,000 people with statins for five years would prevent 200 major vascular events in people with existing CVD and 100 events in high-risk people without CVD while causing one new case of myopathy, one to two haemorrhagic strokes and 10–20 new cases of diabetes.<sup>225</sup>

Table 11: Numbers needed to treat and harm for outcomes associated with five years of daily high-intensity statin therapy

	Primary prevention		Secondary prevention	
	NNH	NNT	NNH	NNT
Major vascular events		20		10
New diabetes	100–200		100–200	
Haemorrhagic stroke	1,000–2,000		1,000–2,000	
Myopathy	2,000		2,000	

Based on data from Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet* 2016;388(10059):2532–61.

## 10.5 SPECIAL CONSIDERATIONS

### 10.5.1 PEOPLE WITH DIABETES

Individuals with diabetes are at higher risk of CVD than those without diabetes. The European guidelines on cardiovascular disease prevention in clinical practice reports that the relative risk of CVD events in Scottish patients with type 1 diabetes is two to three times the risk in individuals without diabetes. It also reports a meta-analysis of 102 studies including almost 700,000 people with any form of diabetes. This showed that diabetes confers about a twofold excess risk for a wide range of vascular diseases, independently from other conventional risk factors.<sup>231</sup>

Statin therapy in people with diabetes appears to be associated with a statistically significant reduction in the risk of various clinical end points including all-cause mortality and fatal and non-fatal MI.<sup>232</sup>

Data from 18,686 patients with diabetes across 14 trials of lipid lowering showed the same 21% reduction in first major vascular events per mmol/l reduction in LDL cholesterol as is seen in non-diabetic participants.<sup>233</sup> Coronary events, stroke, and revascularisation procedures were also reduced to the same extent as in non-diabetic patients with reductions of 22%, 21% and 25% respectively. Among diabetic patients there were 42 fewer major vascular events per 1,000 patients on statin per mmol/l LDL-cholesterol reduction. Absolute benefit was, as expected, larger in those with vascular disease at baseline (57 fewer vascular events per 1,000 compared with 36 per 1,000 in those without vascular disease) although the proportional effects of statin therapy were similar irrespective of whether there was a prior history of vascular disease. The authors commented that if generic statin treatment producing a reduction in LDL cholesterol of 1 mmol/l is cost effective in individuals with a risk of a major vascular event as low as 1% per year, almost all diabetic patients would be eligible for treatment.

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### 10.5.2 FAMILIAL HYPERCHOLESTEROLAEMIA

Patients with FH based on clinical or genetic evidence should be considered for aggressive statin therapy, irrespective of their calculated cardiovascular risk. Their total cholesterol and LDL cholesterol will usually exceed 8 mmol/l and 4.9 mmol/l respectively and may be substantially higher than this. In general, this treatment should only be considered in children of 12 years or older although it may be applied to younger patients at high risk because of severe hypercholesterolaemia, under specialist supervision.<sup>234,235</sup> Ezetimibe may be added to maximally-tolerated statin therapy where adequate cholesterol lowering has not been achieved with the statin alone, or given as monotherapy in those in whom statin therapy is contraindicated.<sup>236,237</sup>

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The NICE guideline on identification and management of familial hypercholesterolaemia reported evidence which showed that statins reduce both TC and LDL cholesterol in adults with FH, and adverse events on statins are rare in the general population (*see section 10.4.5*).<sup>237</sup> Based on the evidence of safety, tolerability and efficacy, statins are recommended as initial therapy in adults with FH. Economic modelling indicated that higher-intensity statins (simvastatin 80 mg and appropriate doses of atorvastatin and rosuvastatin) were cost effective when compared with lower-intensity treatment with simvastatin 40 mg. Given that costs for statins have reduced since the publication of the NICE guideline and a number of previously branded agents are now available in generic forms, these results are likely to be conservative.

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Results of the IMPROVE-IT trial (*see section 10.6.2*) indicated that combination therapy with ezetimibe plus a statin is more clinically effective than a statin alone as shown by lower LDL cholesterol and reduced cardiovascular events.<sup>212</sup> While this trial was conducted in patients with a recent ACS, not FH, and while the baseline LDL-cholesterol level in trial participants was considerably lower than is seen in FH (resulting in a smaller absolute reduction (0.4 mmol/l) in LDL cholesterol), results were consistent with large meta-analyses of statin therapy. Extrapolated to a 1 mmol/l reduction in LDL cholesterol, IMPROVE-IT yielded a similar hazard ratio for cardiovascular events (HR 0.80, 95% CI 0.68 to 0.94) to the meta-analysis (HR 0.78, 95% CI 0.76 to 0.80).<sup>25</sup>

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A NICE technology appraisal notes that combination therapy with ezetimibe and a statin is an option for the treatment of FH.<sup>236</sup>

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The PCSK9 inhibitors alirocumab and evolocumab reduce lipid levels in patients with heterozygous FH both alone and in conjunction with statins and/or ezetimibe (*see section 10.6.5*).<sup>238</sup> The SMC has accepted these agents for restricted use in NHSScotland for patients with heterozygous FH and LDL cholesterol  $\geq 5.0$  mmol/l for primary prevention of cardiovascular events and heterozygous FH patients with LDL cholesterol  $\geq 3.5$  mmol/l for secondary prevention of cardiovascular events (*see section 14.4*).

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✓ Individuals with a possible diagnosis of familial hypercholesterolaemia should be referred to a specialist clinic for investigation and initial management.

**R Individuals with familial hypercholesterolaemia should be offered statin therapy regardless of their calculated cardiovascular risk and may be considered for combination therapy with ezetimibe where LDL cholesterol-lowering is inadequate on maximally-tolerated statin therapy, or for monotherapy where statins are contraindicated.**

**R Individuals with heterozygous familial hypercholesterolaemia and elevated LDL cholesterol despite statin monotherapy or statin/ezetimibe combination therapy should be considered for a PCSK9 inhibitor.**

### 10.5.3 PREGNANCY

Statins should be avoided in women who are pregnant or are likely to be pregnant and in those who are breastfeeding (*see section 10.4.5*).<sup>160</sup> Adequate contraception is required during treatment and for one month afterwards as congenital anomalies have been reported and the decreased synthesis of cholesterol may affect fetal development.<sup>160</sup>

### 10.5.4 OLDER PEOPLE

No trials of initiating statin therapy have specifically recruited the very elderly, that is, those over the age of 85, and many trials define the elderly as those over the age of 65.

One meta-analysis of eight trials including 24,674 patients aged  $\geq 65$  (average age 73) without established cardiovascular disease concluded that statins reduce the incidence of MI (RR 0.61, 95% CI 0.43 to 0.85) and stroke (RR 0.76, 95% CI 0.63 to 0.93) but do not significantly prolong survival.<sup>239</sup> Similarly, an individual patient data analysis of major statin trials has confirmed reductions in first major cardiovascular events of 22% in those aged 66–75 and 16% in those aged  $>75$  per 1 mmol/l reduction in LDL cholesterol.<sup>240</sup>

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There is little reliable evidence regarding the clinical effects of the cessation of statin therapy in the elderly. One RCT investigating the safety and benefit of stopping statins in people aged on average 74.1 years, with advanced, life-limiting illness, found that stopping statins is safe and may be associated with benefits including improved quality of life.<sup>241</sup> The proportion of participants in the discontinuation versus continuation groups who died within 60 days was not significantly different (23.8% v 20.3%, 90% CI 3.5% to 10.5%) and did not meet the non-inferiority end point. Total quality of life (QoL) was better for the group discontinuing statin therapy (mean McGill QoL score 7.11 v 6.85,  $p=0.04$ ). Few participants experienced cardiovascular events (13 in the discontinuation group v 11 in the continuation group).

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In the elderly, the decision to start statin therapy should be based on ten-year cardiovascular risk estimation, life expectancy, and QoL. Age alone is not a contraindication to drug therapy.<sup>32</sup>

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### 10.5.5 SEX

The relative paucity of female participants in the statin trials, and resulting non-significant effect on cardiovascular events in some trials led to previous concerns that statins may not be beneficial for primary prevention in women, or less beneficial than in men.<sup>242</sup> A comprehensive meta-analysis of 174,000 participants from 27 major statin trials addressed this issue.<sup>215</sup> The trials either compared statin therapy to placebo or standard care, or compared intensive statin therapy to moderate-dose therapy. Across the trials, 27% of participants were women (mean age 65 years) and the analysis was conducted with individual participant data. Lipid-modifying effects were similar in men and women. There was, on average, an approximate 1.1

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mmol/l LDL-cholesterol reduction with a statin compared with placebo or standard care, and an approximate 0.5 mmol/l LDL-cholesterol reduction with intensive statin compared with moderate-dose statin in both sexes. Risk reductions for first major cardiovascular events were similar in women (RR 0.84, 99% CI 0.78 to 0.91) and men (RR 0.78, 99% CI 0.75 to 0.81) per 1 mmol/l lower LDL cholesterol (p value for heterogeneity 0.33). Similar results were also achieved for major coronary events and stroke, while there was no change in cancer rates and non-cardiovascular mortality in either sex on statins. Therefore, the available evidence shows no difference in the relative effectiveness of statin therapy in men and women.

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- ✓ The decision to start statin therapy should be based on estimated cardiovascular risk only and not the patient's sex.

### 10.5.6 CHRONIC KIDNEY DISEASE

Individuals with CKD are at elevated cardiovascular risk compared with those with a normal glomerular filtration rate.<sup>52,243</sup> A meta-analysis of 38 studies of statins in a total of 37,274 patients with CKD (including those with impaired renal function, those with structural kidney disease with normal renal function, and those with persisting proteinuria) and without CVD was undertaken.<sup>244</sup> Patients on dialysis and transplant recipients were not included. Treatment with a statin was compared with placebo or no treatment. Most of the data are derived from post hoc analyses of larger studies with median duration of one year. The main outcomes are summarised in Table 12 and demonstrated reductions in total mortality and major cardiovascular events. There was also clear cardiovascular benefit when analysis was restricted to studies in individuals with no cardiovascular disease at baseline.

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The meta-analysis reported no increase in creatine kinase (CK) elevation or rhabdomyolysis, no increase in transaminases, no increase in cancer incidence, nor a significant increase in withdrawals due to adverse events, although not all the studies reported adverse events systematically.

*Table 12: Risk reductions of vascular outcomes associated with statin therapy in individuals with CKD (not adjusted for LDL cholesterol)*

	Control event rate (%)	Statin event rate (%)	Absolute risk reduction (%)	Risk ratios (95% CI)	p-value
Total mortality	2.5	2.0	0.5	0.79 (0.69 to 0.91)	<0.001
Major CV events	2.0	1.4	0.6	0.72 (0.66 to 0.79)	<0.00001
CV mortality	1.5	1.2	0.3	0.77 (0.69 to 0.87)	<0.001
Stroke	1.7	0.97	0.73	0.63 (0.35 to 1.12)	NS
MI (fatal and non-fatal)	3.09	1.67	1.42	0.55 (0.42 to 0.72)	<0.0001

A meta-analysis of individual participant data (n=183,419) from 28 trials examined the effect of statin therapy according to renal function. There was evidence of cardiovascular benefit from statin therapy in participants with CKD not on dialysis, though relative reductions in events reduced as eGFR declined. For a 1 mmol/l reduction in LDL cholesterol, major CVD events were reduced by 22% in participants with eGFR  $\geq 60$  ml/min/1.73 m<sup>2</sup>, by 19% in those with eGFR 45–59 ml/min/1.73 m<sup>2</sup>, and by 15% in those with eGFR below 45 ml/min/1.73 m<sup>2</sup>. There was no evidence of cardiovascular benefit in patients on dialysis (rate ratio 0.94, 95% CI 0.79 to 1.11).<sup>245</sup>

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Another meta-analysis of 18 trials (five trials in a CKD population, 13 including a CKD subgroup) examined the effects of statin monotherapy and combination therapy with ezetimibe.<sup>246</sup> Lipid-lowering therapy decreased the risk of cardiac mortality (RR 0.82, 95% CI 0.74 to 0.91), cardiovascular events including revascularisation (RR 0.78, 95% CI 0.71 to 0.86), and MI (RR 0.74, 95% CI 0.67 to 0.81) but did not improve kidney outcomes. Borderline benefit was observed for all-cause mortality (RR 0.91, 95% CI 0.83 to 0.99) but there was evidence of marked heterogeneity.

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Individuals with CKD stage 3 and above, or any degree of albuminuria above the normal threshold of 30 mg/g are at significantly increased cardiovascular risk compared with individuals without these factors and should be offered medications to reduce cardiovascular risk (*see section 4.2.2*).

**R** Patients with CKD stage 3 and above, or with micro- or macroalbuminuria, who are not on dialysis should be offered statin therapy.

## 10.6 OTHER LIPID-LOWERING AGENTS

Meta-analysis of trials of cholesterol lowering by means other than statins have demonstrated cardiovascular benefit. For example, a meta-analysis of nine RCTs of pharmacological therapy conducted before the advent of statins showed approximately 20% reductions in coronary events in both primary-prevention and secondary-prevention populations.<sup>247</sup>

### 10.6.1 BILE ACID SEQUESTRANTS

The effect of statins can be accentuated by combining them with agents which interfere with bile acid absorption, for example cholestyramine and colestipol. These drugs lower serum, total and LDL cholesterol and cause mild, and usually transient, elevation of triglyceride levels.<sup>248,249</sup>

Clinical trial evidence from the 1980s demonstrates the benefit of these drugs as monotherapy in primary CHD prevention, but their side-effect profile (gastrointestinal irritation, constipation) frequently makes them unacceptable to most patients and adherence to therapy may be problematic.<sup>213</sup> Nevertheless, they may be considered for the treatment of marked hypercholesterolaemia in individuals at high risk (for example, FH) where statins are contraindicated; or they may be added to maximally-tolerated statin therapy to enhance cholesterol reduction in such individuals. Whereas doubling the dose of a statin produces only a six percent further reduction in LDL cholesterol, adding a moderate dose of a bile acid sequestrant to a statin can further lower LDL cholesterol by 12–16%.<sup>250,251</sup>

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### 10.6.2 EZETIMIBE

Ezetimibe is a cholesterol absorption inhibitor which acts by inhibiting Niemann-Pick C1-Like 1 protein (NPC1L1). It has few significant side effects.<sup>252</sup> As monotherapy, its cholesterol lowering capability is modest (a reduction of 15–20% in total cholesterol when prescribed as a single dose of 10 mg).<sup>253,254</sup> Its coprescription with moderate-dose statin therapy results in a cholesterol reduction equivalent to maximum-dose statin monotherapy.

The IMPROVE-IT trial investigated the effect of adding 10 mg daily ezetimibe to 40 mg daily simvastatin in 18,144 patients following recent ACS with a baseline LDL cholesterol 1.3–2.6 mmol/l on lipid-lowering therapy, or 1.3–3.2 mmol/l without therapy.<sup>212</sup> During the trial, LDL cholesterol was 0.4 mmol/l lower on ezetimibe plus simvastatin than simvastatin monotherapy. Over a median of six years, the primary end point (composite of cardiovascular death, non-fatal MI, unstable angina requiring rehospitalisation, coronary revascularisation, or non-fatal stroke) was reduced by 6.4% with an HR of 0.94 (95% CI 0.89 to 0.99,  $p=0.016$ ). No notable side effects occurred.

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Although this trial was conducted in patients with recent ACS and with relatively low baseline LDL cholesterol, the clinical benefit associated with LDL-cholesterol lowering can be extrapolated to other populations with or without CVD and with higher LDL-cholesterol levels. The cost of ezetimibe in 2017 is £26.31 per four-week pack, approximately twenty times more expensive than atorvastatin 20 mg and with a more modest effect on LDL cholesterol.

The SHARP trial studied 9,270 patients with CKD (serum creatinine >150 micromol/l in men or >130 micromol/l in women) and no previous MI or coronary revascularisation, 33% of whom were on dialysis.<sup>255</sup> Patients were randomised to either the combination of simvastatin 20 mg/day and ezetimibe 10 mg/day, or to placebo. During the trial, LDL cholesterol was 0.85 mmol/l lower in the intervention arm which led to a 17% reduction (RR 0.83, 95% CI 0.74 to 0.94) in major cardiovascular events over 4.9 years. Notably, there was no ezetimibe monotherapy arm.

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Use of ezetimibe in patients with FH is covered in section 10.5.2.

**R** Ezetimibe and bile acid sequestrant therapy should only be considered for primary prevention in patients at elevated CVD risk in whom statin therapy is contraindicated, and in patients with familial hypercholesterolaemia.

**R** Ezetimibe and bile acid sequestrant therapy should be considered for secondary prevention in combination with maximum tolerated statin therapy if LDL cholesterol is considered to be inadequately controlled.

### 10.6.3 FIBRATES

Fibrates are primarily used for lowering triglycerides. Their LDL-cholesterol lowering effects are generally in the range of 10% or less in persons with primary hypercholesterolemia. Trials of fibrate therapy were mostly undertaken in the era prior to routine statin treatment.

Fibrates typically raise HDL cholesterol by 5–15% and reduce triglyceride by 25–50%,<sup>256-258</sup> with greater reductions occurring in individuals with severe hypertriglyceridaemia.<sup>259</sup>

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A comprehensive meta-analysis of major-outcome fibrate trials included data for 45,058 participants in 18 trials, although it is important to highlight that only one of these trials was conducted in those on background statin therapy.<sup>260</sup> Notably, this meta-analysis includes trials of fibrates which are no longer used in the UK (clofibrate) or seldom used (gemfibrozil, which is contraindicated in combination with a statin). Changes in lipid concentrations were heterogeneous with average reductions in total cholesterol, LDL cholesterol and triglycerides of 0.44 mmol/l, 0.36 mmol/l and 0.48 mmol/l, respectively. Across these trials, fibrate therapy led to modest cardiovascular benefit with a borderline reduction in first major CVD events (RR 0.90, 95% CI 0.82 to 1.00),  $p=0.048$ ) driven by a 13% reduction in coronary events but without any effect on stroke (RR 0.97), cardiovascular mortality (RR 1.03) or all-cause mortality (RR 1.00). Post hoc analysis has suggested that the cardiovascular effect of fibrates may be more beneficial in those with low HDL cholesterol and/or elevated triglycerides. Serious drug-related adverse events were not increased by fibrates. Few events were recorded and a 14% reduction in the progression of albuminuria was noted in the few trials with available data. Increases in serum creatinine were common on fibrate therapy but these are known to be reversible. The null stroke findings were confirmed in a separate meta-analysis which specifically investigated this endpoint in 10 trials of fibrates compared with placebo.<sup>261</sup>

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Fibrates are known to reversibly increase serum creatinine. In a meta-analysis of eight fibrate trials with 16,869 CKD patients, fibrates reduced TC by 0.32 mmol/l and albuminuria progression by 14% compared with placebo.<sup>262</sup> While fibrate therapy increased serum creatinine by about 30 micromol/l on average, there was no change in progression to end stage renal disease (RR 0.85, 95% CI 0.49 to 1.49) and in the subgroup with eGFR 30–59.9 ml/min/1.73 m<sup>2</sup>, fibrate therapy reduced cardiovascular events by 30% and cardiovascular death by 40%, but did not reduce all-cause mortality.

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The NICE guideline on lipid modification conducted meta-analyses of RCTs which compared the effect of fibrates with placebo and the effects of fibrates added to statins with statins alone on a range of cardiovascular outcomes. Across all comparisons, there were no statistically significant differences in all-cause or cardiovascular mortality, sudden cardiac death, stroke or rate of hospitalisation. Moderate-quality evidence suggested that fibrates are potentially more clinically effective when compared with placebo at reducing non-fatal MI at six years (five studies, n=25,015). The only study that compared fibrates plus statin versus statin found no evidence of benefit from the addition of fibrates for any of the outcomes including non-fatal MI. These results applied to populations with and without CVD, and in people with diabetes in mixed primary and secondary prevention populations.<sup>31</sup>

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**R** Fibrates are not routinely recommended for primary or secondary prevention of cardiovascular disease.

✓ Individuals with:

- CVD or who are at high cardiovascular risk, and
- marked hypertriglyceridaemia, and
- low HDL cholesterol level

should be considered for treatment with a fibrate.

#### 10.6.4 NICOTINIC ACID

Nicotinic acid, or niacin, is a powerful HDL-cholesterol-raising agent.<sup>263</sup> Two forms of niacin are available, crystalline immediate release which is taken three times daily and modified (extended) release taken once daily. Elevations of 15–35% in HDL cholesterol are reported following dosing with 1–3 g of the drug in its crystalline form, and are usually accompanied by a drop of 20–30% in LDL cholesterol and of 35–50% in triglyceride.<sup>264</sup> An RCT that compared the efficacy and safety of treatment with 1.5 g/day of immediate-release (IR) with modified-release (MR) niacin found similar effects on lipids for both preparations.<sup>265</sup>

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In the Coronary Drug Project niacin was administered in a daily dose of 3 g over 6.5 years to men who had already had an MI. Treatment reduced the frequency of subsequent events by 14% (p<0.005), although there was no effect on overall mortality.<sup>266</sup> After another eight years follow up and despite no attempt being made to maintain those conditions, total mortality showed significant reduction in the niacin-treated cohort.<sup>267</sup>

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By contrast, two more recent placebo-controlled trials have failed to show cardiovascular benefit from niacin when added to background statin therapy (and ezetimibe if needed for optimal control of LDL cholesterol). The AIM-HIGH trial studied 3,414 patients with established CVD, low HDL cholesterol and elevated triglycerides.<sup>268</sup> The trial was discontinued after three years due to lack of benefit from niacin. The HPS2-THRIVE trial studied 25,673 adults with cardiovascular disease but eligibility for the trial was not based on lipid thresholds.<sup>269</sup> During the trial, niacin recipients had 0.25 mmol/l lower LDL cholesterol and 0.16 mmol/l higher HDL cholesterol. After 3.9 years, there was also no evidence of cardiovascular benefit on combination of niacin with laropiprant (an antagonist of the prostaglandin D2 receptor DP<sub>1</sub> that has been shown to improve adherence to niacin therapy by reducing flushing) (RR 0.96, 95% CI 0.90 to 1.03).

Both HPS2-THRIVE and AIM-HIGH also showed harms, such as increased risks of gastrointestinal, bleeding and infection adverse events. New-onset diabetes was increased and diabetes-related complications were also increased in those on niacin therapy. Niacin therapy also causes skin flushing which limits adherence to it.

**R** Nicotinic acid is not recommended for cardiovascular risk reduction in any group.

#### 10.6.5 PCSK9 INHIBITORS

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an important regulator of cholesterol homeostasis. PCSK9 binds to LDL receptors and facilitates their degradation leading to increased serum LDL-cholesterol. Inhibition of PCSK9 with monoclonal antibodies decreases degradation of the LDL receptors and leads to substantial reductions in cholesterol levels. Two PCSK9 inhibitors, alirocumab and evolocumab, have been most extensively researched to date.

A meta-analysis of 25 short-term studies reported that monthly evolocumab (420 mg) significantly reduced LDL cholesterol by -54.6% compared with placebo (95% CI -58.7 to 50.5%), although significant heterogeneity was noted,  $I^2=80.4\%$ , and by -36.3% (95% CI 38.8 to -33.9%) compared with ezetimibe. There was an increase in HDL cholesterol of 7.6% (95% CI 5.7 to 9.5%) compared with placebo and 6.4% (95% CI 4.3 to 8.4%) compared with ezetimibe. Fortnightly administration of 140 mg evolocumab led to even greater LDL reductions than 420 mg monthly treatment compared with placebo (-60.4%, 95% CI -68.8% to -52.0%). Fortnightly alirocumab (50 to 150 mg) lowered LDL cholesterol by -52.6% (95% CI -58.2 to 47.0%) compared with placebo, by -29.9% (95% CI -32.9 to -26.9%) compared with ezetimibe, and increased HDL cholesterol by 8.0% (95% CI 4.2 to 11.7%) compared with placebo. There was a synergistic effect in those already receiving statin therapy.<sup>238</sup> 1++

Advice on PCSK9 inhibitors from NICE<sup>270,271</sup> and SMC<sup>272,273</sup> is based on 10 RCTs of alirocumab and four RCTs of evolocumab all of which are included within this meta-analysis.<sup>238</sup>

A meta-analysis of 24 RCTs reported that PCSK9 inhibitors reduced all-cause mortality in patients with a wide range of hypercholesterolaemia, (OR 0.45, 95% CI 0.23 to 0.86,  $p=0.015$ ) but not cardiovascular mortality (OR 0.50, 95% CI 0.23 to 1.10;  $p=0.084$ ). The rate of myocardial infarction was significantly reduced with use of PCSK9 antibodies (OR 0.49, 95% CI 0.26 to 0.93;  $p=0.030$ ).<sup>274</sup> 1++

A further meta-analysis of 17 RCTs reported that PCSK9 inhibitors reduced the incidence of all-cause mortality (OR 0.43, 95% CI 0.22 to 0.82,  $p=0.01$ ) but were associated with an increased incidence of neurocognitive adverse events (OR 2.34, 95% CI 1.11 to 4.93) compared with placebo, although these were restricted to two studies.<sup>275</sup> 1++

The first large RCT of PCSK9 inhibition which was powered to assess long-term cardiovascular outcomes using evolocumab (FOURIER) showed that evolocumab significantly reduced the risk of the composite primary end point (cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina, or coronary revascularisation) compared with placebo (1,344 patients (9.8%) v 1,563 patients (11.3%); HR 0.85, 95% CI 0.79 to 0.92,  $p<0.001$ ). Evolocumab also reduced the risk of the key composite secondary end point (cardiovascular death, myocardial infarction, or stroke) (816 patients (5.9%) v 1,013 patients (7.4%); HR 0.80, 95% CI, 0.73 to 0.88,  $p<0.001$ ). At 2.2 years of treatment there was no impact on cardiovascular mortality (HR 1.05, 95% CI 0.88 to 1.25,  $p=0.62$ ) or total mortality (HR 1.04, 95% CI 0.91 to 1.19,  $p=0.54$ ).<sup>276</sup> 1++

No difference in adverse events or serious adverse events between either evolocumab or alirocumab and placebo was reported in a meta-analysis of 25 trials. Serious adverse events occurred in 1.9% patients on evolocumab, and 1.2% patients on placebo (HR 0.96, 95% CI 0.60 to 1.55). Adverse events leading to discontinuation occurred in 1.6% patients on evolocumab and 1.1% patients on placebo at 12 weeks (HR 0.78, 95% CI 0.46 to 1.32). Serious adverse events occurred in 8.6% patients on alirocumab, and 9.3% patients on placebo (HR 0.94, 95% CI 0.79 to 1.12). Adverse events leading to discontinuation occurred in 4.8% patients on alirocumab and 4.6% patients on placebo at 12 weeks (HR 1.07, 95% CI 0.78 to 1.47).<sup>238</sup> 1++

In the FOURIER trial, there was no significant difference between the study groups with regard to adverse events (including new-onset diabetes and neurocognitive events), with the exception of injection-site reactions, which were more common with evolocumab (2.1% v 1.6%).<sup>276</sup> 1++

**R** PCSK9 inhibitors should be considered in patients at high risk of vascular events with cholesterol levels remaining above target levels despite other tolerated lipid-lowering therapy.

The SMC has accepted alirocumab and evolocumab for restricted use in NHS Scotland. Both medicines are indicated in adults with primary hypercholesterolaemia (heterozygous familial hypercholesterolaemia and non-familial) or mixed dyslipidaemia as an adjunct to diet:

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach low-density LDL cholesterol goals with the maximum tolerated dose of a statin or,
- alone or in combination with other lipid-lowering therapies in patients who are statin intolerant, or for whom a statin is contraindicated.

Both medicines are restricted for specialist use only in patients at high cardiovascular risk as follows:

- patients with heterozygous familial hypercholesterolaemia and LDL cholesterol  $\geq 5.0$  mmol/l, for primary prevention of cardiovascular events or,
- patients with heterozygous familial hypercholesterolaemia and LDL cholesterol  $\geq 3.5$  mmol/l, for secondary prevention of cardiovascular events or,
- patients at high risk due to previous cardiovascular events and LDL cholesterol  $\geq 4.0$  mmol/l or,
- patients with recurrent/polyvascular disease and LDL cholesterol  $\geq 3.5$  mmol/l.

Evolocumab should be administered at a dose of 140 mg every two weeks.

## 10.7 MANAGEMENT OF COMBINED DYSLIPIDAEMIA

Combined dyslipidaemia, characterised by abnormalities in all of the major lipoprotein species, is associated with increased risk of vascular disease which goes beyond that produced by raised LDL cholesterol alone. Plasma triglyceride is elevated, HDL cholesterol is low and LDL particles are smaller, denser and more atherogenic than normal.<sup>277,278</sup> This profile can be seen in particular disease states and is particularly characteristic of obesity and diabetes mellitus (diabetic dyslipidaemia). Evidence from genetic studies suggests that triglycerides or triglyceride-mediated pathways may be causally related to the risk of cardiovascular disease.<sup>279,280</sup>

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A number of clinical trials have shown that LDL-cholesterol lowering with statins reduces the risk of vascular events (myocardial infarction, stroke and coronary revascularisation) in participants with diabetes with raised LDL cholesterol (see section 10.5.1).<sup>281,282</sup> The greater the LDL-cholesterol reduction, the greater the benefit.<sup>283</sup>

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The largest vascular end-point trial undertaken with fibrates (FIELD, conducted in participants with diabetes with total-cholesterol/HDL-cholesterol ratio of 4.0 or more and/or plasma triglyceride of 1.0–5.0 mmol/l) provided limited evidence for their benefit in a similar diabetic cohort.<sup>284</sup> Although treatment with fenofibrate did not significantly reduce the risk of a coronary event, it produced a 24% relative reduction ( $p=0.01$ ) in risk of non-fatal MI. There was a non-significant rise in coronary deaths, but overall cardiovascular disease events (fatal and non-fatal myocardial infarction, stroke and coronary and carotid revascularisation) fell by 11% ( $p=0.35$ ). Fenofibrate treatment resulted in less albuminuria progression ( $p=0.002$ ) and fewer cases of retinopathy requiring laser treatment ( $p=0.0003$ ). Pancreatitis and pulmonary embolism risk rose in the actively-treated group ( $p=0.031$  and  $0.022$ , respectively).

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Combined statin/fibrate therapy improves the entire dyslipidaemic profile over that seen with statin therapy alone. Trials have reported a significant increase in HDL-cholesterol levels and significant reductions in triglyceride and LDL-cholesterol levels in patients on combined statin/fibrate therapy compared with patients on statins or fibrate monotherapy.<sup>285,286</sup>

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The effect of combined statin/fibrate therapy compared with statin monotherapy was investigated in the ACCORD-Lipid trial.<sup>287</sup> In this study 5,518 patients with type 2 diabetes and established CVD or excess risk and with dyslipidaemia (LDL cholesterol 1.55–4.65 mmol/l, HDL cholesterol below about 1.3 mmol/l and triglycerides below 8.5 mmol/l if not receiving lipid therapy or otherwise below 4.5 mmol/l) were randomised to fenofibrate or placebo in addition to ongoing open-label statin therapy. No cardiovascular benefit was noted over 4.7 years. There was, however, a borderline interaction suggesting possible benefit in the subgroup with low HDL cholesterol ( $<0.9$  mmol/l) and elevated triglycerides ( $>2.3$  mmol/l), similar to what has been found in post hoc analyses of other fibrate trials.<sup>260</sup>

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It appears that the potential for impaired metabolism of statins with gemfibrozil<sup>288</sup> is greater than with other fibrates, such as fenofibrate.<sup>289</sup> This is supported by evidence from healthy volunteers that the combination of fenofibrate with statins is associated with minimal differences in the concentrations of either fenofibrate or statin and also by the safety demonstrated by statin plus fenofibrate combination therapy in ACCORD-Lipid.<sup>287,290</sup> In contrast, the concurrent use of certain statins with gemfibrozil has shown a two- to three fold increase in statin levels.<sup>291</sup> Analyses of the US Food and Drug Administration Adverse Event Reporting System have suggested that the use of fenofibrate with statins results in fewer reports of rhabdomyolysis per million prescriptions than with gemfibrozil and statins.<sup>292</sup>

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**R** | **Statins are the drugs of choice in the management of patients with diabetes with mixed dyslipidaemia and elevated low density lipoprotein cholesterol.**

- ✓ | Combination therapy with a statin and a fibrate may be considered for combined dyslipidaemia.
- ✓ | Statins should not be coadministered with gemfibrozil.
- ✓ | Lifestyle advice involving healthy eating habits and physical activity is particularly important in individuals with combined dyslipidaemia.

# 11 Blood pressure lowering

Elevated blood pressure (BP) increases the risk of CHD, heart failure, stroke and renal failure.<sup>293</sup> Systematic reviews of trials of antihypertensive drugs versus placebo have shown that blood pressure lowering is associated with reductions in CHD, stroke, heart failure, and cardiovascular and total mortality.<sup>294</sup>

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A dietary pattern low in total fat, saturated fatty acids, and dietary cholesterol, and rich in fruits, vegetables, and low-fat dairy products can produce blood pressure reductions exceeding 11/5 mm Hg in people at higher cardiovascular risk.<sup>295</sup> Weight loss and the restriction of dietary sodium may enhance these effects (see section 5).<sup>296,297</sup>

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An important additional consideration is the use of 24-hour ambulatory blood pressure monitoring (ABPM) for diagnosis of hypertension as recommended in other national guidelines.<sup>42</sup> This issue is not addressed in detail as diagnosis of hypertension is not included in this guideline, and major intervention trials of blood pressure-lowering treatment have not used ABPM.

## 11.1 BLOOD PRESSURE THRESHOLDS FOR INTERVENTION WITH DRUG THERAPY

The relationship between 'usual' blood pressure and cardiovascular risk is approximately linear between the values of 115/70 and 170/100 mm Hg. Within this range, lower usual blood pressure is associated with lower cardiovascular risk.<sup>298</sup> People at greater cardiovascular risk derive the most absolute benefit from treatment. Once a first cardiovascular event has occurred, blood pressure is a poor predictor of recurrent events. In patients without known cardiovascular disease, age is the most important determinant of risk. Setting an arbitrary blood pressure threshold for the use of blood pressure-lowering therapy may therefore not be the most effective way to reduce risk, although this concept has yet to be tested prospectively.

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Lowering blood pressure has been shown to reduce the risk of both cardiovascular and total mortality, without adverse effect on quality of life. Trials of antihypertensive drugs show a similar relative reduction in coronary heart disease risk of 15–25% and reduction in ischaemic stroke risk of 30–45%.<sup>299–305</sup> One Health Technology Assessment showed that the risk from pre-existing vascular disease strongly outweighs any other risk factor calculation, and concluded that all such patients should be offered, and will benefit from, blood pressure lowering.<sup>306</sup>

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A large meta-analysis which included 147 RCTs of antihypertensive drug therapy involving 464,000 patients reported that lowering systolic blood pressure by 10 mm Hg or diastolic blood pressure by 5 mm Hg reduced the risk of stroke by an estimated 41% (95% CI 33 to 48) and ischaemic heart disease by 22% (95% CI 17 to 27).<sup>305</sup> The percentage reduction in major cardiovascular events was similar in patients with and without prior cardiovascular disease, irrespective of pretreatment blood pressure values (as low as 110 mm Hg systolic and 70 mm Hg diastolic). The proportional reduction in stroke risk may be greater at higher levels of pretreatment blood pressure. The studies included in this meta-analysis were in participants with no history of cardiovascular disease, where the baseline blood pressure was usually high, and patients with established CVD, where baseline blood pressure was not an inclusion criterion.

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The Blood Pressure Treatment Trialists' Collaboration published a meta-analysis of 32 RCTs involving 201,566 participants with and without established CVD. In general, the results suggested that it was unlikely that the effectiveness of BP-lowering treatment depends substantively on the starting blood pressure level. Furthermore, the data support the use of blood pressure-lowering medication in high-risk patients and support the proposition that patients should be selected for treatment on the basis of the absolute level of cardiovascular risk, rather than simply on blood pressure alone.<sup>307</sup>

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The NICE/British Hypertension Society guideline indicates that the following lifestyle activities are associated with a potential reduction in blood pressure:<sup>42</sup>

- weight reduction
- reduced salt intake
- limitation of alcohol consumption
- increased physical activity
- increased fruit and vegetable consumption
- reduced total fat and saturated fat intake.

✓ All individuals with a persistent clinic blood pressure  $\geq 140/90$  mm Hg or a family history of hypertension should receive lifestyle advice to help reduce their blood pressure and CVD risk. Lifestyle advice should continue even when drug therapy is initiated.

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### 11.1.1 BLOOD PRESSURE THRESHOLDS FOR INDIVIDUALS WITH SYMPTOMATIC CARDIOVASCULAR DISEASE

In the past, the decision to introduce BP-lowering medication was influenced not only by baseline level of BP but also by the presence or absence of pre-existing target organ damage. Increasingly the decision is based on an overall assessment of CVD risk. Many patients in Scotland with elevated BP, though asymptomatic, have subclinical CVD. Furthermore, many of the RCTs and meta-analyses of antihypertensive therapy include patients with and without CVD, with very few reporting on mutually exclusive populations. Nevertheless, for ease of reference the general distinction of individuals with and without symptomatic CVD is retained in this guideline, as the former group still bears a proportionately higher risk.

The Joint British Societies' guideline on the prevention of cardiovascular disease defines target organ damage as any of the following:<sup>30</sup>

- heart failure
- established coronary heart disease
- stroke or transient ischaemic attack
- peripheral arterial disease
- abnormal renal function (elevated serum creatinine or proteinuria/microalbuminuria)
- hypertensive or diabetic retinopathy
- left ventricular hypertrophy on electrocardiogram or echocardiogram.

Systematic reviews have demonstrated beyond doubt the benefit of lowering blood pressure. The higher the cardiovascular risk, the greater the absolute risk reduction.

The effects of blood pressure lowering at different baseline BP were examined in a meta-analysis of 104,359 individuals from 32 RCTs.<sup>308</sup> Stage 1 hypertension was defined at SBP 140–159 or diastolic blood pressure (DBP) 90–99 mm Hg; stage 2 hypertension SBP 160–179 or DBP 100–109; and stage 3 hypertension SBP at least 180 mm Hg or DBP at least 110 mm Hg. Significant benefits were observed from BP lowering at all hypertension grades and this applied to all outcome measures except heart failure in grade 1 hypertension and all-cause mortality in grade 3 hypertension. The largest relative risk reductions were for stroke (27–42% across different baseline hypertension grades) and heart failure (20–55%), with smaller reductions in CHD (12–17%), cardiovascular mortality (13–22%), and all-cause mortality (7–18%). Risk ratios did not show any significant trend to change with increasing baseline BP levels. Even in patients with stage 1 hypertension, with a low to moderate cardiovascular risk (<5% risk of cardiovascular death over 10 years), and a mean baseline BP of 146/91 mm Hg, the NNT over five years to prevent one cardiovascular event was 29.

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In a meta-analysis of individual patient data in 201,566 patients across 32 RCTs when blood pressure was analysed as a continuous variable, no consistent interaction was found between the baseline blood pressure level and the effectiveness of blood pressure-lowering treatment.<sup>307</sup> Blood pressures reported in this study ranged from <140 mm Hg to >180 mm Hg systolic and from <80 mm Hg to >100 mm Hg diastolic. The authors suggest that these data imply a greater role for blood pressure lowering in high-risk patients with blood pressure levels that are not conventionally hypertensive. This meta-analysis included studies of blood pressure lowering irrespective of the cardiovascular status of the populations involved, therefore includes data from patients without CVD in addition to those with established disease.

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Given the evidence that blood pressure lowering reduces the risk of CVD irrespective of pretreatment blood pressure, it could be argued that blood pressure-lowering treatment could be offered to any person at high risk of cardiovascular disease, not just those with hypertension. The safety and effectiveness of such an approach has not been tested, however, and the balance between benefits and harms, especially in people with low baseline blood pressure, as well as the cost effectiveness of such a strategy remain unclear.

**R** | **Individuals with clinical evidence of cardiovascular disease and sustained clinic systolic blood pressure >140 mm Hg systolic and/or diastolic blood pressure >90 mm Hg should be offered blood pressure-lowering drug therapy.**

*Patients who have had a stroke or TIA*

The PROGRESS trial randomised patients who had had a stroke to blood pressure-lowering therapy or placebo irrespective of initial blood pressure.<sup>301</sup> This trial convincingly demonstrated the benefits of BP lowering in reducing both ischaemic and haemorrhagic stroke. The relative reduction in risk of recurrent stroke was similar in hypertensive and non-hypertensive individuals (32% v 27%), the mean baseline BP in the latter group being 136/79 mm Hg. Significant reductions in risk of recurrent stroke were reported in patients receiving combination therapy with perindopril plus indapamide in whom BP was lowered by an average of 12/5 mm Hg, but not in those on perindopril alone in whom BP was lowered by an average of 5/3 mm Hg.

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**R** | **Individuals who have had a haemorrhagic or ischaemic stroke, or TIA should be offered blood pressure-lowering medication, even when their baseline blood pressure is at a level that would be considered conventionally normotensive, to reduce the risk of recurrence.**

#### 11.1.2 BLOOD PRESSURE THRESHOLDS FOR INDIVIDUALS WITHOUT SYMPTOMATIC CARDIOVASCULAR DISEASE

A number of meta-analyses were identified which report on the effects of BP lowering in patients without CVD. These studies involve a total of over 250,000 participants, giving substantial power to support the conclusions. In general, BP lowering reduces the risk of stroke, heart failure, coronary events, cardiovascular and all-cause mortality. In subsets of patients with specific clinical factors, slightly different conclusions may be drawn about the strength of these effects, which may reflect the smaller numbers and limited power in such subgroup analyses.

One meta-analysis of 11 trials, each of which had a minimum of 1,000 patient-years of planned follow up, included a total of 51,917 participants. Seventy five per cent of the participants had no prior history of CVD. Participants were stratified into four groups according to estimated baseline absolute cardiovascular risk. The mean estimated baseline level of five-year cardiovascular risk for each group was 6%, 12.1%, 17.7% and 26.8% respectively. Although the relative risk reduction was similar in each group (around 15%), in absolute terms, treating 1,000 patients in each risk group with BP-lowering treatment for five years would prevent 14, 20, 24 and 38 cardiovascular events respectively. These results support the use of predicted cardiovascular risk equations to inform BP-lowering treatment decisions.<sup>309</sup>

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A series of publications provide an overview, meta-analyses and meta-regression analyses of 68 trials of BP lowering incorporating 245,885 individuals.<sup>310</sup> In 47 trials BP lowering was the primary aim while in the remainder at least 40% of the randomised patients were hypertensive. Trials exclusively in patients with acute MI, acute stroke, heart failure or dialysis were excluded. Risk reductions were expressed in relation to a standardised 10/5 mm Hg reduction in BP (which is close to the achieved effects shown in intentional

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placebo-controlled BP-lowering trials). All cardiovascular outcomes were reduced by BP lowering, with mean absolute reductions of 17 (95% CI 14 to 20) strokes, 28 (95% CI 19 to 35) major cardiovascular events and 8 (95% CI 4 to 12) deaths for every 1,000 patients treated for five years. Absolute risk reduction significantly increased with increasing baseline cardiovascular risk (p for trend <0.001 except for CHD). A 10/5 mm Hg BP reduction reduced the incidence of major cardiovascular events by 7 (95% CI 3 to 10), 30 (95% CI 9 to 50), 56 (95% CI 35 to 76) and 87 (95% CI 62 to 112) events every 1,000 patient treated for five years across groups defined according to risk.

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A meta-analysis of 68 trials of BP lowering showed that while absolute risk reductions associated with BP lowering were greatest in those at highest baseline cardiovascular risk compared with those at low to moderate risk (87 instead of seven major cardiovascular events prevented by treating 1,000 patients for five years), the risk level that is found after BP lowering (residual risk) remains much higher (almost 10 times higher for cardiovascular death) when treatment is initiated at the highest rather than at the lowest stratum of cardiovascular risk. In other words, reserving treatment of hypertension to patients at high cardiovascular risk may not allow the accumulative risk to be reversed as patients get older and may increase the risk of treatment failure.<sup>311</sup>

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No studies were identified that directly address this issue, however it suggests further support to the development of risk estimation tools which stratify risk intervention thresholds by age, rather than provide a single threshold which applies to all (see section 3.4).

Evidence of target organ damage such as retinopathy, proteinuria or left ventricular hypertrophy, supports a decision to implement drug therapy in patients with stage 1 hypertension.<sup>30</sup>

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**R** Individuals at high cardiovascular risk, but without established CVD, and sustained clinic systolic blood pressure >140 mm Hg systolic and/or diastolic blood pressure >90 mm Hg should be offered blood pressure-lowering treatment.

Some patients at high cardiovascular risk, but without established CVD, with baseline BP <140/90 mm Hg should be considered for BP-lowering treatment, for example those with diabetes or CKD (see section 11.1.3).

The following good practice point is based on recommendations from the JBS3 and NICE/BHS guidelines.<sup>30,42</sup>

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✓ Individuals with hypertension whose ten-year risk of a first CVD event is below the threshold for consideration of pharmacological therapy should continue with lifestyle strategies and have their blood pressure and total CVD risk reassessed every one to five years, depending on clinical circumstances.

Persistent blood pressure elevation  $\geq 160$  mm Hg systolic and/or  $\geq 100$  mm Hg diastolic, equivalent to stage 2 hypertension, causes sufficient CVD risk on the basis of blood pressure levels alone to require drug therapy to reduce blood pressure (see section 4.4).<sup>30,56</sup>

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**R** Individuals with clinic blood pressure greater than 160 mm Hg systolic or 100 mm Hg diastolic should be offered antihypertensive treatment and specific lifestyle advice to lower their blood pressure and risk of cardiovascular disease.

### 11.1.3 BLOOD PRESSURE THRESHOLDS FOR SPECIFIC GROUPS AT HIGH CARDIOVASCULAR RISK

Some patients are at high CVD risk, almost approaching that of individuals with established CVD, and are included in this section, especially as many of the studies relating to such individuals included people with and without symptomatic CVD.

#### *People with type 2 diabetes*

A meta-analysis of blood pressure lowering in people with type 2 diabetes included 100,354 patients in 40 RCTs.<sup>312</sup> Blood pressure lowering was associated with improved survival and reduced risk of major cardiovascular events in addition to significant benefits in respect of progression of retinopathy and development of albuminuria. A 10 mm Hg reduction in SBP was associated with reduced relative risk of all-cause mortality (0.87, 95% CI 0.78 to 0.96), cardiovascular events (0.89, 95% CI 0.83 to 0.95), coronary events (0.88, 95% CI 0.80 to 0.98), stroke (0.73, 95% CI 0.64 to 0.83), albuminuria (0.83, 95% CI 0.79 to 0.87)

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and retinopathy (0.87, 95% CI 0.76 to 0.99). The corresponding ARR, in events per 1,000 patient-years of follow up, were 3.16 (95% CI 0.90 to 5.22) for all-cause mortality, 3.90 (95% CI 1.57 to 6.06) for CVD events, 1.81 (95% CI 0.35 to 3.11) for CHD events, 4.06 (95% CI 2.53 to 5.40) for stroke events, 9.33 for albuminuria (95% CI 7.13 to 11.37) and 2.23 (95% CI 0.15 to 4.04) for retinopathy events. When trials were stratified by baseline SBP, those trials where the baseline was <140 mm Hg showed clear benefit for prevention of stroke and reducing progression of retinopathy and albuminuria, whereas the other end points were not affected. The quality of this evidence is compromised by the literature searches only including one database.

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**R** Individuals with diabetes should be offered blood pressure-lowering treatment if the baseline clinic systolic pressure is >140 mm Hg, to prevent mortality, macrovascular events, and progression of nephropathy and retinopathy.

**R** Individuals with diabetes should be considered for blood pressure-lowering treatment, even if the systolic clinic blood pressure is <140 mm Hg, to reduce the risk of stroke, progression of retinopathy and albuminuria. At this level of blood pressure, treatment should be targeted at patients thought to be at greatest risk of those complications.

#### *People with chronic kidney disease*

In a meta-analysis from the Blood Pressure Treatment Trialists' Collaboration data from 152,290 individuals with and without chronic kidney disease participating in 26 RCTs were analysed.<sup>313</sup> Compared with placebo, BP-lowering regimens reduced the risk of major cardiovascular events by 17% per 5 mm Hg reduction in SBP, irrespective of whether they had CKD or not. Specifically, blood pressure lowering in itself, rather than the effects of a particular drug class, seemed to lower the cardiovascular risk. Unfortunately in this analysis no information is provided on baseline blood pressures.

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Meta-analyses of cohort studies including over 1.4 million individuals reported that after adjustment for traditional cardiovascular risk factors and albuminuria, the risk gradient for cardiovascular mortality was approximately flat when eGFR rates were higher than 75 ml/min/1.73 m<sup>2</sup> but linearly increased with decreasing eGFR rates below this threshold. Cardiovascular mortality was about twice as high in patients with stage 3 chronic kidney disease (eGFR 30–59 ml/min/1.73 m<sup>2</sup>) and three times higher at stage 4 (15–29 ml/min/1.73 m<sup>2</sup>) than that in individuals with normal kidney function. In contrast to the non-linear risk relationship for eGFR, no threshold effect was reported for the association of albuminuria with cardiovascular risk, even after adjustment for traditional cardiovascular risk factors and eGFR. The adjusted risk of cardiovascular mortality is more than doubled at the upper end of the microalbuminuria range (30–299 mg/g), compared with the risk in individuals with normal albuminuria.<sup>314,315</sup> This lack of threshold effect indicates that albuminuria even at the upper end of the normal range (threshold 30 mg/g) confers cardiovascular risk.

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**R** All people with stage 3 or higher chronic kidney disease, or micro- or macroalbuminuria should be offered blood pressure-lowering treatment.

#### *People on dialysis*

In patients on dialysis, BP lowering was associated with a lower risk of cardiovascular events (RR 0.71, 95% CI 0.55 to 0.92), all-cause mortality (RR 0.80, 95% CI 0.66 to 0.96), and cardiovascular mortality (RR 0.71, 95% CI 0.50 to 0.99).<sup>316</sup> The effects were not clearly associated with the presence or absence of hypertension, although the analysis was not adequately powered to state this with confidence. Similarly, it was underpowered to distinguish the effects of blood pressure lowering from the effects of individual drug classes. Because of the wide range of baseline blood pressures included in these trials, the wide range of blood pressures reductions achieved, and the innate variability of blood pressure in patients undergoing dialysis, it is not possible to comment on a specific threshold BP for treatment, although the data strongly support the use of BP-lowering treatment in patients on dialysis to prevent cardiovascular events and improve survival.

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**R** All patients on dialysis should be offered blood pressure-lowering treatment.

*Older people*

Data in the elderly are less robust, but one major RCT examined blood pressure lowering in patients aged over 80.<sup>317</sup> At baseline patients had a sustained SBP of  $\geq 160$  mm Hg, with a mean baseline BP of 173.0/90.8 mm Hg. First-line treatment in the active-therapy group was indapamide, supplemented by perindopril. In the active-treatment group there was a 30% reduction in fatal and non-fatal stroke, 21% reduction in all-cause mortality, 23% fewer deaths from cardiovascular disease, and a 64% lower risk of heart failure. Adverse events were less frequent in the active-treatment group.

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**11.2 TARGET VALUES FOR BLOOD PRESSURE LOWERING**

The relationship between blood pressure and cardiovascular risk is continuous and targets have been lowered over recent years as evidence of benefit and safety has accumulated. Numerous overviews and meta-analyses have documented beyond reasonable doubt the benefits of blood pressure lowering in patients with hypertension with respect to virtually all major outcome measures. In very general terms, they have also shown that the lower the achieved blood pressure the greater the benefits.

A meta-analysis of studies published between 1966 and 2013 included 245,885 patients.<sup>310</sup> Although the quality of the individual trials was mixed and heterogeneity was not fully explored, the analysis provides a precise estimate of treatment effects. Overall, lowering BP prevented 28 (95% CI 19 to 35) major cardiovascular events per 1,000 patients treated for five years, including 17 (95% CI 14 to 20) strokes and eight (95% CI 4 to 12) deaths. Benefits were proportional to the reduction of both SBP and DBP, although progressively greater BP reductions resulted in progressively lower increments of risk reduction.

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In a subset analysis of achieved blood pressures (104,359 individuals) the relative and absolute risk reductions were greater at an achieved SBP of 140 mm Hg compared with 150 mm Hg. At SBP less than 130 mm Hg, only stroke and all-cause mortality were significantly reduced. Outcomes were significantly reduced at DBP of 80 mm Hg compared with 90 mm Hg, but only stroke was reduced at an achieved DBP below 80 mm Hg.<sup>308</sup>

Evidence for an optimal level of diastolic blood pressure, drawn from a large meta-analysis of antihypertension intervention trials, indicates that the further the diastolic blood pressure can be reduced, the greater the reduction in cardiovascular risk without any convincing evidence of a J-curve relationship.<sup>318</sup> The HOT trial reported that the optimal target blood pressure in patients with a diastolic BP of 100–115 mm Hg was 139/83 mm Hg.<sup>299</sup>

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One meta-analysis reported on more, compared with less strict blood pressure targets, identifying 19 trials of 44,989 patients of any age including those with hypertension, high risk of CVD or renal disease or both.<sup>319</sup> During a mean 3.8 years of follow up 2,496 major cardiovascular events were recorded. Patients in the more intensive blood pressure-lowering treatment group had mean blood pressure levels of 133/76 mm Hg, compared with 140/81 mm Hg in the less intensive treatment group. Intensive blood pressure-lowering treatment achieved relative reductions in the risk of major cardiovascular events (14%, 95% CI 4 to 22), myocardial infarction (13%, 95% CI 0 to 24), stroke (22%, 95% CI 10 to 32), albuminuria (10%, 95% CI 3 to 16), and retinopathy progression (19%, 95% CI 0 to 34). More intensive treatment had no clear effects on heart failure (15%, 95% CI -11 to 34), cardiovascular death (9%, 95% CI -11 to 26), total mortality (9%, 95% CI -3 to 19) or end stage kidney disease (10%, 95% CI -6 to 23). The absolute benefits were greatest in trials in which all enrolled patients had vascular disease, renal disease or diabetes. Serious adverse events associated with blood pressure lowering were only reported in six trials, and had an event rate of 1.2% per year with intensive treatment compared with 0.9% with less intensive treatment. Severe hypotension was more frequent with the more intensive treatment regimens (RR 2.68, 95% CI 1.21 to 5.89,  $p=0.015$ ) although the absolute excess was small (0.3% v 0.1% per person-year for the duration of follow up). The authors conclude that this analysis provides clear evidence of the benefits of more intensive blood pressure lowering, particularly in high-risk patient groups.

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The Systolic Blood Pressure Intervention (SPRINT) trial<sup>320</sup> recruited hypertensive patients at high cardiovascular risk, but excluded those with diabetes or prior stroke. Standard treatment aimed for a systolic BP of less than 140 mm Hg, while the intensive treatment group aimed for a systolic BP of less than 120 mm Hg. Critically, these pressures were measured by semiautomated devices, in the absence of a medical attendant, after several

minutes rest. The study was stopped after only 3.3 years of follow up because of a significantly lower rate of the composite primary outcome (1.65% per year v 2.19%) in the intensive group, although at the expense of an increase in the number of adverse effects from treatment. A number of features of this trial make interpretation of the results problematic, particularly in the context of usual practice within NHSScotland. As a result the GDG has chosen not to give undue emphasis to this individual study, whilst acknowledging that it broadly supports the strategy of considering tighter blood pressure targets in high-risk patients.

The cost effectiveness of different targets for the reduction in BP was analysed using clinical data from the HOT trial.<sup>321</sup> The trial randomised patients to three DBP target groups, with the hypothesis that the lower the target, the better the outcome but the higher the drug costs. No statistical difference in the number of events avoided for the three target groups was shown. Significant reductions in event rates were found in a subset analysis of people with diabetes, which limited the cost-effectiveness analysis to this group. The study concluded that in patients with diabetes, compared with maintenance doses of calcium channel blockers, intensive treatment to a lower blood pressure target ( $\leq 80$  mm Hg), was cost effective.

### 11.2.1 TYPE 2 DIABETES

A meta-analysis of blood pressure reduction targets in 37,736 participants with type 2 diabetes or impaired fasting glucose from 13 RCTs investigated intensive blood pressure reduction.<sup>322</sup> Lowering blood pressure to a more intensive target of  $<135$  mm Hg systolic compared with a less intensive target ( $<140$  mm Hg) was associated with a 10% reduction in risk of all-cause mortality (OR 0.90, 95% CI 0.83 to 0.98, ARR 0.53%) a 17% reduction in the risk of stroke (OR 0.83, 95% CI 0.73 to 0.95, ARR 0.41%), and a 20% relative increase in the risk of serious adverse events (OR 1.20, 95% CI 1.08 to 1.32). Although there was a direct linear relationship between SBP and stroke, with lower better, the same was not true for other outcomes. Even more intensive BP control ( $\leq 130$  mm Hg) was associated with a further reduction in stroke but did not affect cardiac and microvascular outcomes and there was a 40% increase in serious adverse events.

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A Cochrane review of five RCTs with a mean follow up of 4.5 years involved 7,314 patients with type 2 diabetes.<sup>323</sup> The largest of these trials (ACCORD 2) compared outcomes in respect of achieved systolic blood pressure in patients with cardiovascular disease or with increased cardiovascular risk. The incidence of cardiovascular disease (primary event rate) was very close to 2% in both groups. Whilst achieving a blood pressure of 119.3/64.4 mm Hg compared with 133.5/70.5 mm Hg, the only significant benefit in the 'tighter control' group was a reduction in the incidence of stroke (RR 0.58, 95% CI 0.39 to 0.88, ARR 1.1%). The tighter target was achieved only with a significant increase in the risk of serious adverse events (RR 2.58, 95% CI 1.70 to 3.91). In four other trials that examined outcomes by DBP targets no significant differences were found. These trials included some patients who were not hypertensive by conventional definition, and excluded patients with known cardiovascular disease.

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### 11.2.2 CHRONIC KIDNEY DISEASE

Little evidence was identified which investigated the impact of different blood pressure treatment targets on cardiovascular outcomes in patients with CKD. A large meta-analysis involving over 150,000 patients with and without CKD reported no clear benefit for more intensive compared with less intensive blood pressure-lowering regimens in people with CKD, although there was only limited power for these analyses and little capacity to detect whether the effects of treatment varied according to kidney function.<sup>313</sup>

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### 11.2.3 DIALYSIS

No evidence was identified which supported the definition of an optimal blood pressure target for patients on dialysis. Physiological and dialysis-related mechanisms influencing blood pressure in patients on dialysis are complex with the effect on cardiovascular risk unclear.

A consensus conference of the Kidney Disease: Improving Global Outcomes (KDIGO) group discussed the existence of a 'U-shaped' association between predialysis blood pressure and mortality based on a cohort study showing that the risk of death is lowest in dialysis patients with a pre-dialysis SBP between 100 and 125 mm Hg, whereas SBP  $>150$  mm Hg was associated with increased mortality. KDIGO notes that the modifying effect of cardiomyopathy in hypertensive patients resulting in attainment of blood pressure targets relevant

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to non-dialysis patients make it difficult, without further cardiac investigation, to distinguish patients with a satisfactory target blood pressure from those with severe cardiac disease. Use of echocardiography is essential to understand this problem.<sup>324</sup>

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#### 11.2.4 CONCLUSIONS

The optimal target blood pressures to be achieved with therapy have not yet been unequivocally established from the available evidence. A long-term trend towards lower target pressures has been reversed in recent years, at least for some patient subgroups, for example patients with diabetes, those with CHD, and the elderly. This has been reflected in reports and position statements from the European Society of Cardiology/European Society of Hypertension,<sup>325</sup> from the US Eighth Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8)<sup>326</sup> and from the American Heart Association/American College of Cardiology/American Society of Hypertension.<sup>327</sup> More recent evidence, referred to in the current guideline (*see section 11.2*), points to a potential revision of this position. Translating very strict targets from tightly controlled clinical trials to routine practice presents many challenges, including choice of combination therapy, dose titration, more frequent supervision, and monitoring for patient safety, not to mention patient engagement. In order to balance current evidence for benefit and harm within the context of feasible service delivery, the guideline development group has adopted a reasonably conservative approach, recognising that even with the targets recommended here, the control of about half of all patients with hypertension may remain suboptimal.

**R** Individuals with uncomplicated hypertension should be supported to achieve a BP target of <140/90 mm Hg (clinic measurement).

**R** For individuals with established CVD and diabetes, chronic renal disease or target organ damage a lower blood pressure target of <135/85 mm Hg (clinic measurement) should be considered.

**R** Lowering BP below 130/80 mm Hg is not routinely recommended as this brings limited additional benefits and causes significant adverse effects.

✓ These target figures are a general guide, and may be adapted in the light of medicines tolerance, and in particular in the frail or elderly, who may be more susceptible to adverse effects of treatment. In such patients, more modest reductions in blood pressure may still be beneficial.

### 11.3 SELECTION OF ANTIHYPERTENSIVE THERAPY

The weight of evidence suggests that blood pressure lowering, rather than pharmacological action, confers almost all the benefit in preventing cardiovascular events.<sup>307</sup>

There are four major classes of antihypertensive drug (thiazides, ACE inhibitors, angiotensin receptor blockers (ARB, also known as angiotensin-II receptor antagonists) and calcium channel blockers) which are equally effective, and more effective than beta-blockers, at reducing cardiovascular morbidity and mortality per unit fall in blood pressure. There are some important cautions and contraindications for all of the antihypertensive drug classes.<sup>318,328,329</sup>

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In a meta-analysis, all classes of blood pressure-lowering drugs significantly reduced blood pressure from all pretreatment levels. The extent of blood-pressure reduction increased with pretreatment blood pressure. The reductions were similar at standard dose for each class; the average reduction was 9.1 mm Hg systolic and 5 mm Hg diastolic. The effect of combinations of two drugs on blood pressure was additive.<sup>306</sup> The adverse effect profiles of drugs could be minimised by using half-standard or standard doses, rather than titrating any given drug to higher doses. This does not apply to ACE inhibitors or ARBs, where the adverse effects are present or absent, regardless of dose. The meta-analysis presents a rationale for polypharmacy, utilising modest doses of more than one antihypertensive agent in order to maximise control whilst minimising adverse effects.

1<sup>++</sup>

The ASCOT-BPLA study recruited 19,257 patients, including many from Scotland, to treatment with two combinations of antihypertensive drugs.<sup>330</sup> The study tested whether a newer antihypertensive combination treatment, comprising the calcium channel blocker (CCB) amlodipine and the ACE inhibitor perindopril, was more effective than an older combination regimen of the beta blocker atenolol and the diuretic bendroflumethiazide. The trial was terminated early because of a large difference in mortality between the older drugs and the newer ones, favouring the amlodipine+perindopril combination. The trial showed that amlodipine+perindopril were significantly more effective at reducing strokes (327 v 422; unadjusted HR 0.77, 95% CI 0.66 to 0.89,  $p=0.0003$ ), total cardiovascular events (1,362 v 1,602; HR 0.84, 95% CI 0.78 to 0.90,  $p<0.0001$ ) and all-cause mortality (738 v 820; HR 0.89, 95% CI 0.81 to 0.99,  $p=0.025$ ) than atenolol with bendroflumethiazide.

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A large RCT of 33,357 patients reported on blood pressure lowering in individuals with high global risk and hypertension. A significant proportion of the participants had overt vascular disease as indicated by previous cardiovascular events (MI, stroke), or ongoing symptoms (angina, intermittent claudication). All had moderate hypertension, whether on therapy or untreated. Extensive analysis of this trial and data subsets shows evidence of reduced event rate regardless of starting blood pressure, within the parameters of trial inclusion.<sup>331</sup> Participants were randomised to receive a thiazide-like diuretic (chlorthalidone, 12.5 to 25 mg daily); a CCB (amlodipine, 2.5 to 10 mg daily); or an ACE inhibitor (lisinopril, 10 to 40 mg daily). There was no significant difference between groups in combined fatal CHD or non-fatal MI. Five-year SBP was significantly higher in the amlodipine (0.8 mm Hg,  $p=0.03$ ) and lisinopril (2 mm Hg,  $p<0.001$ ) groups compared with chlorthalidone, and five-year DBP was significantly lower with amlodipine (0.8 mm Hg,  $p<0.001$ ). For amlodipine versus chlorthalidone, outcomes were similar except for a higher six-year rate of heart failure with amlodipine (10.2% v 7.7%; RR, 1.38, 95% CI 1.25 to 1.52).

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- ✓ In any individual with hypertension, consideration should be given to using two or more antihypertensive agents, in half to standard doses, to achieve additive blood pressure lowering whilst minimising the adverse effect profile.

### 11.3.1 THE BRITISH HYPERTENSION SOCIETY ALGORITHM

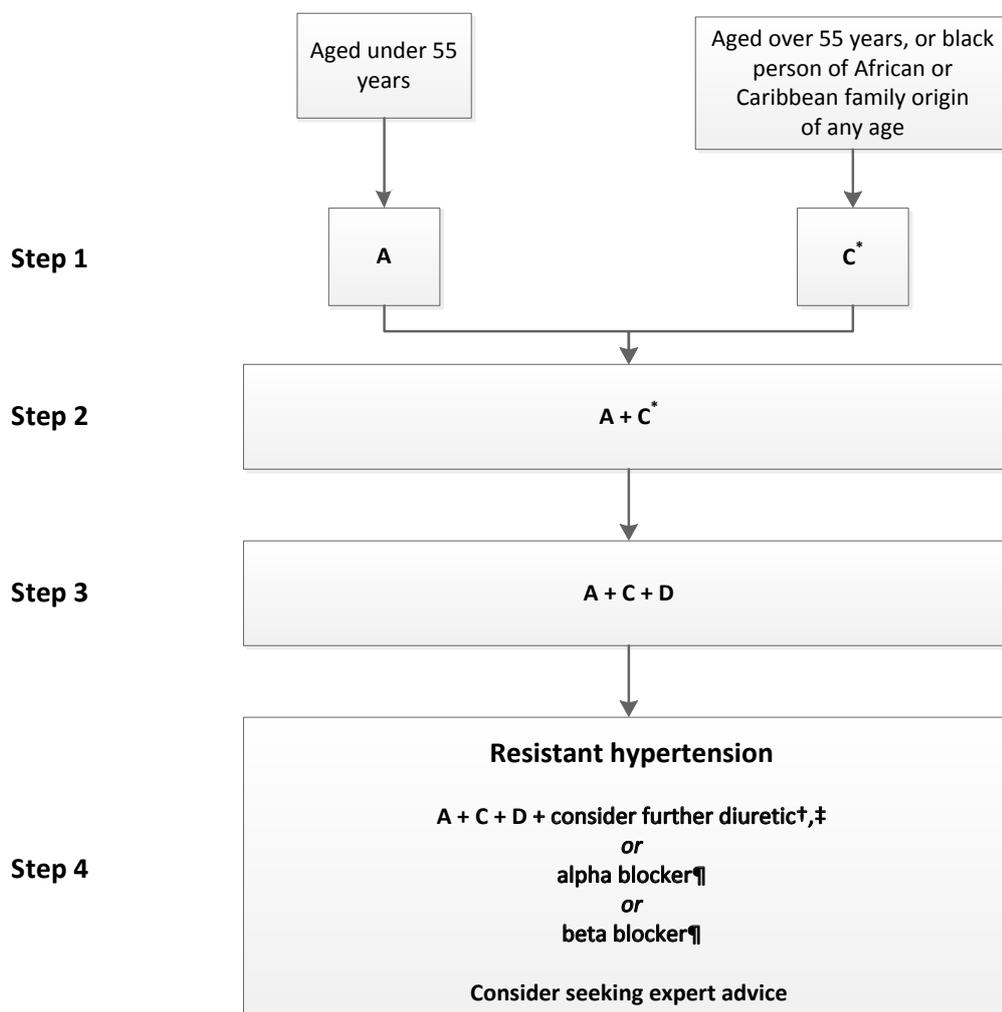
The British Hypertension Society A/CD algorithm has been widely adopted for deciding upon drug therapy for an individual. The algorithm was ratified by the ASCOT trial and accepted by The Joint British Societies' Guidelines as the best method of defining combination drug therapy.<sup>30</sup> The algorithm and subsequent adaptations established that initial therapy for primary hypertension should be stratified according to age and ethnicity.

In 2011 NICE and the BHS released jointly a revised guideline that updated the clinical evidence base to include recent RCTs and included a cost-effectiveness analysis comparing the various blood pressure-lowering drug classes.<sup>42</sup> The results showed that:

- beta blockers are the least clinically and cost-effective drug at preventing major cardiovascular events
- calcium channel blockers are the most clinically and cost-effective choice for the majority of people aged over 55 years but thiazide-type diuretics represent an alternative for those with heart failure or the very elderly who are intolerant of calcium channel blockers
- when choosing a thiazide-like diuretic chlorthalidone or indapamide may be more effective than bendroflumethiazide
- for people under the age of 55, drugs affecting the renin-angiotensin system are recommended.

The recommendations based on this evidence are summarised in the A/CD algorithm shown in Figure 1. It incorporates the recommended classes of antihypertensive drugs. Although not specifically validated by a clinical trial, the recommended drug combinations and sequencing are similar to those used in many clinical trials of blood pressure-lowering drugs.

Figure 1: The NICE/British Hypertension Society A/CD algorithm for blood pressure



A = ACE inhibitor or low cost ARB, C = calcium channel blocker, D = thiazide-type diuretic.

\* A CCB is preferred but consider a thiazide-like diuretic if a CCB is not tolerated or the person has oedema, evidence of heart failure or a high risk of heart failure.

† Consider a low dose of spironolactone<sup>‡</sup> or higher doses of thiazide-type diuretic.

‡ At the time of publication of this NICE/BHS guideline (August 2011), spironolactone did not have a UK marketing authorisation for this indication. Informed consent should be obtained and documented.

¶ Consider an alpha or beta blocker if further diuretic therapy is not tolerated, or is contraindicated or ineffective.

National Institute for Health and Clinical Excellence (2011) Hypertension: the clinical management of primary hypertension in adults. Methods, evidence, and recommendations (CG127). Available from: [www.nice.org.uk/guidance/cg127](http://www.nice.org.uk/guidance/cg127). NICE has not checked the use of its content in this guideline to confirm that it accurately reflects the NICE publication from which it is taken. This material is provided under the terms of NICE's Open Content licence ([www.nice.org.uk/re-using-our-content/uk-open-content-licence](http://www.nice.org.uk/re-using-our-content/uk-open-content-licence)).

## 11.4 MULTIPLE RISK INTERVENTIONS

One Cochrane review of 55 trials, including 163,471 participants, investigated the effects of interventions which used counselling and education to facilitate behaviour change that aimed to reduce more than one risk factor (multiple risk-factor interventions) in people without evidence of cardiovascular disease.<sup>332</sup> Pooled effects suggested that multiple risk-factor interventions had no effect on mortality (RR 1.00, 95% CI 0.96 to 1.05) but yielded small reductions in blood pressure and cholesterol. Significant reductions in total mortality and combined fatal and non-fatal cardiovascular events were reported from results of trials involving people with hypertension (16 trials) and diabetes (five trials): OR 0.78 (95% CI 0.68 to 0.89) and OR 0.71 (95% CI 0.61 to 0.83), respectively. The authors note that multiple risk-factor interventions appear to be more effective in high-risk populations who may be more highly motivated to act on counselling and education and may also benefit because they were more likely to adhere to their drug medications.

1+

Treating large numbers of individuals in low-risk populations may result in small treatment benefits being outweighed by small treatment risks.<sup>333,334</sup> Evidence suggests that health promotion interventions achieve limited benefits in general populations at relatively low cardiovascular risk and the high costs of such approaches may be better used in people at higher cardiovascular risk.

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## 12 Psychological issues

### 12.1 THE IMPACT OF PSYCHOLOGICAL WELLBEING ON CARDIOVASCULAR RISK

Stress is perceived by the majority of cardiac patients to have been an important cause of their heart disease. This belief is also common among the general public, and confusion exists among health professionals as to its role in the development of and outcome with CHD. Stress is a commonly used global term which has different interpretations making accurate measurement problematic. Social isolation or lack of social support, work stress, and acute and chronic life events can serve as stressors, with resulting psychological outcomes such as depression and anxiety.

A review of systematic reviews undertaken by an Expert Working Group of the National Heart Foundation of Australia identified 15 reviews showing strong and consistent evidence that depression and social isolation or lack of quality social support are independent risk factors for the development of CHD and subsequent prognosis.<sup>335</sup> The largest of these reviews provides strong and consistent evidence for both of these factors but also evidence that aspects of work-related stress may be associated with increased risk.<sup>336</sup> The review concluded that depression, social isolation and lack of social support are significant risk factors for CHD and are independent of conventional risk factors such as smoking, hypercholesterolaemia and hypertension with a similar strength of association (one to two-fold increased risk of developing CHD with minor depression and three to five-fold increase with major depression). Social isolation/lack of quality social support is also of a clinically significant magnitude (two to three-fold increased risk of developing CHD and three to five-fold increased risk of death in patients with CHD).

2<sup>++</sup>

There is no clear evidence to suggest that treating depression is effective in reducing risk. Increased attention to conventional risk factors in patients with depression may be appropriate.<sup>337</sup> Further research is necessary to determine the underlying mechanisms accounting for this increased risk and to determine which interventions are effective in treating it.

There is evidence that anxiety is an independent risk factor for CVD.<sup>338</sup> A systematic review and meta-analysis of 37 prospective population studies (including 1,565,699 participants), with mean follow up of 1–24 years, suggested that anxiety (defined as anxiety disorder or increased anxiety symptoms) was associated with new onset of atherosclerotic CVD, relative to no anxiety in people free from CVD at baseline. There was a high likelihood of publication bias in the studies but, when this was adjusted for, there remained an increased incidence of CVD associated with anxiety (HR 1.41, 95% CI 1.26 to 1.57). This risk estimate might be an overestimation because confounders were insufficiently accounted for, for example only a third of studies adjusted for comorbid depression and only a minority of studies adjusted for psychotropic medication, which has been associated with increased cardiovascular risk. Nevertheless, risk estimates from studies that accounted for depression (14 comparisons, HR 1.57, 95% CI 1.29 to 1.90) or multiple CVD risk factors (34 comparisons, HR 1.50, 95% CI 1.33 to 1.71) were comparable with the overall pooled HR, reinforcing the suggestion that anxiety may be an independent risk factor for CVD.

2<sup>++</sup>

A systematic review and meta-regression of factors associated with anxiety disorder diagnosis, treatment and morbidity risk in 7,973 patients with CHD found a non-specific association between generalised anxiety disorder and MCE.<sup>339</sup> The association was significant in outpatient groups only, mainly referring to people who have had an MCE and are subsequently discharged from hospital. It was not clear if anxiety had a contributory effect on CHD. It was also not possible to assess the extent of the increase in MCE by anxiety subtypes independent of depression, due to high levels of comorbidity. The studies included were of low quality, included no RCTs and were highly heterogeneous.

2<sup>+</sup>

There is consistent evidence that catastrophic life events of a highly stressful nature such as earthquakes or terrorist attacks and, to a lesser degree, bereavement are associated with increased cardiac risk.<sup>335</sup>

2<sup>++</sup>

A systematic review of 26 cohort studies investigating work stress revealed moderate evidence that stress at work is related to cardiovascular morbidity and mortality.<sup>340</sup> The association between job stress and cardiovascular disease in women was not clear and associations were weaker in participants above the age of 55.

A meta-analysis of 13 cohort studies found that job strain was associated with a small increased risk of an incident cardiovascular event.<sup>341</sup> However, contrary to the previous review, this study showed broadly similar results for men and women, and for those younger and over 50. There were a number of limiting factors. The methodological quality of the included studies was not assessed and included unpublished studies. The analysis found a substantial difference between the published and unpublished studies with unpublished studies showing a weaker association between job strain and CHD. 2+

The INTERHEART study reported on risk factors, including psychosocial factors, in 11,119 cases of MI and 13,648 controls across 52 countries.<sup>342</sup> Composite variables of subjective stress (home, work, and financial stress, low self-efficacy and self-reported retrospective rating of depression) appeared to be associated with increased risk of developing an acute MI across gender, nationality, ethnic groups, and to be independent of smoking and socioeconomic status. There are some major concerns regarding the methods of measuring stress in this study, which was undertaken in a non-standardised way, and retrospectively relying on patient memory and perception over the previous 12 months. It does indicate that some undefined elements of stress contribute to increased risk of cardiac events across cultures. 2++

A precise definition of work stress and consistency of measurement in studies is lacking. Previously, there was some evidence that work-related CHD risk was affected by individual personality factors such as coping styles, availability of support and other psychosocial factors rather than work-specific characteristics. While early studies suggested that personality traits such as type A behaviour or hostility might be associated with increased cardiovascular risk, there is now clear evidence that this is not the case.<sup>336</sup> 2++

**R** | **Depression, anxiety and social isolation or lack of quality social support are risk factors for the development and prognosis of cardiovascular disease and should be taken into account when assessing individual risk.**

The National Institute for Health and Care Excellence has published guidelines on recognition and management of depression in adults with and without a chronic physical health problem.<sup>343,344</sup>

## 12.2 INTERVENTIONS FOR PSYCHOLOGICAL DISTRESS

### 12.2.1 PSYCHOLOGICAL INTERVENTIONS

Psychological interventions are based on psychological concepts and theory and aim to help people understand and change their thinking, behaviour and relationships to relieve distress and to improve functioning.<sup>345</sup> The stepped-care model which organises the provision of services in a structured manner and emphasises offering the least intrusive but most effective intervention first and progressing to further steps only if the patient does not benefit, or declines the intervention, is described in a UK guideline.<sup>343</sup>

#### *Cognitive behavioural therapy*

Cognitive behavioural therapy (CBT) is a structured therapy addressing individuals' core beliefs, assumptions, thinking patterns and behaviour. It has been shown to be effective in patients with a wide range of conditions, including anxiety, depression, post-traumatic stress disorder and medical conditions.<sup>346</sup> Some of the following evidence and recommendation is derived from the SIGN guideline on non-pharmaceutical management of depression in adults.<sup>347</sup> 4

There is robust and consistent meta-analysis and systematic review evidence that CBT is more effective than either treatment as usual or waiting list control in the treatment of depression in adults and older adults and is at least as effective as antidepressant medication. For those studies where follow up was examined CBT was at least as effective as antidepressant medication over six months to two years' follow up. In some studies CBT was more effective than other psychological therapies whilst other studies suggest CBT has similar effectiveness to other systematic therapies such as psychodynamic therapy and interpersonal therapy.<sup>348-353</sup> 1++

One systematic review included a comparison of group versus individual CBT and found that patients receiving individual CBT were more likely to improve and had fewer symptoms at follow up than patients receiving group CBT.<sup>348</sup> 1++

Use of CBT in patients with either cardiac or other physical health problems (chronic fatigue and chronic pain) as part of an educational and rehabilitation programme has addressed beliefs and attributions and used goal setting and pacing principles to shape the desired behaviour. Studies note positive outcomes in exercise, activities and mood.<sup>288-291</sup> 1<sup>++</sup>

The NICE guideline on management of generalised anxiety disorder (GAD) and panic disorder in adults recommends CBT in people with GAD and marked functional impairment, or those whose symptoms have not responded adequately to step 2 interventions (low-intensity psychological interventions, individual non-facilitated self-help and individual guided self-help and psychoeducational groups).<sup>354</sup> 4

**R** Individual CBT is recommended as a treatment option for patients with depression or anxiety disorders.

#### *Mixed interventions*

A Cochrane review of psychological interventions for patients with CHD included 24 studies where the effect of psychological interventions could be distinguished from other components of rehabilitative treatment (for example exercise).<sup>355</sup> There was no strong evidence that psychological intervention reduced total deaths, risk of revascularisation, or non-fatal MI. Amongst a smaller group of studies reporting cardiac mortality there was a modest positive effect from the psychological intervention (RR 0.80, 95% CI 0.64 to 1.00), however, there was some evidence of small-study bias. There was evidence that psychological interventions may produce small to moderate reductions in depression (standardised mean difference (SMD) -0.21, 95% CI -0.35 to -0.08) and anxiety (SMD -0.25, 95% CI -0.48 to 0.03). There was a wide variation in the types of psychological intervention used to treat cardiac patients included in this review which reflects the uncertainty in the literature linking emotion with cardiac outcomes, however all interventions were delivered by healthcare workers with specific training in the particular psychological techniques required. There was substantial clinical heterogeneity observed in the included studies, which was reflected in significant statistical heterogeneity for psychological outcomes. 1<sup>++</sup>

A systematic review examined the effectiveness of psychological interventions for patients with CHD and their partners.<sup>356</sup> The review included only seven studies, comprising 673 patients, of which two studies demonstrated modest improvements in depression, anxiety, knowledge of disease and treatment, and satisfaction with care, and in partners' anxiety, knowledge and satisfaction. One study showed a beneficial effect on blood pressure. There was no evidence of significant effects on mortality, morbidity or cardiovascular risk factors. The studies were generally of poor methodology and excluded studies were not listed. 1<sup>++</sup>

Lifestyle interventions, including relaxation, are often recommended as initial treatment for mild hypertension, although the efficacy is unclear. A Cochrane review was conducted to clarify the effects of relaxation therapies on cardiovascular outcomes and blood pressure in people with elevated blood pressure. This review included 25 RCTs with 1,198 participants. It noted that the poor quality of the trials included and the unexplained variation between the trials meant that evidence in favour of causal association between relaxation and blood pressure reduction is weak.<sup>357</sup> 1<sup>++</sup>

**R** Psychological treatments for patients with mood and anxiety disorders and comorbid cardiovascular disease should be considered.

✓ Patients who present with more complex psychological problems should be considered for referral to mental health services for assessment and delivery, where appropriate, of high-intensity or specialist treatments.

*Therapist training, skill and competence*

The effectiveness of any intervention depends on the training and competence of the therapist. NHS Education for Scotland recommends that therapists need to be trained to recognised standards, have the competences necessary to deliver psychological interventions effectively to the tier of service within which they work; deliver well-articulated therapy, adhering to the appropriate model and; operate within a well-governed system which offers regular high-quality, model-specific clinical supervision, support and relevant CPD.<sup>345</sup>

1+  
4

- ✓ | Practitioners using psychological techniques should receive appropriate training and supervision from a clinical psychologist or therapist with similar level of expertise.

## 12.2.2 PHARMACOLOGICAL INTERVENTIONS FOR DEPRESSION

Three systematic reviews of selective serotonin reuptake inhibitors (SSRIs) in patients with both CHD and diagnosed depression reported that SSRIs showed a small benefit in reducing depression however they showed no impact on mortality or cardiac events.<sup>358-360</sup> Data on the effect on hospital readmission were inconsistent.

1++

A systematic examination of recommendations for drug treatment in 12 NICE guidelines for single disease conditions calculated the potential for interactions between drugs recommended across different guidelines and between drugs and diseases.<sup>361</sup> Drug-disease interactions were not common, with the exception of those related to CKD. However 89 potential important drug-drug interactions were identified between drugs recommended in the depression guideline and those recommended in the other 11 guidelines analysed. The authors note that by taking account explicitly of the patient's comorbidities there is the potential to avoid unnecessary interactions. For example, SSRIs are noted to interact with a number of medications which are commonly prescribed in patients with CHD, such as aspirin, clopidogrel, warfarin and dabigatran, increasing the risk of bleeding. In addition there is a noted interaction between SSRIs and tramadol, which is often used to manage pain. Given that around a quarter of people with depression also suffer painful physical conditions, clinicians may wish to consider alternative treatments for depression in such patients.<sup>362</sup>

- R | **Pharmacological treatment with SSRIs in patients with depression and coronary heart disease should be considered, although caution should be taken over patients receiving polypharmacy in whom bleeding risk may be increased.**

## 13 Provision of information

This section reflects the issues likely to be of most concern to patients and their carers. These points are provided for use by health professionals when discussing cardiovascular disease with patients and carers and in guiding the production of locally-produced information materials.

### 13.1 SOURCES OF FURTHER INFORMATION

In addition to the information provided at the time of consultation, both patients and carers may be encouraged to access trusted websites or national third sector provider helplines to answer any non-urgent/non-emergency enquiries. National helplines help provide clarity to patients and carers on a number of topics, most commonly a recent diagnosis or test result and/or providing support in reducing cardiovascular risk.

#### **NHS inform**

Telephone: 0800 22 44 88 (8am–10pm)

[www.nhsinform.scot](http://www.nhsinform.scot)

NHS inform is the national health and care information service for Scotland. It includes a section on heart conditions with information and links to resources to support patients with heart disease. [www.nhsinform.scot/illnesses-and-conditions/heart-and-blood-vessels](http://www.nhsinform.scot/illnesses-and-conditions/heart-and-blood-vessels)

There is also a section providing advice on healthy living for physical and mental wellbeing [www.nhsinform.scot/healthy-living](http://www.nhsinform.scot/healthy-living)

#### **British Heart Foundation**

Ocean Point 1, 94 Ocean Drive, Edinburgh, EH6 6JH

Telephone: 020 7554 0000; Heart Helpline: 0300 330 3311

[www.bhf.org.uk](http://www.bhf.org.uk) • Email: [bhfhi@bhf.org.uk](mailto:bhfhi@bhf.org.uk)

The BHF is a national heart charity and the largest independent funder of cardiovascular research in the UK. In addition to fundraising activities and allocating research funding, the BHF provides vital support, information and care for patients and their carers. The BHF is leading the fight to prevent more people from developing cardiovascular disease and helping more people to survive a cardiac arrest or heart attack. It provides forums to listen to, engage and influence both patients and key stakeholders.

#### **Chest Heart & Stroke Scotland**

Third Floor, Rosebery House, 9 Haymarket Terrace, Edinburgh, EH12 5EZ

Telephone: 0131 225 6963; Advice Line Nurses - 0808 801 0899. (9.30am–4.00pm, Mon–Fri)

[www.chss.org.uk](http://www.chss.org.uk) • Email: [admin@chss.org.uk](mailto:admin@chss.org.uk)

Chest Heart & Stroke Scotland is a health charity set up to improve the quality of life for people in Scotland affected by chest, heart and stroke illness, through medical research, influencing public policy, advice and information and support in the community.

#### **Diabetes UK**

Careline Scotland, The Venlaw, 349 Bath Street, Glasgow, G2 4AA

Telephone: (Careline Scotland) 0141 212 8710

[www.diabetes.org.uk](http://www.diabetes.org.uk) • Email: [careline.scotland@diabetes.org.uk](mailto:careline.scotland@diabetes.org.uk)

Diabetes UK provides information, advice and support to help people with diabetes manage the condition well, and bring people together for support when it's needed most.

**Heart UK**

Cholesterol Helpline: 0345 450 5988 (Mon–Fri 10am–3pm)  
www.heartuk.org.uk • Email: ask@heartuk.org.uk

Heart UK is a national charity which provides support, guidance and education services to healthcare professionals and people and families affected by raised cholesterol or other blood fats.

**Smokeline**

Caledonia House, Fifty Pitches Road, Cardonald Park, Glasgow, G51 4EB  
Telephone: 0800 84 84 84 (8am–10pm)  
www.canstopsmoking.com • Email: smokeline@nhs24.scot.nhs.uk

Smokeline is Scotland's national smoking cessation helpline; open every day from 8am–10pm

**13.2 CHECKLIST FOR PROVISION OF INFORMATION**

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the GDG based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

For all patients:

- discuss the relevance of non-modifiable risk factors and empower the patient to change modifiable risk factors where feasible, using positive health promotion. Set goals which are both SMART and person centred
- describe and, where appropriate, provide referral to support services, for example smoking cessation, alcohol services and exercise referral schemes
- ensure that the patient understands the importance of any required follow up.

In patients without established CVD:

- be aware of the different routes of presentation to primary care for risk estimation, for example:
  - patient request
  - at-risk population called by practice
  - referred by another professional, for example optician, pharmacist or secondary-care clinic (high cholesterol, high BP etc detected)
  - following work/private medical insurance check up
- check the patient's understanding of the information provided at the beginning and end of the consultation
- explain the purpose of cardiovascular risk estimation using terminology appropriate to the patient
- explain the individual's specific levels of risk using terminology and visual tools appropriate to the patient, and
- make patients aware of the role of pharmacists in providing advice about avoiding drug interactions and supporting adherence to prescribing.

In patients with established CVD:

- be aware of the different routes of presentation to primary care, for example:
  - following first cardiovascular event
  - arranged follow up
- presenting after a first cardiovascular event, explain the purpose of accurate history taking, examination and blood tests and prioritise lifestyle modifications to reduce future risk, and
- arrange a polypharmacy review which should include advice on stopping medications which are no longer required, and raising awareness of possible drug interactions and adverse effects.

## 14 Implementing the guideline

This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

### 14.1 IMPLEMENTATION STRATEGY

Implementation of national clinical guidelines is the responsibility of each NHS board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

Implementation of this guideline will be encouraged and supported by SIGN. The implementation strategy for this guideline encompasses the following tools and activities.

### 14.2 RESOURCE IMPLICATIONS OF KEY RECOMMENDATIONS

No recommendations are considered likely to reach the £5 million threshold which warrants a resource impact analysis.

### 14.3 AUDITING CURRENT PRACTICE

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

The GDG has identified the following as key points to audit to assist with the implementation of this guideline:

- the proportion of patients who discontinue statin treatment due to reported muscle pain or weakness who are rechallenged with either the same statin or a different statin at the same dose
- the proportion of patients who discontinue statin treatment due to reported muscle pain or weakness who are rechallenged with either the same statin or a different statin at the same dose and remain on treatment one year later
- the proportion of patients with familial hypercholesterolaemia receiving statin treatment
- the proportion of individuals prescribed statins who report statin intolerance and are rechallenged on an alternative statin
- the proportion of patients with BP  $\geq$ 160/100 mm Hg who are on blood pressure-lowering treatment
- The proportion of patients being treated with blood pressure-lowering medication whose last recorded BP result was <140/90 mm Hg, <135/85 mm Hg or <130/80 mm Hg
- the proportion of patients with diagnosed CKD receiving blood pressure-lowering treatment
- the proportion of patients with CVD receiving:
  - any statin therapy
  - intensive statin therapy
- the proportion of GP consultation in which moderate physical activity is recommended.

## 14.4 HEALTH TECHNOLOGY ASSESSMENT ADVICE FOR NHSSCOTLAND

In February 2017 the SMC advised that evolocumab was accepted for restricted use within NHSScotland in adults with primary hypercholesterolaemia (heterozygous familial (HeFH) and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-cholesterol goals with the maximum tolerated dose of a statin or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

It is restricted for specialist use only, when administered at a dose of 140 mg every two weeks, in patients at high cardiovascular risk as follows:

- patients with HeFH and LDL cholesterol  $\geq 5.0$  mmol/l, for primary prevention of cardiovascular events, or
- patients with HeFH and LDL cholesterol  $\geq 3.5$  mmol/l, for secondary prevention of cardiovascular events, or
- patients at high risk due to previous cardiovascular events and LDL cholesterol  $\geq 4.0$  mmol/l, or
- patients with recurrent/polyvascular disease and LDL cholesterol  $\geq 3.5$  mmol/l.

In August 2016 the SMC advised that alirocumab was accepted for restricted use within NHSScotland in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-cholesterol goals with the maximum tolerated dose of a statin, or
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

It is restricted for specialist use only in patients at high cardiovascular risk as follows:

- patients with HeFH and LDL cholesterol  $\geq 5.0$  mmol/l, for primary prevention of cardiovascular events, or
- patients with HeFH and LDL cholesterol  $\geq 3.5$  mmol/l, for secondary prevention of cardiovascular events, or
- patients at high risk due to previous cardiovascular events and LDL cholesterol  $\geq 4.0$  mmol/l, or
- patients with recurrent/polyvascular disease and LDL cholesterol  $\geq 3.5$  mmol/l.

In January 2007 the SMC advised that varenicline was accepted for use within NHSScotland for smoking cessation in adults. The benefits of an additional treatment course in those who have stopped smoking after the initial 12 weeks of therapy appear modest.

Efficacy and safety in patients with significant comorbidity are uncertain.

In October 2005 the SMC advised that atorvastatin calcium was accepted for restricted use in NHSScotland as an adjunct to diet for the reduction of elevated total cholesterol, LDL cholesterol, apolipoprotein B and triglycerides in children aged 10 years and older with primary hypercholesterolaemia, heterozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia when response to diet and other non-pharmacological measures is inadequate.

It is restricted to initiation by paediatricians or physicians specialising in the management of lipid disorders.

In June 2005 the SMC advised that ezetimibe/simvastatin was accepted for restricted use in NHSScotland only for patients who have failed to achieve target cholesterol levels after titration and optimisation of statin monotherapy and where the combination of ezetimibe 10 mg and simvastatin 20 mg, 40 mg or 80 mg is appropriate.

This reflects advice on ezetimibe issued by the Scottish Medicines Consortium in September 2003 (61/03) and is based on the combined tablets being priced at approximately the same level as the individual ingredients.

In September 2003 the SMC advised that ezetimibe may be considered in combination with a statin for patients who have failed to reach target cholesterol levels despite treatment with titrated/optimised statins alone. It may also be considered as monotherapy where statins are inappropriate or poorly tolerated.

# 15 The evidence base

## 15.1 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Evidence and Information Scientist. Databases searched included Cochrane Central Register of Controlled Trials (CENTRAL), National Institute for Health Research - Health Technology Assessment (NIHR-HTA), Medline, Medline In-Process, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2009–2015. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two Evidence and Information Scientists using standard SIGN methodological checklists before conclusions were considered as evidence by the GDG.

### 15.1.1 LITERATURE SEARCH FOR PATIENT ISSUES

At the start of the guideline development process, a SIGN Evidence and Information Scientist conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to risk estimation and prevention of CVD. Databases searched included Medline, Embase, Cinahl and PsycINFO and the results were summarised by the SIGN Patient Involvement Officer and presented to the GDG.

### 15.1.2 LITERATURE SEARCH FOR COST-EFFECTIVENESS EVIDENCE

The GDG identified key questions with potential cost-effectiveness implications, based on the following criteria, where it was judged particularly important to gain an understanding of the additional costs and benefits of different treatment strategies:

- treatments which may have a significant resource impact
- opportunities for significant disinvestment or resource release
- the potential need for significant service redesign
- cost-effectiveness evidence could aid implementation of a recommendation.

A systematic literature search for economic evidence for these questions was carried out by a SIGN Evidence and Information Scientist covering the years 2009–2015. Databases searched include Medline, Embase, NHS Economic Evaluation Database (NHS EED) and Health Economics Evaluation Database (HEED). Each of the selected papers was evaluated by a Health Economist, and considered for clinical relevance by guideline group members.

Interventions are considered to be cost effective if they fall below the commonly-accepted UK threshold of £20,000 per QALY.

## 15.2 RECOMMENDATIONS FOR RESEARCH

The GDG was not able to identify sufficient evidence to answer all of the key questions asked in this guideline (see Annex 1). The following areas for further research have been identified:

- robust economic, epidemiological and feasibility analyses of novel age-stratified and/or life-expectancy maximisation risk estimation tools.
- population studies to assess the incidence of statin intolerance reported in primary care.
- adequately powered RCTs to investigate the effects of stopping statin therapy in people aged  $\geq 85$ , including cardiovascular and QoL primary outcomes.
- studies investigating the causality of association between anxiety and cardiovascular risk.
- randomised controlled trials of interventions to reduce anxiety in people with diagnosed anxiety disorders and CVD.
- randomised controlled trials in patients with established CVD to determine the benefits and harms of initiating blood pressure-lowering treatment at any level of baseline BP.
- randomised controlled trials in patients without established CVD but elevated BP to determine the benefits and harms of initiating blood pressure-lowering treatment at different levels of baseline estimated cardiovascular risk.
- randomised controlled trials in patients with type 2 diabetes to determine the level of baseline BP at which absolute benefit outweighs risks of initiating blood pressure-lowering treatment.
- exploration of the means whereby blood pressure-lowering treatment in the frail elderly may be optimised.
- randomised controlled trials that directly compare the clinical effectiveness of varenicline with combination nicotine-replacement therapy in respect of biochemically-confirmed quit rates at six months post-treatment; also measuring the impact of attendance at group support sessions or individual support.
- randomised controlled trials on the clinical effectiveness of varenicline in diverse populations and settings (such as older people with comorbidities), particularly including investigation of the risk of a significant adverse occurring in a person taking varenicline.
- long-term surveillance studies to consider the potential health impacts of inhaling the contents of e-cigarettes, electronic nicotine delivery systems and vaporisers.
- randomised controlled trials to directly compare the effectiveness of e-cigarettes and electronic nicotine delivery systems with other smoking cessation treatments on biochemically-confirmed quit rates at six months post-treatment.
- large-scale studies to compare carriers of the *ADH1B* genetic variant with non-carriers, adequately powered to investigate the impact of alcohol consumption on the different sub-types of stroke and the impact of different patterns of alcohol consumption on cardiovascular risk.
- randomised controlled trials in patients at high cardiovascular risk or with CVD who have high triglycerides and low HDL cholesterol investigating the effect of fibrate therapy on CVD events.
- exploration of the putative mechanisms accounting for the association between cardiovascular risk and depression and RCTs to evaluate the efficacy of interventions to treat depression and their impact on cardiovascular risk.
- long-term RCTs of the efficacy and safety of stanol esters and plant sterols for LDL cholesterol lowering and whether this translates into reductions in CVD events.
- long-term RCTs of the efficacy and safety of substitution of soya products into the diet for LDL cholesterol lowering and whether this translates into reductions in CVD events.
- randomised controlled trials in patients with CKD but no CVD of the efficacy and safety of aspirin for primary prevention of cardiovascular disease.

## 16 Development of the guideline

### 16.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of Healthcare Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising healthcare professionals using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in 'SIGN 50: A Guideline Developer's Handbook', available at [www.sign.ac.uk](http://www.sign.ac.uk)

This guideline was developed according to the 2014 edition of SIGN 50.

### 16.2 THE GUIDELINE DEVELOPMENT GROUP

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The membership of the GDG was confirmed following consultation with the member organisations of SIGN. All members of the GDG made declarations of interest. A register of interests is available in the supporting material section for this guideline at [www.sign.ac.uk](http://www.sign.ac.uk)

Guideline development and literature review expertise, support and facilitation were provided by SIGN Executive and Healthcare Improvement Scotland staff. All members of the SIGN Executive make yearly declarations of interest. A register of interests is available on the contacts page of the SIGN website [www.sign.ac.uk](http://www.sign.ac.uk)

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### 16.2.1 ACKNOWLEDGEMENTS

SIGN would like to acknowledge the GDG responsible for the development of SIGN 97: Risk estimation and the prevention of cardiovascular disease, on which this guideline is based. SIGN is also grateful to the following who have contributed to the ongoing work in risk estimation.

Dr Kathleen Boyd	<i>Lecturer, Institute of Health and Wellbeing, University of Glasgow</i>
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Dr Jim Lewsey	<i>Reader in Medical Statistics, Institute of Health and Wellbeing, University of Glasgow</i>

### 16.3 THE STEERING GROUP

A steering group comprising the chairs of the six SIGN CHD guidelines and other invited experts was established to oversee the progress of the guideline development. This group met regularly throughout the development of the guidelines.

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## 16.4 CONSULTATION AND PEER REVIEW

A report of the consultation and peer review comments and responses is available in the supporting material section for this guideline on the SIGN website. All expert referees and other contributors made declarations of interest and further details of these are available on request from the SIGN Executive.

### 16.4.1 SPECIALIST REVIEWERS

This guideline was reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments.

Professor Annie Anderson	<i>Professor of Public Health Nutrition, University of Dundee</i>
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Professor Marie Murphy	<i>Professor of Exercise and Health, University of Ulster</i>
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#### 16.4.2 PUBLIC CONSULTATION

The draft guideline was also available on the SIGN website for a month to allow all interested parties to comment. All contributors made declarations of interest and further details of these are available on request from the SIGN Executive.

#### 16.4.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows. All members of SIGN Council make yearly declarations of interest. A register of interests is available on the SIGN Council Membership page of the SIGN website [www.sign.ac.uk](http://www.sign.ac.uk)

Dr Roberta James	<i>SIGN Programme Lead; Co-Editor</i>
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Dr Jenny Bennison	<i>Vice-Chair of SIGN</i>
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Dr Susan Myles	<i>Healthcare Improvement Scotland</i>

## Abbreviations

<b>ABPM</b>	ambulatory blood pressure monitoring
<b>ACE</b>	angiotensin converting enzyme
<b>ACS</b>	acute coronary syndrome
<b>ACCORD-Lipid</b>	The Action to Control Cardiovascular Risk in Diabetes-Lipid trial
<b>ADH1B</b>	alcohol dehydrogenase 1B
<b>AHA</b>	American Heart Association
<b>AIM-HIGH</b>	Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes trial
<b>ARB</b>	angiotensin receptor blocker
<b>ARR</b>	absolute risk reduction
<b>ASCOT-BPLA</b>	Anglo-Scandinavian Cardiac Outcomes Trial - Blood Pressure Lowering Arm
<b>ASH</b>	Action on Smoking and Health
<b>ASSIGN</b>	Assessing cardiovascular risk using SIGN guidelines to ASSIGN preventive treatment
<b>ATT</b>	Antithrombotic Trialists' Collaboration
<b>BC</b>	behavioural counselling
<b>BHF</b>	British Heart Foundation
<b>BHS</b>	British Hypertension Society
<b>BMI</b>	body mass index
<b>BP</b>	blood pressure
<b>CBT</b>	cognitive behavioural therapy
<b>CCB</b>	calcium channel blocker
<b>CENTRAL</b>	Cochrane Central Register of Controlled Trials
<b>CHD</b>	coronary heart disease
<b>CI</b>	confidence interval
<b>CK</b>	creatinine kinase
<b>CKD</b>	chronic kidney disease
<b>CTT</b>	Cholesterol Treatment Trialists' Collaboration
<b>CV</b>	cardiovascular
<b>CVD</b>	cardiovascular disease
<b>DBP</b>	diastolic blood pressure
<b>DM</b>	diabetes mellitus
<b>ECG</b>	electrocardiogram
<b>eGFR</b>	estimated glomerular filtration rate
<b>ENDS</b>	electronic nicotine delivery systems
<b>ETS</b>	environmental tobacco smoke

<b>EVOO</b>	extra virgin olive oil
<b>FH</b>	familial hypercholesterolaemia
<b>FIELD</b>	Fenofibrate Intervention and Event Lowering in Diabetes trial
<b>FOURIER</b>	Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk trial
<b>GAD</b>	generalised anxiety disorder
<b>GDG</b>	guideline development group
<b>GP</b>	general practitioner
<b>HbA1c</b>	glycated haemoglobin
<b>HDL</b>	high-density lipoprotein
<b>HEED</b>	Health Economics Evaluation Database
<b>HeFH</b>	heterozygous familial hypercholesterolaemia
<b>HOT</b>	Hypertension Optimal Treatment trial
<b>HPS2-THRIVE</b>	Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events trial
<b>HR</b>	hazard ratio
<b>HR<sub>max</sub></b>	maximal heart rate
<b>IDF</b>	International Diabetes Federation
<b>IMPROVE-IT</b>	IMProved Reduction of Outcomes: Vytorin Efficacy International Trial
<b>IR</b>	immediate release
<b>JBS</b>	Joint British Societies
<b>JBS3</b>	Joint British Societies' consensus recommendations for the prevention of cardiovascular disease
<b>JNC</b>	Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
<b>JUPITER</b>	Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
<b>KDIGO</b>	Kidney Disease: Improving Global Outcomes
<b>LDL</b>	low-density lipoprotein
<b>LDL-c</b>	low-density lipoprotein cholesterol
<b>MA</b>	marketing authorisation
<b>MCE</b>	major cardiovascular event
<b>METS</b>	metabolic equivalents
<b>MI</b>	myocardial infarction
<b>MR</b>	modified release
<b>MTA</b>	multiple technology appraisal
<b>NHS</b>	National Health Service
<b>NHS EED</b>	NHS Economic Evaluation Database
<b>NICE</b>	National Institute for Health and Care Excellence

<b>NIHR-HTA</b>	National Institute for Health Research - Health Technology Assessment
<b>NNH</b>	number needed to harm
<b>NNT</b>	number needed to treat
<b>NPC1L1</b>	Niemann-Pick C1-Like 1
<b>NRT</b>	nicotine replacement therapy
<b>OR</b>	odds ratio
<b>PAD</b>	peripheral arterial disease
<b>PCSK9</b>	proprotein convertase subtilisin/kexin type 9
<b>PREDIMED</b>	Prevención con Dieta Mediterránea trial
<b>PROGRESS</b>	The perindopril protection against recurrent stroke study
<b>PROSPER</b>	The Prospective Study of Pravastatin in the Elderly at Risk
<b>PTSD</b>	post-traumatic stress disorder
<b>QALY</b>	quality adjusted life year
<b>QoL</b>	quality of life
<b>RA</b>	rheumatoid arthritis
<b>RCT</b>	randomised controlled trial
<b>RPE</b>	rating of perceived exertion
<b>RR</b>	risk ratio or relative risk
<b>SBP</b>	systolic blood pressure
<b>SCD</b>	sudden cardiac death
<b>SHARP</b>	Study of Heart and Renal Protection trial
<b>SIGN</b>	Scottish Intercollegiate Guidelines Network
<b>SMC</b>	Scottish Medicines Consortium
<b>SMD</b>	standardised mean difference
<b>SPRINT</b>	Systolic Blood Pressure Intervention trial
<b>SSRI</b>	selective serotonin reuptake inhibitor
<b>TC</b>	total cholesterol
<b>TG</b>	triglycerides
<b>TIA</b>	transient ischaemic attack
<b>UK</b>	United Kingdom
<b>US</b>	United States
<b>VO<sub>2max</sub></b>	maximal oxygen uptake
<b>WOSCOPS</b>	West of Scotland Coronary Prevention Study

# Annex 1

## Key questions addressed in this update

This guideline is based on a series of structured key questions that define the target population, the intervention, diagnostic test, or exposure under investigation, the comparison(s) used and the outcomes used to measure efficacy, effectiveness, or risk. These questions form the basis of the systematic literature search.

Guideline section	Key question
	DIET
5.4, 5.5	<p>1. What is the evidence that dietary modifications are effective in reducing cardiovascular events?</p> <p><b>Population:</b> adults with and without a clinical diagnosis of CVD consider following subgroups, where possible, BMI <math>\leq 25</math>, <math>&gt;25</math>, <math>&gt;30</math></p> <p><b>Intervention:</b></p> <ul style="list-style-type: none"> <li>• stanol esters and plant sterols</li> <li>• folate, vitamin B<sub>6</sub> or B<sub>12</sub> (homocysteine lowering)</li> <li>• dietary patterns: Mediterranean diet, low GI/GL, low carbohydrate</li> </ul> <p><b>Comparators:</b></p> <ul style="list-style-type: none"> <li>• usual diet or placebo</li> </ul> <p><b>Outcomes:</b></p> <ul style="list-style-type: none"> <li>• all-cause mortality</li> <li>• cardiovascular mortality</li> <li>• cardiovascular events</li> <li>• total cholesterol levels</li> <li>• LDL cholesterol levels</li> <li>• blood pressure</li> <li>• adverse events</li> <li>• QoL</li> </ul>

5.1	<p>2. What is the evidence that altering an individual's dietary fat intake is effective in reducing cardiovascular events?</p> <p><b>Population:</b> adults with and without a clinical diagnosis of CVD consider following subgroups, where possible, BMI <math>\leq 25</math>, <math>&gt;25</math>, <math>&gt;30</math></p> <p><b>Intervention:</b></p> <ul style="list-style-type: none"> <li>• reduction of total fat intake</li> <li>• modified fat intake (increased unsaturated fat)</li> <li>• essential fatty acids: includes dietary intake (fish and other sources), food supplements, prescription omega-3 fatty acids (Omacor, Maxepa)</li> </ul> <p><b>Comparators:</b> usual diet or placebo</p> <p><b>Outcomes:</b></p> <ul style="list-style-type: none"> <li>• all-cause mortality</li> <li>• cardiovascular mortality</li> <li>• cardiovascular events</li> <li>• total cholesterol levels</li> <li>• LDL cholesterol levels</li> <li>• blood pressure</li> <li>• adverse events</li> <li>• QoL</li> </ul>
5.7	<p>3. What is the evidence that losing weight reduces the risk of adverse cardiovascular outcomes?</p> <p><b>Population:</b> adults with and without a clinical diagnosis of CVD consider following subgroups, where possible,</p> <ul style="list-style-type: none"> <li>• BMI <math>\leq 25</math>, <math>&gt;25</math>, <math>&gt;30</math></li> <li>• ethnic minorities</li> <li>• people with hypertension</li> <li>• people with diabetes</li> </ul> <p><b>Intervention:</b></p> <ul style="list-style-type: none"> <li>• weight loss</li> <li>• diet (any)</li> <li>• composite (eg diet and exercise)</li> <li>• pharmaceutical</li> <li>• surgical interventions</li> </ul> <p><b>Comparators:</b></p> <ul style="list-style-type: none"> <li>• no weight loss</li> </ul> <p><b>Outcomes:</b></p> <ul style="list-style-type: none"> <li>• cardiovascular mortality</li> <li>• cardiovascular events</li> <li>• total cholesterol levels</li> <li>• LDL cholesterol levels</li> <li>• blood pressure</li> <li>• adverse events</li> <li>• QoL</li> </ul>

		PHYSICAL ACTIVITY
6.2.3	4.	<p>What is the evidence that high-intensity physical activity is effective in reducing cardiovascular events?</p> <p><b>Population:</b> adults with and without a clinical diagnosis of CVD consider following subgroups, where possible,</p> <ul style="list-style-type: none"> <li>• BMI <math>\leq 25</math>, <math>&gt;25</math>, <math>&gt;30</math></li> <li>• people with hypertension</li> <li>• people with impaired glucose regulation</li> <li>• people with high/low baseline activity levels</li> </ul> <p><b>Intervention:</b> high-intensity physical activity (as defined by authors of individual studies)</p> <p><b>Comparators:</b> moderate-intensity physical activity no physical activity</p> <p><b>Outcomes:</b></p> <ul style="list-style-type: none"> <li>• all-cause mortality</li> <li>• cardiovascular mortality</li> <li>• cardiovascular events</li> <li>• total cholesterol levels</li> <li>• LDL cholesterol levels</li> <li>• blood pressure</li> <li>• QoL</li> </ul>
6.2.3	5.	<p>Is there any evidence that high-intensity physical activity can increase the risk of sudden death or acute cardiovascular events?</p> <p><b>Population:</b> adults with and without a clinical diagnosis of CVD consider following subgroups, where possible,</p> <ul style="list-style-type: none"> <li>• BMI <math>\leq 25</math>, <math>&gt;25</math>, <math>&gt;30</math></li> <li>• people with hypertension</li> <li>• people with impaired glucose regulation</li> <li>• people with high/low baseline activity levels</li> </ul> <p><b>Intervention:</b> high-intensity physical activity (as defined by authors of individual studies)</p> <p><b>Comparators:</b></p> <ul style="list-style-type: none"> <li>• moderate-intensity physical activity</li> <li>• no physical activity</li> </ul> <p><b>Outcomes:</b></p> <ul style="list-style-type: none"> <li>• cardiovascular mortality</li> <li>• cardiovascular events(occurring during or soon after intervention)</li> </ul>

6.2.4	<p>6. Is there any evidence to show that a reduction in sedentary behaviour can decrease the risk of cardiovascular events?</p> <p><b>Population:</b> sedentary adults with and without a clinical diagnosis of CVD</p> <p><b>Intervention:</b> reduction in sedentary behaviour (any intervention)</p> <p><b>Comparators:</b> maintenance of sedentary behaviour</p> <p><b>Outcomes:</b></p> <ul style="list-style-type: none"> <li>• cardiovascular mortality</li> <li>• cardiovascular events</li> <li>• total cholesterol levels</li> <li>• LDL cholesterol levels</li> <li>• blood pressure</li> <li>• QoL</li> </ul>
	SMOKING
7.2.1	<p>7. What is the evidence that varenicline is clinically and cost effective for smoking cessation?</p> <p><b>Population:</b> adult smokers</p> <p><b>Intervention:</b> varenicline</p> <p><b>Comparators:</b></p> <ul style="list-style-type: none"> <li>• placebo</li> <li>• nicotine replacement therapy</li> <li>• bupropion</li> </ul> <p><b>Outcomes:</b></p> <ul style="list-style-type: none"> <li>• quit rate</li> <li>• adverse events</li> <li>• cost effectiveness</li> </ul>
7.2.2	<p>8. Is there any evidence that e-cigarettes are clinically and cost effective for smoking cessation?</p> <p><b>Population:</b> adult smokers</p> <p><b>Intervention:</b> e-cigarettes</p> <p><b>Comparators:</b></p> <ul style="list-style-type: none"> <li>• placebo</li> <li>• other nicotine replacement therapy</li> <li>• bupropion</li> <li>• varenicline</li> </ul> <p><b>Outcomes:</b></p> <ul style="list-style-type: none"> <li>• quit rate</li> <li>• adverse events</li> <li>• cost effectiveness</li> </ul>

		ALCOHOL
8.1	9.	<p>What is the evidence that light to medium alcohol consumption is protective against adverse cardiovascular outcomes?</p> <p><b>Population:</b> adults with and without a clinical diagnosis of CVD</p> <p><b>Intervention:</b> light to moderate alcohol consumption</p> <p><b>Comparators:</b> abstinence</p> <p><b>Outcomes:</b></p> <ul style="list-style-type: none"> <li>• all-cause mortality</li> <li>• cardiovascular mortality</li> <li>• cardiovascular events</li> <li>• total cholesterol levels</li> <li>• LDL cholesterol levels</li> <li>• blood pressure</li> </ul>
		ANTIPLATELET THERAPY
9.2	10	<p>What is the clinical and cost effectiveness and safety of antiplatelet agents for the primary prevention of cardiovascular events?</p> <p><b>Population:</b></p> <ul style="list-style-type: none"> <li>• adults estimated to be at high risk of CVD using formal risk estimation methods</li> <li>• adults with diabetes</li> <li>• adults with hypertension</li> </ul> <p><b>Intervention:</b></p> <ul style="list-style-type: none"> <li>• aspirin</li> <li>• clopidogrel</li> <li>• dipyridamole</li> <li>• prasugrel</li> <li>• ticagrelor</li> </ul> <p><b>Comparators:</b></p> <ul style="list-style-type: none"> <li>• alternative antiplatelet agent</li> <li>• placebo</li> </ul> <p><b>Outcomes:</b></p> <ul style="list-style-type: none"> <li>• all-cause mortality</li> <li>• cardiovascular mortality</li> <li>• cardiovascular events</li> <li>• adverse events</li> <li>• cost effectiveness</li> </ul>

		LIPID-LOWERING THERAPY
10.6	11	<p>For adults with and without established CVD what is the clinical effectiveness, cost effectiveness and safety of lipid-lowering medicines (excluding statins)?</p> <p><b>Population:</b></p> <ul style="list-style-type: none"> <li>• adults with a diagnosis of CVD</li> <li>• adults estimated to be at high risk of CVD</li> </ul> <p>Consider following subgroups, where possible:</p> <ul style="list-style-type: none"> <li>• adults with diabetes</li> <li>• adults with hypertension</li> </ul> <p><b>Intervention:</b></p> <ul style="list-style-type: none"> <li>• bile acid sequestrants (anion-exchange resins)</li> <li>• fibrates</li> <li>• ezetimibe</li> <li>• colestyramine</li> <li>• nicotinic acid</li> <li>• PCSK9 inhibitors</li> </ul> <p><b>Comparators:</b></p> <ul style="list-style-type: none"> <li>• statin</li> <li>• placebo</li> </ul> <p><b>Outcomes:</b></p> <ul style="list-style-type: none"> <li>• all-cause mortality</li> <li>• cardiovascular mortality</li> <li>• cardiovascular events</li> <li>• total cholesterol levels</li> <li>• LDL-cholesterol levels</li> <li>• adverse events</li> <li>• cost effectiveness</li> </ul>

10.1–10.5	12	<p>For adults with and without established CVD what is the clinical effectiveness, cost effectiveness and safety of statins?</p> <p><b>Population:</b></p> <ul style="list-style-type: none"> <li>• adults with a diagnosis of CVD</li> <li>• adults estimated to be at high risk of CVD</li> </ul> <p>Consider following subgroups, where possible:</p> <ul style="list-style-type: none"> <li>• adults with diabetes</li> <li>• adults with hypertension</li> </ul> <p><b>Intervention:</b></p> <p>statin at moderate or intensive dose</p> <p><b>Comparators:</b></p> <ul style="list-style-type: none"> <li>• statin at moderate or intensive dose</li> <li>• placebo</li> </ul> <p><b>Outcomes:</b></p> <ul style="list-style-type: none"> <li>• all-cause mortality</li> <li>• cardiovascular mortality</li> <li>• cardiovascular events</li> <li>• total cholesterol levels</li> <li>• LDL cholesterol levels</li> <li>• adverse events</li> <li>• cost effectiveness</li> </ul>
10.4.6	13	<p>In patients who are intolerant to first line statin therapy, what is the evidence that second or third choice statins can be tolerated?</p> <p><b>Population:</b></p> <p>patients intolerant to statins</p> <p><b>Intervention:</b></p> <p>alternative statin regimen</p> <p><b>Comparators:</b></p> <p>N/A</p> <p><b>Outcomes:</b></p> <ul style="list-style-type: none"> <li>• compliance</li> <li>• adverse events</li> </ul>

10.5.4	14	<p>Is there any evidence to promote the cessation of statins in the very elderly?</p> <p><b>Population:</b> elderly statin users (<math>\geq 85</math> years)</p> <p><b>Intervention:</b> statin cessation</p> <p><b>Comparators:</b> continuation of statin therapy</p> <p><b>Outcomes:</b></p> <ul style="list-style-type: none"> <li>• all-cause mortality</li> <li>• cardiovascular mortality</li> <li>• cardiovascular events</li> <li>• total cholesterol levels</li> <li>• LDL cholesterol levels</li> <li>• adverse events</li> <li>• QoL</li> </ul>
<b>BLOOD PRESSURE-LOWERING THERAPY</b>		
11.1.1, 11.1.3	15	<p>Is there evidence for a lower blood pressure treatment threshold for individuals with established CVD and diabetes or renal disease?</p> <p><b>Population:</b> adults with a diagnosis of CVD and:</p> <ul style="list-style-type: none"> <li>• diabetes, or</li> <li>• CKD, or</li> <li>• target organ damage</li> </ul> <p><b>Intervention:</b> initiation of treatment with antihypertensives at <math>&lt; 140/90</math> mm Hg</p> <p><b>Comparators:</b> initiation of treatment with antihypertensives at <math>\geq 140/90</math> mm Hg</p> <p><b>Outcomes:</b></p> <ul style="list-style-type: none"> <li>• all-cause mortality</li> <li>• cardiovascular mortality</li> <li>• myocardial infarction</li> <li>• stroke or TIA</li> <li>• blood pressure levels</li> <li>• adverse events</li> <li>• cost effectiveness</li> <li>• QoL</li> </ul>

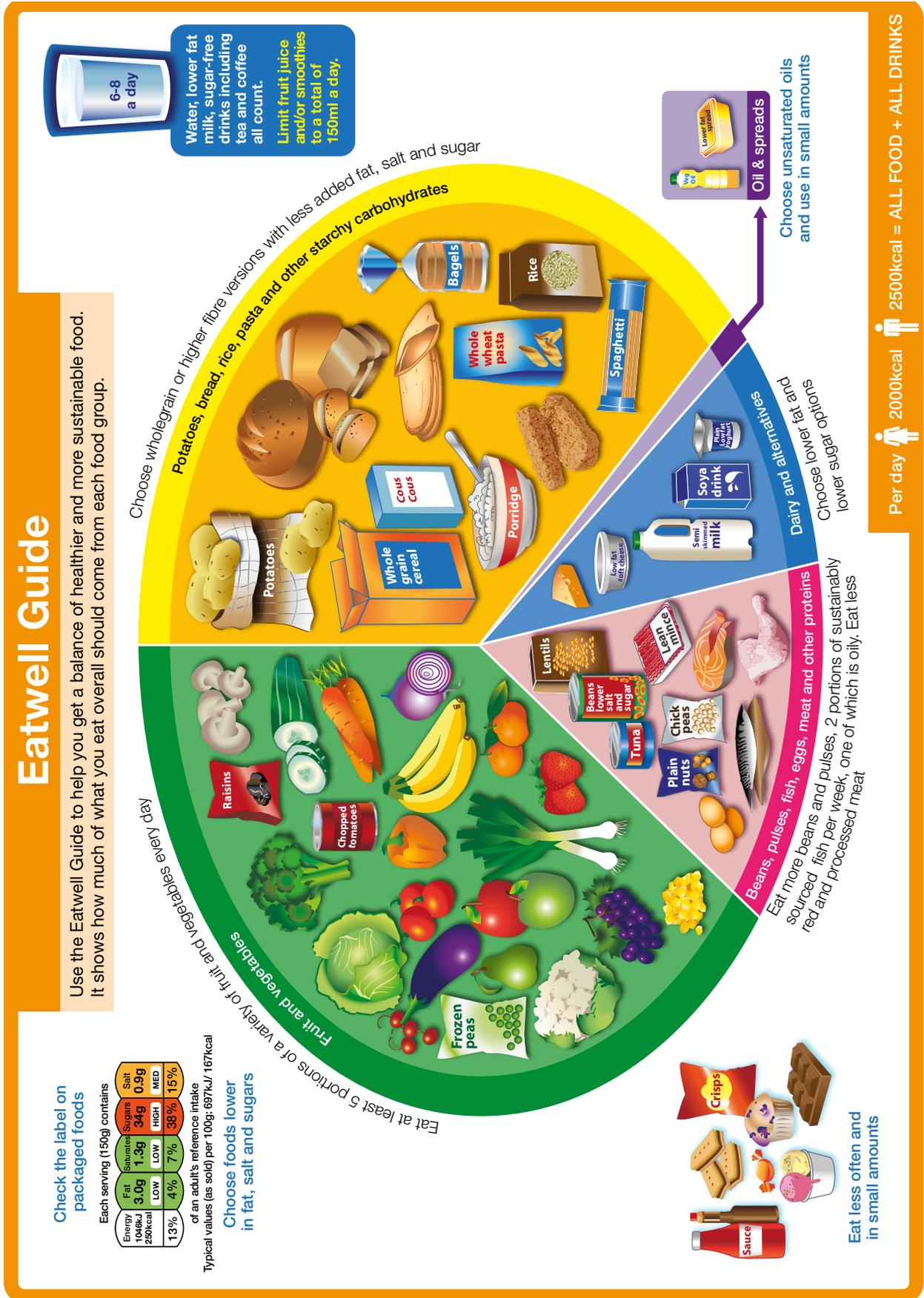
11.1.2	<p>16 Is there evidence that individuals without established CVD but who are estimated to be at high CVD risk gain benefit from antihypertensive treatment at any baseline blood pressure level?</p> <p><b>Population:</b> adults without a diagnosis of CVD but estimated to be at high risk of CVD and:</p> <ul style="list-style-type: none"> <li>• blood pressure <math>\geq</math>140/90 mm Hg</li> <li>• blood pressure &lt;140/90 mm Hg</li> </ul> <p><b>Intervention:</b> antihypertensive therapy</p> <p><b>Comparators:</b> placebo</p> <p><b>Outcomes:</b></p> <ul style="list-style-type: none"> <li>• all-cause mortality</li> <li>• cardiovascular mortality</li> <li>• myocardial infarction</li> <li>• stroke or TIA</li> <li>• blood pressure levels</li> <li>• adverse events</li> <li>• cost effectiveness</li> <li>• QoL</li> </ul>
11.2	<p>17 Is there evidence for an optimal target value for blood pressure lowering?</p> <p><b>Population:</b> adults receiving antihypertensives</p> <p><b>Intervention:</b> lowering blood pressure to &lt;145/85 mm Hg</p> <p><b>Comparators:</b> lowering blood pressure to &lt;130/80 mm Hg</p> <p><b>Outcomes:</b></p> <ul style="list-style-type: none"> <li>• all-cause mortality</li> <li>• cardiovascular mortality</li> <li>• myocardial infarction</li> <li>• stroke or TIA</li> <li>• blood pressure levels</li> <li>• adverse events</li> <li>• cost effectiveness</li> <li>• QoL</li> </ul>

11.2.1, 11.2.2, 11.2.3, 11.2.4	18	<p>Is there evidence for an optimal target value for blood pressure lowering?</p> <p><b>Population:</b> adults with a diagnosis of CVD and:</p> <ul style="list-style-type: none"> <li>• diabetes, or</li> <li>• CKD, or</li> <li>• target organ damage</li> </ul> <p><b>Intervention:</b> lowering blood pressure with antihypertensive therapy to &lt;130/80 mm Hg</p> <p><b>Comparators:</b> lowering blood pressure with antihypertensive therapy to ≥130/80 mm Hg</p> <p><b>Outcomes:</b></p> <ul style="list-style-type: none"> <li>• all-cause mortality</li> <li>• cardiovascular mortality</li> <li>• myocardial infarction</li> <li>• stroke or TIA</li> <li>• blood pressure levels</li> <li>• adverse events</li> <li>• cost effectiveness</li> <li>• QoL</li> </ul>
		PSYCHOLOGICAL ISSUES
12.1	19	<p>Is there evidence that anxiety and/or stress are independent risk factors for cardiovascular disease?</p> <p><b>Population:</b> adults with a diagnosis or at risk of CVD and with a clinical diagnosis of anxiety, post-traumatic stress disorder (PTSD) or chronic stress (eg being a carer or multiple life stressors)</p> <p><b>Intervention:</b> N/A</p> <p><b>Comparators:</b> N/A</p> <p><b>Outcomes:</b></p> <ul style="list-style-type: none"> <li>• cardiovascular mortality</li> <li>• cardiovascular events</li> </ul>

12.2	<p data-bbox="430 237 1380 293">20 Is there evidence that interventions to alleviate anxiety and depression influence cardiovascular risk?</p> <p data-bbox="477 315 616 342"><b>Population:</b></p> <p data-bbox="477 360 1420 421">adults with a diagnosis or at risk of CVD and with a clinical diagnosis of anxiety, PTSD or chronic stress (eg being a carer or multiple life stressors)</p> <p data-bbox="477 443 635 470"><b>Intervention:</b></p> <ul data-bbox="483 481 938 696" style="list-style-type: none"> <li>• pharmacotherapy</li> <li>• cognitive behavioural therapy</li> <li>• stress management</li> <li>• mindfulness</li> <li>• interpersonal therapy</li> <li>• acceptance and commitment therapy</li> </ul> <p data-bbox="477 719 639 745"><b>Comparators:</b></p> <ul data-bbox="483 757 791 817" style="list-style-type: none"> <li>• placebo</li> <li>• alternative interventions</li> </ul> <p data-bbox="477 840 608 866"><b>Outcomes:</b></p> <ul data-bbox="483 878 1018 1093" style="list-style-type: none"> <li>• all-cause mortality</li> <li>• cardiovascular mortality</li> <li>• cardiovascular events</li> <li>• reduction in depression/anxiety/PTSD scores</li> <li>• adverse events</li> <li>• QoL</li> </ul>
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# Annex 2

## The Eatwell Guide



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## Annex 3

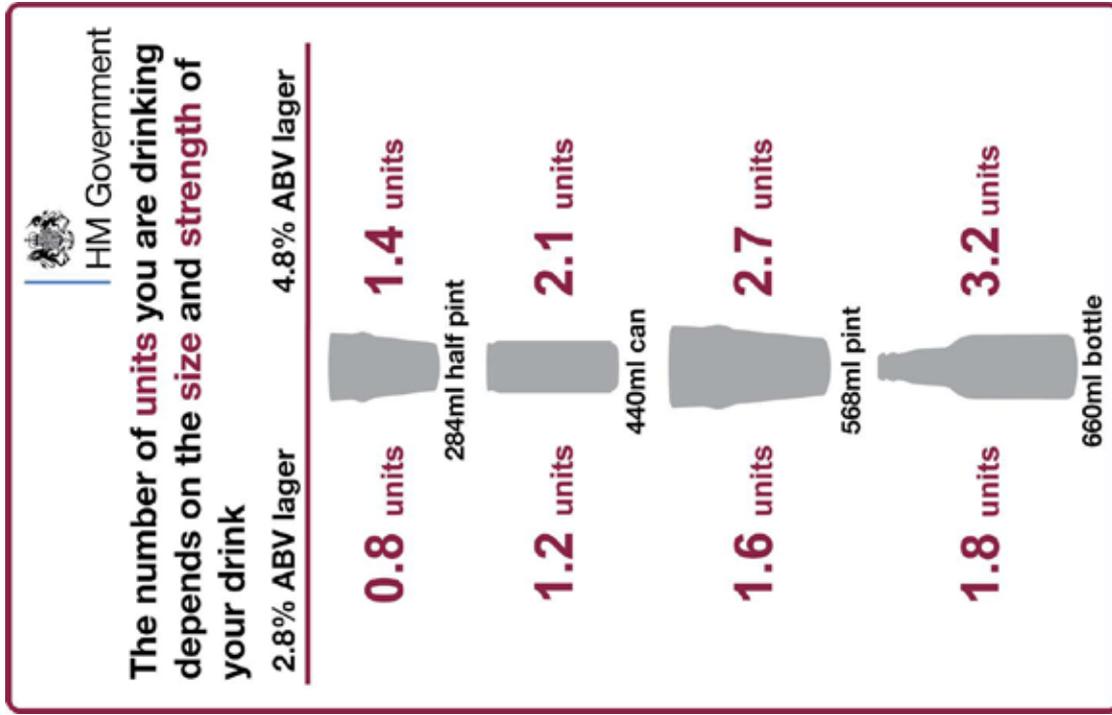
### UK physical activity guidelines

Start Active, Stay Active is a report on physical activity for health from the four home countries' Chief Medical Officers.<sup>41</sup> It presents recommendations on the volume, duration, frequency and type of physical activity required throughout life to achieve general health benefits.



# Annex 4

## Alcohol by volume of wine and lager



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