2016 European Guidelines on cardiovascular disease prevention in clinical practice

The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice

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1. What is cardiovascular disease prevention?

1.1 Definition and rationale

Cardiovascular disease (CVD) prevention is defined as a coordinated set of actions, at the population level or targeted at an individual, that are aimed at eliminating or minimizing the impact of CVDs and their related disabilities.[1] CVD remains a leading cause of morbidity and mortality, despite improvements in outcomes: age-adjusted coronary artery disease (CAD) mortality has declined since the 1980s, particularly in high-income regions.[2] CAD rates are now less than half what they were in the early 1980s in many countries in Europe, due to preventive measure including the success of smoking legislation. However inequalities between countries persist and many risk factors, particularly obesity[3] and diabetes (DM),[4] have been increasing substantially. If prevention was practiced as instructed it would markedly reduce the prevalence of CVD. It is thus not only prevailing risk factors that are of concerns but poor implementation of preventive measures as well.[5, 6] Prevention should be delivered (i) at the general population level by promoting healthy lifestyle behaviour[7] and (ii) at the individual level, i.e. in those subjects at moderate to high risk of CVD or patients with established CVD, by tackling an unhealthy lifestyle (e.g. poor-quality diet, physical inactivity, smoking), and by optimising risk factors. Prevention is effective: the elimination of health risk behaviours would make it possible to prevent at least 80% of CVDs and even 40% of cancers.[8, 9]

1.2 Development of the 6th Joint Task Force guidelines

The present guidelines represent an evidence-base consensus of the Sixth European Joint Task Force involving 10 professional societies.

By appraising the current evidence and identifying remaining knowledge gaps in managing CVD prevention, the Task Force formulated recommendations to guide actions to prevent CVD in clinical practice. The Task Force followed the quality criteria for development of guidelines, which can be found at **www.escardio.org/knowledge/guidelines/rules**. For simplification and in keeping with other European Society of Cardiology (ESC) guidelines, the ESC grading system based on classes of recommendation and levels of evidence has been maintained, recognising that this may be less suitable to measure the impact of prevention strategies, particularly those related to behavioural issues and population based interventions.

This document has been developed to support healthcare professionals communicating with individuals about their cardiovascular (CV) risk and the benefits of a healthy lifestyle and early modification of their CV risk. In addition, the guidelines provide tools for healthcare professionals to promote population-based strategies and integrate these into national or regional prevention frameworks and to translate these in locally delivered healthcare services, in line with the recommendations of the World Health Organization (WHO) global status report on non-communicable diseases 2010.[10]

As in the present guidelines, the model presented in the previous document from the Fifth European Joint Task Force[11] has been structured around four core questions: 1. What is CVD prevention? 2. Who will benefit from prevention? 3. How to intervene? 4. Where to intervene?

Compared to the previous guidelines, greater emphasis has been put on a population-based approach, on disease-specific interventions, and on female specific conditions, younger individuals and ethnic minorities. Due to space restriction for the paper

version, the chapter on disease-specific intervention is on the web, together with a few tables and figures for more detail [**add link to website**].
A lifetime approach to CV risk is important since both CV risk and prevention are dynamic and continuous as patients age and/or accumulate comorbidities. This implies that apart from improving lifestyle and reducing risk factor levels in patients with established CVD and those at increased risk of developing CVD, healthy people of all ages should be encouraged to adopt a healthy lifestyle. Healthcare professionals play an important role in achieving this in their clinical practice.

1.3 Cost effectiveness of prevention

Key messages

- Prevention of CVD, either by implementation of lifestyle changes or use of medication, is cost-effective in many scenarios, including population-based approaches and actions directed at high-risk individuals.
- Cost-effectiveness depends on several factors, including baseline CV risk, cost of drugs or other interventions, reimbursement procedures, and implementation of preventive strategies.

Recommendations for cost-effective prevention of cardiovascular disease

Recommendations	Class[a]	Level[b]	Ref[c]
Measures aimed at promoting healthy lifestyles at the population level should be considered.	IIa	B	12, 13

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

In 2009, costs related to CVD amounted to €106 billion, representing approximately 9% of the total healthcare expenditure across the European Union (EU).[14] Thus, CVD represents a considerable economic burden to society, and effective preventive measures are necessary. There is consensus in favour of an approach combining strategies to improve CV health across the population at large from childhood onwards, with specific actions to improve CV health in individuals at increased risk of CVD or with established CVD.
Most studies assessing cost-effectiveness of CVD prevention combine evidence from clinical research with simulation approaches, while cost-effectiveness data from randomized controlled trials (RCTs) are relatively scarce.[15, 16] Cost-effectiveness strongly depends on parameters such as the target population's age, the overall population risk of CVD, and the cost of interventions. Hence, results obtained in one country may not be valid in another. Furthermore, changes such as the introduction of generic drugs can considerably change cost-effectiveness.[17] According to the WHO, policy and environmental changes could reduce CVD in all countries for less than US$1 per person per year.[18] A report from the National Institute for Health and Care Excellence (NICE) estimated that a UK national programme reducing population CV risk by 1% would prevent 25,000 CVD cases and generate savings of €40 million per year. Coronary artery disease (CAD) mortality rates could be halved by only modest risk factor reduction and it has been suggested that eight dietary priorities alone could halve CVD death.[13]
In the last three decades, over half of the reduction in CV mortality has been attributed to changes in risk factor levels in the population, primarily the reduction in cholesterol and blood pressure (BP) levels and smoking. This favourable trend is partly off-set by an increase in other risk factors, mainly obesity and type 2 DM.[19, 20] Aging of the population also increases CVD events.[21]

Several population interventions have efficiently modified the lifestyle of individuals. For example, increased awareness of how healthy lifestyles prevent CVD has helped to reduce smoking and cholesterol levels. Lifestyle interventions act on several CV risk factors and should be applied prior to or in conjunction with drug therapies. Also, legislation aimed at decreasing salt and *trans* fatty acid content of foods and smoking habits is cost-effective in preventing CVD [12, 13, 19].

Cholesterol lowering using statins[15, 16] and improvement in BP control are cost-effective if targeted at persons with high CV risk.[22] Importantly, a sizable portion of patients on lipid lowering drugs or BP lowering drug treatment fails to take their treatment adequately or to reach therapeutic goals [23, 24], with clinical and economic consequences.

Gaps in evidence

- Most cost-effectiveness studies rely on simulation. More data, mainly from RCTs, are needed.

2. Who will benefit from prevention? When and how to assess risk and prioritize

2.1 Estimation of total cardiovascular risk

All current guidelines on the prevention of CVD in clinical practice recommend the assessment of total CVD risk because atherosclerosis is usually the product of a number of risk factors. Prevention of CVD in an individual should be adapted to his or her total CV risk: the higher the risk, the more intense the action should be.

The importance of total risk estimation in apparently healthy people before management decisions are made is illustrated in Table 1 derived from the high risk SCORE chart **[http://www.escardio.org/Guidelines-&-Education/Practice-tools/CVD-prevention-toolbox/SCORE-Risk-Charts**]. This shows that a person with a cholesterol level of 7 mmol/L can be at 10 times *lower* risk than someone with a cholesterol level of 5 mmol/L if the former is a female and the latter is a male hypertensive smoker.

Table 1 Impact of combinations of risk factors on risk

Gender	Age (years)	Cholesterol (mmol/l)	SBP (mmHg)	Smoker	Risk (10 year risk of fatal CVD)
F	60	7	120	No	2%
F	60	7	140	Yes	5%
M	60	6	160	No	9%
M	60	5	180	Yes	21%

CVD = cardiovascular disease; F = female; M = male; SBP = systolic blood pressure.

A recent meta-analysis on CV risk reduction by treatment with BP lowering drugs does, however, support the concept that absolute risk reduction is larger in those at higher baseline risk.[25] This was confirmed in a further meta-analysis which also showed a greater residual risk during treatment in those at higher baseline risk, supporting earlier intervention [26, 27].

Although clinicians often ask for decisional thresholds to trigger intervention, this is problematic since risk is a continuum and there is no exact point above which, for example, a drug is automatically indicated, nor below which lifestyle advice may not usefully be offered.

The risk categories presented later in this section are to assist the physician in dealing with individual people. They acknowledge that although individuals at the highest levels of risk gain most from risk factor interventions, most deaths in a community come from those at lower levels of risk, simply because they are more numerous compared to high risk individuals. Thus a strategy for individuals at high risk must be complemented by public health measures to encourage a healthy lifestyle and to reduce population levels of CV risk factors.

It is essential for clinicians to be able to assess CV risk rapidly and with sufficient accuracy. This realization led to the development of the risk chart used in the 1994 and 1998 Guidelines. This chart, developed from a concept pioneered by Anderson,[28] used age, sex, smoking status, blood cholesterol and systolic BP (SBP) to estimate the 10 year risk of a first fatal or non-fatal CAD event. There were several problems with this chart, which are outlined in the Fourth Joint European Guidelines on prevention.[11, 29] This led to the presently recommended Systematic Coronary Risk Estimation (SCORE) system, estimating an individual's 10 year risk of fatal CVD. [30] The SCORE charts have been developed to estimate risk in both high and low risk European populations, but its applicability to non-Caucasian populations has not been examined.

2.2 When to assess total cardiovascular risk?

Recommendations for cardiovascular risk assessment

Recommendations	Class[a]	Level[b]
Systematic CV risk assessment is recommended in individuals at increased CV risk, i.e. with family history of premature CVD, familial hyperlipidaemia, major CV risk factors (such as smoking, high BP, DM or raised lipid levels) or comorbidities increasing CV risk.	I	C
It is recommended to repeat CV risk assessment every 5 years, and more often for individuals with risks close to thresholds mandating treatment.	I	C
Systematic CV risk assessment may be considered in men > 40 years of age and in women >50 years of age or post-menopausal with no known CV risk factors.	IIb	C
Systematic CV risk assessment in men < 40 and women < 50 years of age with no known CV risk factors is not recommended.	III	C

BP = blood pressure; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus.
[a]Class of recommendation.
[b]Level of evidence.

Screening is the identification of unrecognized disease or, in this case, of an unknown increased risk of CVD in individuals without symptoms. CV risk assessment or screening can be done opportunistically or systematically. Opportunistic screening means without a predefined strategy, but is done when the opportunity arises (e.g. when the individual is consulting his or her general practitioner (GP) for some other reason). Systematic screening can be done in the general population as part of a screening programme or in targeted subpopulations, such as subjects with a family history of premature CVD or familial hyperlipidemia.

While the ideal scenario would be for all adults to have their risk assessed, this is not practical in many societies. The decision about who to screen must be made by individual countries and will be resource-dependent.

In a meta-analysis, GP based health checks on cholesterol, BP, body mass index (BMI) and smoking were effective in improving surrogate outcomes, especially in high-risk patients.[31] A large study of CV risk assessment in the general population found that although there were overall improvements in risk factors, there was no impact on CV outcomes at population level[32]. A Cochrane review of RCTs using counselling or education to modify CV risk factors in adults from the general population, occupational groups or those with specific risk factors (i.e. DM, hypertension) concluded that risk factor improvements were modest and interventions did not reduce total or CV mortality in general populations but reduced mortality in high-risk hypertensive and DM populations.[33] Although the benefits of treating asymptomatic conditions such as hypertension, DM and dyslipidemia on morbidity and mortality outcomes have been documented, a Cochrane review of the existing trials concluded that general health checks (including screening for these conditions) do not reduce all cause or CV morbidity or mortality.[34] However, most studies were performed 3 to 4 decades ago, and thus risk factor interventions were not contemporary. Perhaps application of medical treatment in addition to the lifestyle interventions that were the core component of most trials would improve efficacy.

Most guidelines recommend a mixture of opportunistic and systematic screening.[11, 35-38] Screening in people at relatively low risk of CVD is not particularly effective in reducing the risk of CV events. The costs of such screening interventions are high and these resources may be better used in people at higher CV risk, or with established CVD. In many countries GPs have a unique role in identifying individuals at risk of, but without established, CVD and assessing their eligibility for intervention (see section 4a.1.1). A modelling study based on the European Prospective Investigation of Cancer-Norfolk (EPIC-Norfolk) cohort data concluded that, compared with the National Health Service (NHS) national strategy to screen all adults aged 40–74 years for CV risk, Inviting the 60% of the population at the highest risk according to an integrated risk score was equally effective in preventing new cases of CVD and had potential cost savings.[39]

A general concern in screening, including CV risk assessment, is its potential to do harm. False positive results can cause unnecessary concern and medical treatment. Conversely, false negative results may lead to inappropriate reassurance and lack of lifestyle changes. However, current data suggest that participating in CV screening in general does not cause worry in the screeners.[40-43] More research is needed on how certain subgroups, such as older people, the socially deprived and ethnic minorities, react to screening.

Despite limited evidence, these guidelines recommend a systematic approach to CV risk assessment targeting populations likely to be at higher CV risk, such as those with a family history of premature CVD. Thus systematic CV risk assessment in men younger than 40 and women younger than 50 years of age with no known CV risk factors is not recommended. Additionally, screening of specific groups with jobs that place other people at risk, e.g. bus drivers and pilots, may be reasonable, as is screening for CV risk factors in women before prescribing combined oral contraception, although there is no data to support the beneficial effects. Beyond this, systematic CV risk assessment in adults below the age of 40 years with no known CV risk factors is not recommended as a main strategy due to the low cost-effectiveness. Systematic CV assessment may be considered in adult men > 40 years of age and in women > 50 years of age or post-

menopausal with no known CV risk factors. Risk assessment is not a one-time event; it should be repeated, for example every 5 years.

2.3 How to estimate total cardiovascular risk?

Key messages

- In apparently healthy persons, CV risk in general is the result of multiple, interacting risk factors. This is the basis for the total CV risk approach to prevention.
- SCORE, which estimates 10-year risk of fatal CVD, is recommended for risk assessment and can assist in making logical management decisions, and may help to avoid both under- and over-treatment. Validated local risk estimation systems are useful alternatives to SCORE.
- Individuals automatically at high to very high CV risk (table 5) do not need the use of a risk score and require immediate attention to risk factors.
- In younger persons, a low absolute risk may conceal a very high relative risk and use of the relative risk chart or calculation of their "risk age" may help in advising them of the need for intensive preventive efforts.
- While women are at lower CV risk than men, their risk is deferred by about 10 years rather than avoided.
- The total risk approach allows flexibility; if perfection cannot be achieved with one risk factor, trying harder with others can still reduce risk.

Recommendations for how to estimate cardiovascular risk

Recommendations	Class[a]	Level[b]	Ref[c]
Total CV risk estimation, using a risk estimation system such as SCORE, is recommended for adults >40 years of age, unless they are automatically categorised as being at *high risk* or *very high risk* based on documented CVD, DM (> 40 years of age), kidney disease or highly elevated single risk factor (table 5).	1	C	11, 25

CV = cardiovascular; DM = diabetes mellitus; SCORE = Systematic Coronary Risk Estimation.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

2.3.1 Ten-year cardiovascular risk

Many CV risk assessment systems are available for use in apparently healthy individuals (Table 2), including Framingham,[44] SCORE,[30] ASSIGN (CV risk estimation model from the Scottish Intercollegiate Guidelines Network),[45] Q-Risk,[46, 47] PROCAM (Prospective Cardiovascular Munster Study),[48] CUORE,[49] the Pooled Cohort equations,[50] Arriba[51] and Globorisk.[52] In practice, most risk estimation systems perform rather similarly when applied to populations recognizably comparable to those from which the risk estimation system was derived. Since 2003, the European Guidelines on CVD prevention in clinical practice recommend the use of the SCORE system because it is based on large, representative European cohort datasets. The SCORE risk function has been externally validated.[53]

Table 3 lists the advantages of the SCORE risk charts.

	Framingham[44]	SCORE[30]	ASSIGN – SCORE[45]	QRISK1[46] & QRISK2[47]	PROCAM[48]	Pooled Cohort Studies Equations[50]	CUORE[49]	Globorisk[52]
Data:	Prospective studies: Framingham Heart Study and Framingham offspring study. Latest version includes both	12 pooled prospective studies	SHHEC Prospective study	QRESEARCH database	Prospective study	4 Pooled prospective studies ARIC CHS CARDIA Framingham (original and offspring studies)	CUORE	Derivation cohort: Eight pooled prospective studies - Atherosclerosis Risk in Communities, Cardiovascular Health Study, Framingham Heart Study original cohort and offspring cohort, Honolulu Program, Multiple Risk Factor Intervention Trial, Puerto Rico Heart Health Program, and Women's Health Initiative Clinical Trial
Population:	General population, Framingham, Massachusetts, USA. Baselines: 1968-1971, 1971-1975, 1984-1987	12 prospective studies from 11 European countries. Baselines: 1972 to 1991	Random sample from general population in Scotland, baseline 1984-1987	Data collected from 1993 to 2008 from GP databases – imputation of missing data	Healthy employees. Baseline: 1978 to 1995	Baselines 1987-89 (ARIC), 1990 and 1992-3 (CHS), 1985-6 (CARDIA), 1968-1971, 1971-1975, 1984-1987 (Framingham)	1980s and 1990s	8 prospective studies from North America. Baselines: 1948 - 1993
Sample size:	3969 men and 4522 women	117,098 men and 88,080 women	6540 men and 6757 women	1.28 million (QRISK1) 2.29 million (QRISK2)	18,460 men and 8515 women	11,240 white women, 9098 white men, 2641 African-American women and 1647 African-American men	7520 men and 13,127 women	33,323 men and 16,806 women
Calculates:	**10-year risk of CAD events** originally. Latest version: 10-year risk of CVD events NCEP ATP III version: 10 year risk of hard coronary events	**10-year risk of CVD mortality**	**10-year risk of CVD events**	**10-year risk of CVD events.** Lifetime risk	Two separate scores calculate 10-year risks of **major coronary events** and **cerebral ischaemic events**	**10-year risk for a first atherosclerotic CVD (ASCVD) event.** **Lifetime risk**	**10-year probability of developing a first major CV event (myocardial infarction or stroke)**	**10 year risk of fatal cardiovascular disease**
Age range (years):	30–75	40–65	30–74	35–74	20–75	20–79	35–69	40-84
Variables:	Sex, age, total cholesterol, HDL-C, SBP, smoking status, DM, hypertensive treatment	Sex, age, total cholesterol or total cholesterol/HDL-C ratio, SBP, smoking status. Versions for use in high and low risk countries	Sex, age, total cholesterol, HDL-C, SBP, smoking – no. cigs, DM, area based index of deprivation, family history	QRISK1 - sex, age, total cholesterol to HDL-C ratio, SBP, smoking status, DM, area based index of deprivation, family history, BMI, BP treatment, ethnicity and chronic diseases	Age, sex, LDL-C, HDL-C, DM, smoking, SBP	Age, sex, race (white or other/African American), total cholesterol, HDL-C, SBP, antihypertensive treatment, DM, smoking	Age, sex, SBP, total cholesterol, HDL-C, antihypertensive therapy and smoking habit	Age, sex, smoking, total cholesterol, DM, systolic BP
Comments/ developments:	Latest version includes version based on non-laboratory values only, substituting BMI from lipid measurements	National, updated recalibrations		QRISK2 includes interaction terms to adjust for the interactions between age and some of the variables	Recent change in the methods (Weibull) allows extension of risk estimation to women and broader age	Race specific beta coefficients for risk factors have been incorporated. Calculator shown to overestimate risk in external validations – this may indicate the need for recalibration		Recalibrations have been undertaken for 11 countries

					range	in certain populations
Recommended by guidelines	NCEP guidelines,[54] Canadian CV guidelines,[55] other national guidelines recommend adapted versions including New Zealand[56]	European guidelines on CVD prevention[29]	SIGN[37]	NICE guidelines on lipid modification,[57] QRISK Lifetime recommended by JBS3 guidelines[58]	International Task Force for Prevention of Coronary Disease guidelines	2013 AHA ACC guideline on the assessment of CVD risk[50]

Table 2 Current cardiovascular disease risk estimation systems for use in apparently healthy persons, updated from [59 60]

ACC = American College of Cardiology; AHA = American Heart Association; ARIC = Atherosclerosis Risk in Communities; ATP = Adult Treatment Panel; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CARDIA = Coronary Artery Risk Development in Young Adults; CHS = Cardiovascular Health Study; CVD = cardiovascular disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; JBS = Joint British Societies; LDL-C = low-density lipoprotein cholesterol; NCEP = National Cholesterol Education Program; NICE = National Institute for Health and Care Excellence; no. cigs = number of cigarettes; PROCAM = Prospective Cardiovascular Munster Study; SBP = systolic blood pressure; SIGN = Scottish Intercollegiate Guidelines Network; SHHEC = Scottish Heart Health Extended Cohort

The SCORE system estimates the 10-year risk of a first *fatal* atherosclerotic event. All ICD (International Classification of Diseases) codes that could reasonably be assumed to be atherosclerotic are included, including CAD, stroke and aneurysm of the abdominal aorta. Traditionally most systems estimated CAD risk only; however, more recently a number of risk estimation systems have changed to estimate risk of all CVD.[44, 47, 50, 58]

The choice of CV mortality rather than total (fatal plus non-fatal) events was deliberate although not universally popular. Non-fatal event rates are critically dependent upon definitions and the methods used in their ascertainment. Critically, the use of mortality allows re-calibration to allow for time-trends in CV mortality. Any risk estimation system will over-predict in countries in which mortality has fallen and under-predict in those in which it has risen. Recalibration to allow for secular changes can be undertaken if good quality, up-to-date mortality and risk factor prevalence data are available. Data quality does not permit this for non-fatal events. For these reasons, the CV mortality charts were produced and have indeed been recalibrated for a number of European countries.

Naturally, the risk of total fatal and non-fatal events is higher, and clinicians frequently ask for this to be quantified. The SCORE data indicate that the total CV event risk is about three times higher than the risk of fatal CVD for men, so that a SCORE risk of fatal CVD of 5% translates approximately into a fatal plus non-fatal CV risk of 15%; the multiplier is about four in women and somewhat lower than three in older persons, in whom a first event is more likely to be fatal. [61]

As noted in the introduction, thresholds to trigger certain interventions are problematic since risk is a continuum and there is no threshold at which, for example, a drug is automatically indicated. Obviously, decisions on whether treatment is initiated should also be based on patient preferences.

A particular problem relates to young people with high levels of risk factors, where a low absolute risk may conceal a very high relative risk requiring intensive lifestyle advice. Several approaches to communicating about risk to younger people are presented below (refer also to section 2.5.1). These include use of the relative risk chart or “risk age” or “lifetime risk”. The aim is to communicate that lifestyle changes can reduce the relative risk substantially as well as reduce the increase in risk that will occur with ageing.

Another problem relates to older people. In some age categories the vast majority, especially of men, will have estimated CV death risks exceeding the 5–10% level, based on age (and gender) only, even when other CV risk factor levels are low. This could lead to excessive use of drugs in the elderly. This issue is dealt with later (see section 2.3.5). It should be noted that randomised controlled trial evidence to guide drug treatments in older persons is limited (refer to section 2.5.2).

The role of high-density lipoprotein cholesterol (HDL-C) in risk estimation has been systematically re-examined using the SCORE database.[62-64] HDL-C can contribute substantially to risk estimation if entered as an independent variable. For example, HDL-C modifies risk at all levels as estimated from the SCORE cholesterol charts,[63] and this effect is seen in both genders and in all age groups.[64] This is particularly important at levels of risk just below the threshold for intensive risk modification of 5%, where many of these subjects will qualify for intensive advice if their HDL-C is low.[63] This point is illustrated in supplementary figures A and B (see web addenda). In these charts HDL-C is used categorically. The electronic version of SCORE, HeartScore (www.HeartScore.org), has been modified to take HDL-C into account on a continuous basis, and is therefore more accurate.

The role of a plasma triglyceride as a predictor of CVD has been debated for many years. Fasting triglycerides relate to risk in univariable analyses but the effect is attenuated by adjustment for other factors, especially HDL-C.[65]

Dealing with the impact of additional risk factors such as body weight, family history and newer risk markers is difficult within the constraint of a paper chart. It should be stressed,

however, that although many other risk factors have been identified, their contribution is generally very modest to both absolute CV risk estimations and in terms of reclassification of an individual to another risk category[66] (Table 4).

Table 3 Advantages and limitations in using the SCORE risk charts

Advantages

- Intuitive, easy to use tool
- Establishes a common language of risk for healthcare professionals
- Allows a more objective assessment of risk
- Takes account of the multifactorial nature of CVD
- Allows flexibility in management; if an ideal risk factor level cannot be achieved, total risk can still be reduced by reducing other risk factors
- Deals with the problem of a low absolute risk in young people with multiple risk factors: the relative risk chart helps to illustrate how a young person with a low absolute risk may be at a substantially high and reducible relative risk; calculation of an individual's "risk age" may also be of use in this situation

Limitations

- Estimates risk of fatal but not total (fatal + non-fatal) CV risk for reasons outlined in text
- Adapted to suit different European populations, but not different ethnic groups within these populations
- Limited to the major determinants of risk
- Other systems have more functionality, although applicability to multiple countries is uncertain
- Limited age range (40-65)

CVD = cardiovascular disease; SCORE = Systematic Coronary Risk Estimation.

The SCORE risk charts are shown in Figures 1–4, including a chart of relative risks (Figure 3). Instructions on their use follow.

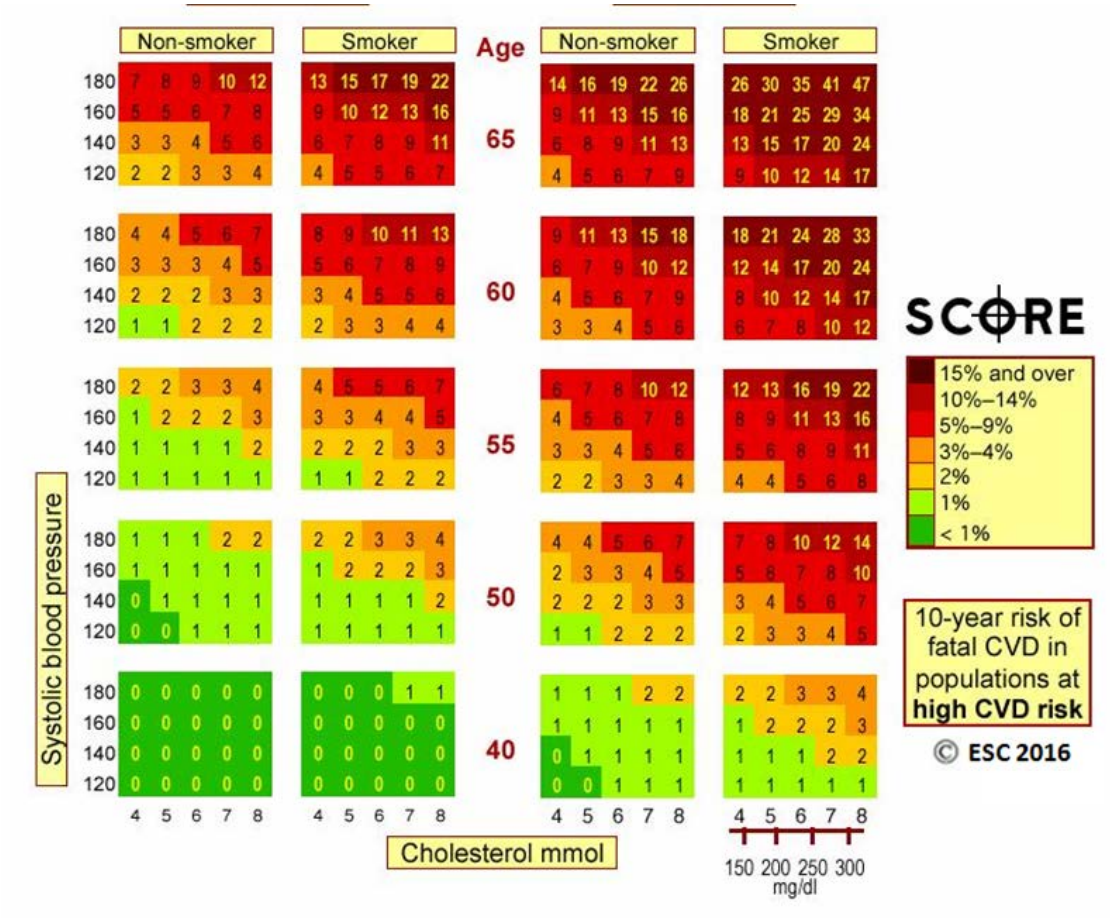

Figure 1: SCORE chart: 10-year risk of fatal CVD in populations of countries at **high** CV risk based on the following risk factors: age, sex, smoking, SBP, total cholesterol **(copyright 2016).** CVD = cardiovascular disease; SCORE = Systematic Coronary Risk Estimation.

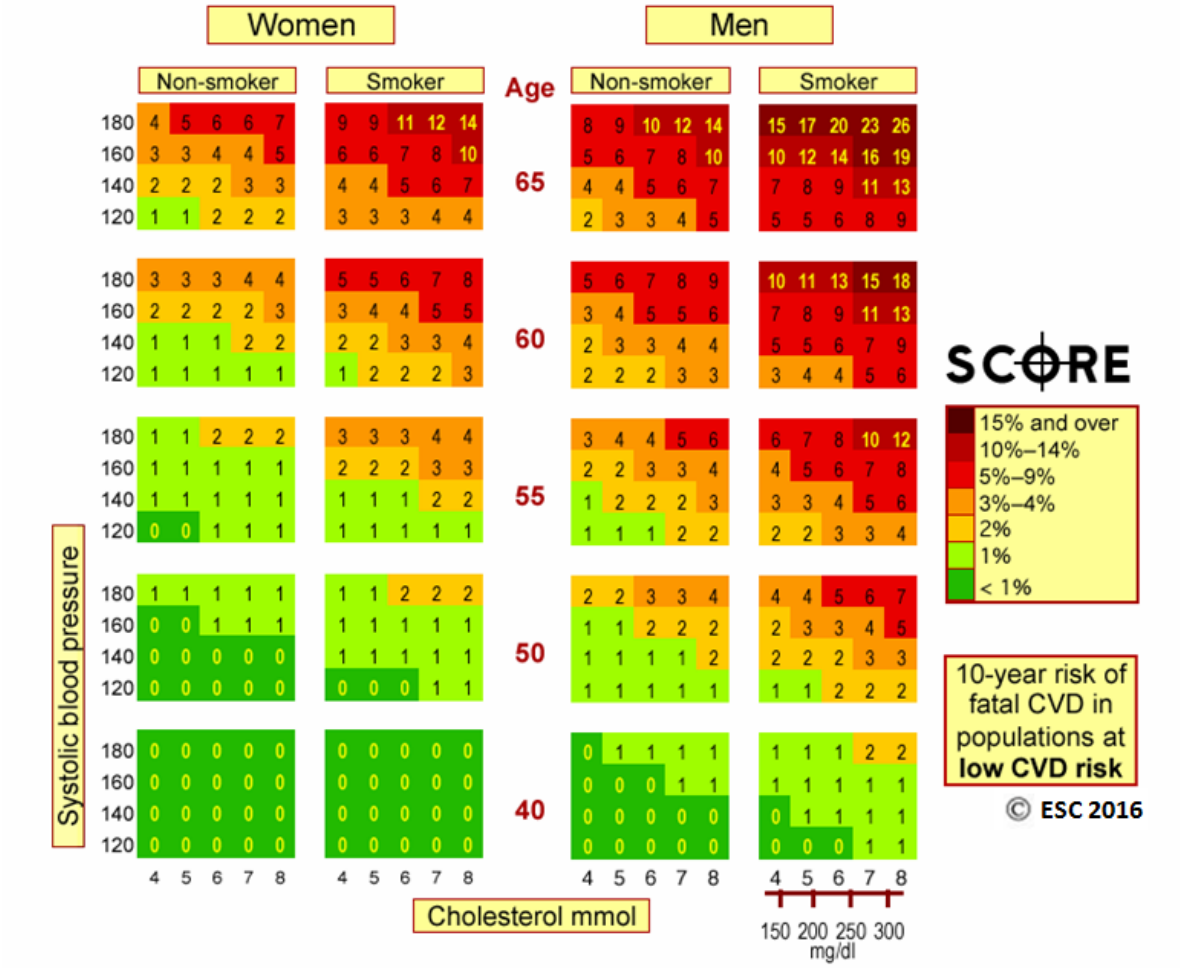

Figure 2: SCORE chart: 10-year risk of fatal CVD in populations of countries at **low** CV risk based on the following risk factors: age, sex, smoking, SBP, total cholesterol (copyright 2016). CVD = cardiovascular disease; SCORE = Systematic Coronary Risk Estimation.

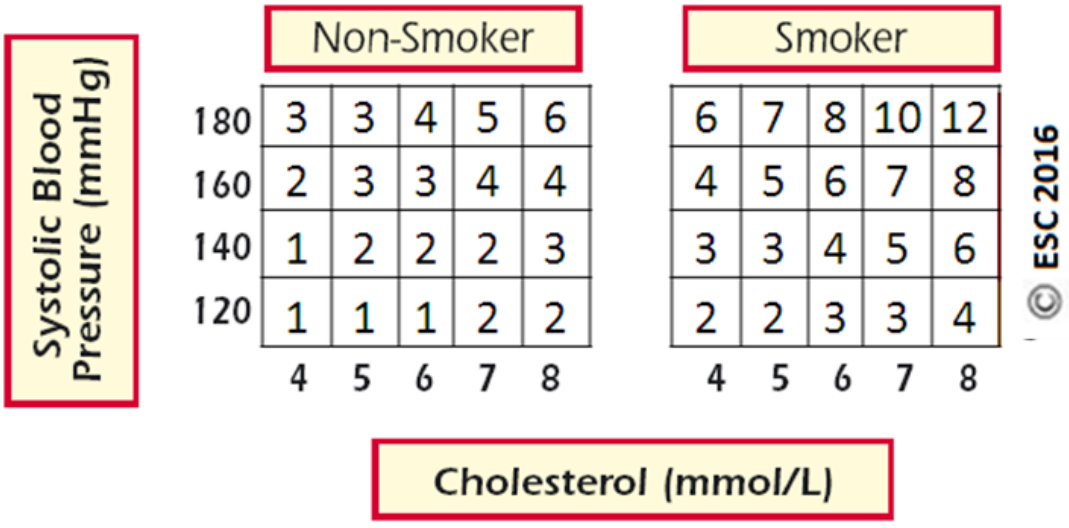

Figure 3 Relative risk chart, derived from SCORE. Conversion of cholesterol: mmol/L➔ mg/dL: 8 = 310, 7 = 270, 6 = 230, 5 = 190, 4 = 155.

Please note that Figure 3 shows RELATIVE not absolute risk. Thus a person in the top right hand box, with multiple CV risk factor, has a risk that is 12 times higher than a person in the bottom left with normal risk factor levels. This may be helpful when advising a young person with a **low absolute** but **high relative risk** of the need for lifestyle change.

2.3.2 Cardiovascular risk age

The risk age of a person with several CV risk factors is the age of a person of the same gender with the same level of risk but with ideal levels of risk factors. Thus a 40-year-old with high levels of some risk factors may have a risk age of a 60-year-old (Figure 4), because the risk equals that of a 60-year-old with ideal risk factor levels; i.e. non-smoking, total cholesterol of 4 mmol/L and BP of 120 mmHg.[67] Risk age is an intuitive and easily understood way of illustrating the likely reduction in life expectancy that a young person with a low absolute but high relative risk of CVD will be exposed to if preventive measures are not adopted.[67] Table A showing different risk factor combinations is included in the supplementary material (web addenda) to provide a more accurate estimation of risk ages. Risk age is also automatically calculated as part of the latest revision of HeartScore.

Risk age has been shown to be independent of the CV end point used,[67] which bypasses the dilemma of whether to use a risk estimation system based on CV mortality or on total CV events. Risk age can be used in any population regardless of baseline risk and of secular changes in mortality, and therefore avoids the need for recalibration.[68] At present, risk age is recommended for helping to communicate about risk, especially to younger people with a low absolute risk but a high relative risk.

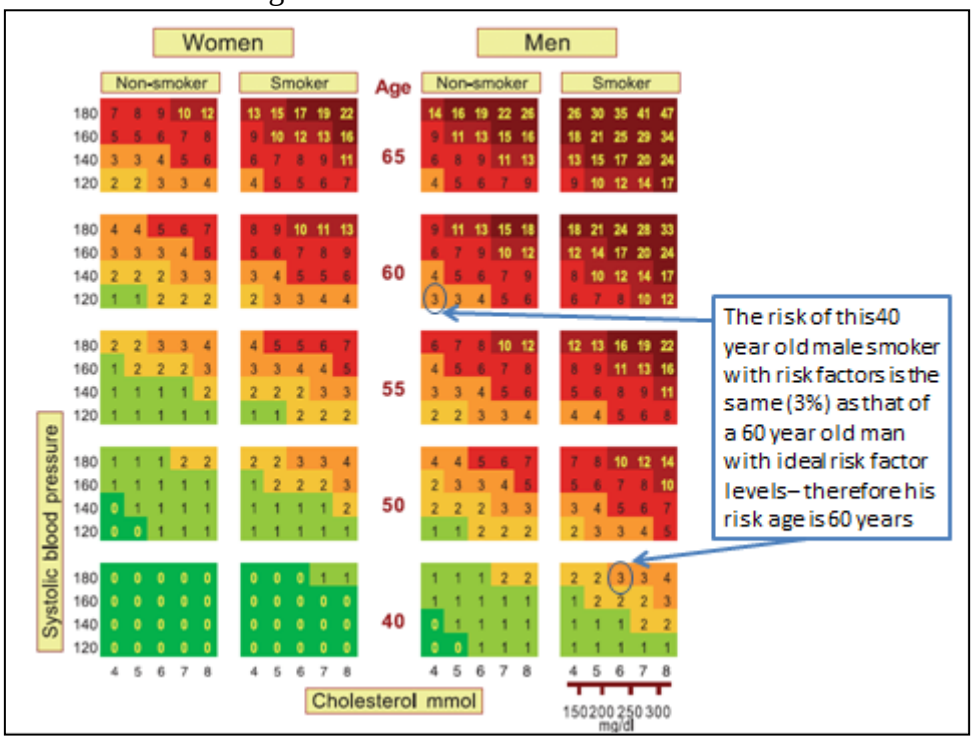

Figure 4: SCORE chart (for use in high risk European countries) illustrating how the approximate risk age can be read off the chart. SCORE = Systematic Coronary Risk Estimation.

2.3.3 Lifetime versus 10-year cardiovascular risk estimation

Conventional CV risk prediction schemes estimate 10-year risk of CV events. Lifetime CV risk prediction models identify high risk individuals both in the short- and long-term. Such

models account for predicted risk in the context of competing risks from other diseases over the remaining expected lifespan of an individual.
Notably, 10-year risk identifies individuals who are most likely to benefit from drug therapy in the near term. Drug treatment starts to works quite rapidly, and drug treatment can be largely informed by short-term risk, such as 10-year risk. One problem with short-term risk is that it is mostly governed by age and consequently few younger individuals, in particular women reach treatment thresholds. It has therefore been argued that lifetime risk estimation may enhance risk communication, particularly among younger individuals and women.
Evidence for the role of lifetime risk in treatment decisions is lacking. Sufficient data for robust lifetime risk estimations, as well as meaningful risk categorization thresholds, are lacking. Providing lifetime CV risk estimates for some groups at high risk of mortality due to competing non-CVD causes can be difficult to interpret. Importantly, evidence of the benefits of lifelong preventive therapy (e.g. BP or lipid lowering drugs) in younger individuals with low short-term but higher lifetime risks is lacking. For these reasons, we do not recommend risk stratification for treatment decisions to be based on lifetime risk. However, like risk age and relative risk, it may be a useful tool in communicating about risk to individuals with high risk factor levels, but at a low 10-year absolute risk of CV events, such as some younger people. Whatever approach is used, if absolute risk is low, a high relative risk or risk age signals the need for active lifestyle advice and awareness that drug treatment may need consideration as the person ages. Both risk age and lifetime risk are closer to relative than absolute risk, and none provide an evidence base for drug treatment decisions.

2.3.4 Low risk, high risk and very high risk countries

The countries considered here are those with national cardiology societies that belong to the ESC, both European and non-European.

2.3.4.1 What are low risk countries?

The fact that CVD mortality has declined in many European countries means that more now fall into the low risk category. While any cut-off point is arbitrary and open to debate, in these guidelines the cut-off points for calling a country “low risk” are based on age-adjusted 2012 CVD mortality rates in those aged 45–74 years (<225/100,000 in men and <175/100,000 in women).[69] This defines the following countries as low risk countries: **Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, The Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland and United Kingdom.**

2.3.4.2 What are high and very high risk countries?

High risk countries are: **Bosnia and Herzegovina, Croatia, Czech Republic, Estonia, Hungary, Lithuania, Montenegro, Morocco, Poland, Romania, Serbia, Slovakia and Turkey**.
Very high risk European countries present levels of risk which are more than double that of low risk countries, i.e. CVD mortality > 450/100,000 for men and > 350/100,000 for women. Additionally, the male: female ratio is smaller than in low risk countries, suggesting a major problem for women. These countries are: **Albania, Algeria, Armenia, Azerbaijan, Belarus, Bulgaria, Egypt, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Macedonia FYR, Moldova, Russian Federation, Syrian Arab Republic, Tajikistan, Turkmenistan, Ukraine and Uzbekistan.**

2.3.5 How to use the risk estimation charts

- The SCORE charts are used in apparently healthy people, not for those with established CVD or at very high risk or high risk for other reasons (e.g. DM, see section 3a.8, or chronic kidney disease (CKD), see section 2.4.5.1), who need intensive risk advice anyway.
- Use of the **low risk chart** is recommended for the countries listed above. Use of the **high risk chart** is recommended for all other European and Mediterranean countries, taking into account that the high risk charts may underestimate the risk in very high risk countries (see above). Note that several countries have undertaken national recalibrations to allow for time trends in mortality and risk factor distributions. Such charts are likely to better represent risk levels.
- To estimate a person's 10-year risk of CV death, find the table for their gender, smoking status and (nearest) age. Within the table find the cell nearest to the person's BP and total cholesterol (or total cholesterol: HDL-C ratio). Risk estimates will need to be adjusted upwards as the person approaches the next age category.
- While no threshold is universally applicable, the intensity of advice should increase with increasing risk. The effect of interventions on the absolute probability of developing a CV event increases with an increasing baseline risk; i.e. the number of individuals needed to treat (NNT) to prevent one event decreases with increasing risk.

  - **Low- to moderate-risk persons (calculated SCORE <5%)** should be offered lifestyle advice to maintain their low to moderate risk status.
  - **High-risk persons (calculated SCORE ≥5% and <10%)** qualify for intensive lifestyle advice, and may be candidates for drug treatment.
  - **Very-high-risk persons (calculated SCORE ≥10%):** drug treatment is more frequently required. In persons >60 years of age these thresholds should be interpreted more leniently, because their age-specific risk is normally around these levels, even when other CV risk factor levels are "normal". In particular, uncritical initiation of drug treatments of all elderly with risks greater than the 10% threshold should be discouraged.

Use of the risk charts should be qualified by knowledge of the following aspects:

- The charts assist in risk estimation but must be interpreted in the light of the clinician's knowledge and experience and in view of the factors that may modify the calculated risk (see below).
- Relative risks may be high in young persons, even if 10 year absolute risks are low, because events usually occur later in life. The relative risk chart or estimating risk age may be helpful in identifying and counselling such persons.
- The lower risk in women is explained by the fact that risk is deferred by 10 years—the risk of a 60-year-old woman is similar to that of a 50-year-old man. Ultimately more women than men die of CVD.
- The charts may be used to give some indication of the effects of reducing risk factors, given that there will be a time lag before risk reduces and that the results of RCTs in general give better estimates of the benefits of interventions. Those who stop smoking in general halve their risk.

2.3.6 Modifiers of calculated total cardiovascular risk

Apart from the conventional major CV risk factors included in the risk charts, there are other risk factors that could be relevant for assessing total CVD risk. The Task Force recommends additional risk factor assessment if such a risk factor improves risk classification (for example, by calculation of a net reclassification index (NRI)) and if the assessment is feasible

in daily practice. In general, reclassification is of most value when the individual's risk lies close to a decisional threshold, such as a SCORE risk of 5%. In very high or very low risk situations, the impact of additional risk factors is unlikely to alter management decisions. While the presence of risk modifiers may move an individual's estimated risk upward, absence of these modifiers should lead to lowering an individual's estimated risk.

Table 4 lists examples of factors that fulfil the aforementioned criteria. Several other factors that are frequently discussed in the literature, but may not have the ability to reclassify subjects, are discussed in subsequent paragraphs. Also discussed further in this section are the roles of ethnicity and of specific conditions or diseases that may be associated with a higher than calculated risk, such as CKD, autoimmune diseases, etc. The way modifiers are related to CV risk may be very different. Social deprivation and being overweight, for example, are important as "causes of the causes" of CVD, in that they may be associated with higher levels of conventional risk factors. Family history may reflect a shared environment, genetic factors, or both. Markers such as computed tomography (CT) calcium scoring are indicators of disease rather than risk factors for future disease.

Table 4 Examples of risk modifiers that are likely to have reclassification potential (see following sections for details)

Socio-economic status, social isolation, or lack of social support
Family history of premature CVD
BMI and central obesity
CT coronary calcium score
Atherosclerotic plaques determined by carotid artery scanning
ABI

ABI = ankle–brachial blood pressure index; BMI = body mass index; CVD = cardiovascular disease; CT = computed tomography.

2.3.7 Risk categories: priorities

Individuals at highest risk gain most from preventive efforts, and this guides the priorities, which are detailed in Table 5.

Table 5 Risk categories

Very high risk	Subjects with any of the following: • Documented CVD, clinical or unequivocal on imaging. Documented clinical CVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD. Unequivocally documented CVD on imaging includes significant plaque on coronary angiography or carotid ultrasound. It does NOT include some increase in continuous imaging parameters such as intima–media thickness of the carotid artery. • DM with target organ damage such as proteinuria or with a major risk factor such as smoking or marked hypercholesterolemia or marked hypertension. • Severe CKD (GFR <30 mL/min/1.73 m^2). • A calculated SCORE ≥10%.

High risk	Subjects with: • Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (e.g. in familial hypercholesterolemia) or BP ≥180/110 mmHg. • Most other people with DM (with the exception of young people with type 1 DM and without major risk factors that may be at low or moderate risk). • Moderate CKD (GFR 30–59 mL/min/1.73 m^2) • A calculated SCORE ≥5% and <10%.
Moderate risk	SCORE is ≥1% and <5% at 10 years. Many middle-aged subjects belong to this category.
Low risk	SCORE <1%.

ACS = acute coronary syndrome; AMI = acute myocardial infarction; BP = blood pressure; CKD = chronic kidney disease; DM = diabetes mellitus; GFR = glomerular filtration rate; PAD = peripheral artery disease; SCORE = systematic coronary risk estimation; TIA = transient ischaemic attack.

2.3.8 Risk factor targets

Table 6 Risk factor goals and target levels for important cardiovascular risk factors

Smoking	No exposure to tobacco in any form.
Diet	Low in saturated fat with a focus on wholegrain products, vegetables, fruit and fish.
Physical activity	At least 150 minutes a week of moderate aerobic PA (30 min for 5 days/week) or 75 minutes a week of vigorous aerobic PA (15 minutes for 5 days/week) or a combination thereof.
Body weight	BMI 20–25 kg/m^2. Waist circumference < 94 cm (men) or < 80 cm (women).
Blood pressure	< 140/90 mmHg [a]
Lipids [b] LDL [c] is the primary target	**Very high risk: <1.8 mmol/L (<70 mg/dL**), or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) [d] **High risk**: **<2.6mmol/L (<100 mg/dL),** or a reduction of at least 50% if the baseline is between 2.6 and 5.1 mmol/L (100 and 200 mg/dL) **Low to moderate risk**:**<3 mmol/L (<115 mg/dL).**
HDL-C	No target but >1.0 mmol/L (>40mg/dL) in men and >1.2 mmol/L (>48mg/dL) in women indicate lower risk.
Triglycerides	No target but <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.
Diabetes	HbA1c <7%. (<53 mmol/mol)

BMI = body mass index; HbA1c = glycated haemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol.

[a] Blood pressure <140/90 mmHg is the general target. The target can be higher in frail elderly, or lower in most patients with DM (see chapter 3.a.8) and in some (very) high risk patients without DM who can tolerate multiple blood pressure lowering drugs (see chapter 3.a.9)

[b] **Non-HDL-C is a reasonable and practical alternative target** because it does not require fasting. Non HDL-C secondary targets of <2.6, <3.3 and <3.8 mmol/L (<100, <130 and <145 mg/dL) are recommended for very high, high and low to moderate risk subjects, respectively. See section 3a.7.10 for more details.
[c] A view was expressed that primary care physicians might prefer a single general LDL-C goal of 2.6 mmol/L. While accepting the simplicity of this approach and that it could be useful in some settings, there is better scientific support for the three targets matched to level of risk.
[d] This is the general recommendation for those at very high risk. It should be noted that the evidence for patients with CKD is less strong

2.3.9 Conclusions

Estimation of **total CV risk** remains a crucial part of the present guidelines. The priorities (risk categories) defined in this section are for clinical use and reflect the fact that those at highest risk of a CVD event gain most from preventive measures. This approach should complement public actions to reduce community risk factor levels and promote a healthy lifestyle. The principles of risk estimation and the definition of priorities reflect an attempt to make complex issues simple and accessible. Their very simplicity makes them vulnerable to criticism. Above all they must be interpreted in the light of the physician's detailed knowledge of his/her patient and in the light of local guidance and conditions.

Gaps in evidence

- There are no recent RCTs of a total risk approach to (a) risk assessment, or (b) risk management.
- The young, women, older people and ethnic minorities continue to be under-represented in clinical trials.
- A systematic comparison of current international guidelines is needed to define areas of agreement and the reasons for discrepancies.

2.4 Other risk markers

2.4.1 Family history/(epi)genetics

Key messages

- Family history of premature CVD in first degree relatives, before 55 years in men and 65 years in women, increases the risk of CVD.
- Several genetic markers are associated with increased risk of CVD, but their use in clinical practice is not recommended.

Recommendations for assessment of family history/(epi) genetics

Recommendations	Class[a]	Level[b]	Ref[c]
Assessment of family history of premature CVD (defined as a fatal or non-fatal CVD event or/and established diagnosis of CVD in first degree male relatives before 55 years or female relatives before 65 years) is recommended as part of cardiovascular risk assessment.	I	C	[70]
The generalized use of DNA-based tests for CVD risk assessment is not recommended.	III	B	[71, 72]

CVD = cardiovascular disease.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

2.4.1.1 Family history

Familial history of premature CVD is a crude but simple indicator of the risk of developing CVD, reflecting both the genetic trait and the environment shared among household members.[70] A positive family history of premature CV death is associated with an increased risk of early and lifetime CVD.[73] In the few studies that simultaneously assessed and reported the effects of family history and genetic scores, family history remained significantly associated with incidence of CVD after adjusting for the genetic scores.[74, 75] Limited data exist regarding the ability of family history to improve prediction of CVD beyond conventional CV risk factors.[76-78] One possible explanation is the varying definitions of family history applied[79] and that conventional CV risk factors can partly explain the impact of family history.

Family history of premature CVD is simple, inexpensive information that should be part of CV risk assessment in all subjects. Family history can be a risk modifier to optimal management after the calculated risk using SCORE lies around a decisional threshold: a positive family history would favour more intensive interventions while a negative family history would translate into less intensive treatment.[80]

2.4.1.2 Genetic markers

Genetic screening and counselling is effective in some conditions such as familial hypercholesterolaemia (FH) (see section 3a.7.9). This paragraph will focus on genetic screening for high CV risk in the general population.

Several recent genome-wide association studies have identified candidate genes associated with CVD. As the effect of each genetic polymorphism is small, most studies used genetic scores to summarize the genetic component. There is a lack of consensus regarding which genes and their corresponding single nucleotide polymorphisms (SNPs) should be included in a genetic risk score, and which method should be used to calculate the genetic score.

The association of genetic scores with incident CVD has been prospectively studied, adjusting for the main CV risk factors, and most studies found a significant association, with the relative risks varying between 1.02 and 1.49 per increase in one score unit.[81] The ability of genetic scores to predict CV events beyond traditional CV risk factors (i.e. defined by the Net Reclassification Index or NRI) was found in about half of the studies. The NRI is a statistical measure quantifying the usefulness of adding new variables to a risk prediction equation [82]. The biggest improvements in the NRI were observed in participants at intermediate risk, while little or no improvement was observed in participants at high risk.[74, 83] One study estimated that one additional CAD event for every 318 people screened at intermediate risk could be prevented by measuring the CAD-specific genetic score in addition to established risk factors.[83] Importantly, as the frequency of polymorphisms might differ, the results may vary between populations.[75, 84, 85] Recently, a genetic risk score based on 27 genetic variants enabled the identification of subjects at increased risk of CAD and who would benefit the most from statin therapy, even after adjustment on family history [86] Still, it is likely that some reported associations might be due to chance[87] and replication studies are needed to confirm positive findings.

Currently, many commercial tests are available, allowing an almost complete assessment of an individual's genome, and strong pressure is applied to use this information to predict genetic risk and to make genetic testing a routine measure.[88] Given the lack of agreement regarding which genetic markers should be included, how genetic risk scores should be calculated, and uncertainties about improvement in CV risk prediction, the use of genetic markers for prediction of CVD is therefore not recommended.

2.4.1.3 Epigenetics

Epigenetics studies the chemical changes in DNA that affect gene expression. Methylation of genes related to CV risk factors is associated with variation in CV risk factor levels,[89, 90] and lower DNA methylation levels are associated with increased risk of CAD or stroke[91]. No information exists, however, regarding the effect of epigenetic markers in improving CVD risk prediction beyond conventional risk factors. Thus, epigenetic screening of CVD is not recommended.

Gaps in evidence

- The impact of adding family history to the current SCORE risk equation should be assessed.
- Future studies should assess the power of different genetic risk scores to improve CVD risk prediction in several different populations, the number of events prevented, and the cost-effectiveness of including genetic data in risk assessment.

2.4.2 Psychosocial risk factors

Key messages

- Low socio-economic status, lack of social support, stress at work and in family life, hostility, depression, anxiety, and other mental disorders contribute both to the risk of developing CVD and a worse prognosis of CVD, with the absence of these items being associated with a lower risk of developing CVD and a better prognosis of CVD.
- Psychosocial risk factors act as barriers to treatment adherence and efforts to improve lifestyle, as well as to promoting health in patients and populations.

Recommendations for assessment of psychosocial risk factors

Recommendations	Class[a]	Level[b]	Ref[c]
Psychosocial risk factor assessment, using clinical interview or standardized questionnaires, should be considered to identify possible barriers to lifestyle change or adherence to medication in individuals at high CVD risk or with established CVD.	IIa	B	92-94

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Low socio-economic status, defined as low educational level, low income, holding a low-status job, or living in a poor residential area, confer an increased risk of CAD; the relative risk (RR) of CAD mortality risk is 1.3 to 2.0.[95, 96] Compared to the Framingham risk score, adding social deprivation to CV risk assessment was able to reduce unattributed risk substantially.[45]

People who are isolated or disconnected from others are at increased risk of developing and dying prematurely from CAD. Similarly, lack of social support increases CAD risk and worsens the prognosis of CAD.[97]

Acute mental stressors may act as triggers of acute coronary syndromes (ACS). These stressors include exposure to natural catastrophe as well as personal stressors, e.g. defeat or other serious life events, resulting in acute strong negative emotions, e.g. outbursts of anger or grief.[98] After death of a significant person, the incidence rate of acute myocardial infarction (AMI) is elevated 21-fold during the first 24 hours, declining steadily during the subsequent days.[99]

Chronic stress at work (e.g. long working hours, extensive overtime work, high psychological demands, unfairness, and job strain) predicts premature incident CAD in men (RR ~ 1.2 to

1.5).[100] In addition, long-term stressful conditions in family life increase CAD risk (RR ~ 2.7–4.0).[101 102]

Clinical depression and depressive symptoms predict incident CAD (RR 1.6 and 1.9)[103] and worsen its prognosis (RR 1.6 and 2.4).[94, 98, 103, 104] Vital exhaustion, most likely representing somatic symptoms of depression, significantly contributed to incident CAD (population attributable risk 21.1% in women, and 27.7% in men). The net reclassification index improved significantly.[105] Panic attacks also increase the risk of incident CAD (RR 4.2). [106] Anxiety is an independent risk factor for incident CAD (RR 1.3)[94], for cardiac mortality following AMI (OR 1.2) [107] and cardiac events (OR 1.7) [108].

Meta-analyses reported a 1.5-fold risk of CVD incidence, a 1.2-fold risk of CAD, and 1.7-fold risk for stroke in patients with schizophrenia,[109] and a 1.3-fold risk for incident CAD, even after adjustment for depression, in patients with post-traumatic stress disorder.[110]

Hostility is a personality trait, characterized by extensive experience of mistrust, rage, and anger, and the tendency to engage in aggressive, maladaptive social relationships. A meta-analysis confirmed that anger and hostility are associated with a small but significant increased risk for CV events in both healthy and CVD populations (RR 1.2).[111] The type D ("distressed") personality involves an enduring tendency to experience a broad spectrum of negative emotions (negative affectivity) and to inhibit self-expression in relation to others (social inhibition). The type D personality has been shown to predict poor prognosis in patients with CAD (RR 2.2).[112]

In most situations, psychosocial risk factors cluster in individuals and groups. For example, both women and men of lower socio-economic status and/or with chronic stress are more likely to be depressed, hostile, and socially isolated.[113] The INTERHEART study has shown that a cluster of psychosocial risk factors (i.e. social deprivation, stress at work or in family life, and depression) is associated with increased risk for myocardial infarction (MI) (RR 3.5 for women and 2.3 for men). The population attributable risk was 40% in women and 25% in men.[114]

Mechanisms that link psychosocial factors to increased CV risk include unhealthy lifestyle (more frequent smoking, unhealthy food choice, and less physical activity (PA)) and low adherence to behaviour-change recommendations or CV medication.[95, 115] In addition, depression and/or chronic stress are associated with alterations in autonomic function, in the hypothalamic–pituitary axis and in other endocrine markers, which affect haemostatic and inflammatory processes, endothelial function, and myocardial perfusion.[113] Enhanced risk in patients with depression may also be due in part to adverse effects of tricyclic antidepressants.[93]

Assessment of psychosocial factors in patients and persons with CV risk factors should be considered for use as risk modifiers in CV risk prediction, especially in individuals with SCORE risks around decisional thresholds. In addition, psychosocial factors can help identify possible barriers to lifestyle change and adherence to medication. Standardized methods are available to assess psychosocial factors in many languages and countries.[92] Alternatively, a preliminary assessment of psychosocial factors can be made within the physicians' clinical interview, as shown in Table 7.

Table 7 Core questions for the assessment of psychosocial risk factors in clinical practice

Low socio-economic status	What is your highest educational degree? Are you a manual worker?
Work and family stress	Do you lack control over how to meet the demands at work? Is your reward inappropriate for your effort? Do you have serious problems with your spouse?
Social isolation	Are you living alone? Do you lack a close confidant?

	Have you lost an important relative or friend over the last year?
Depression	Do you feel down, depressed and hopeless? Have you lost interest and pleasure in life?
Anxiety	Do you suddenly feel fear or panic? Are you frequently unable to stop or control worrying?
Hostility	Do you frequently feel angry over little things? Do you often feel annoyed about other people's habits?
Type D personality	In general, do you often feel anxious, irritable, or depressed? Do you avoid sharing your thoughts and feelings with other people?
Post-traumatic stress disorder	Have you been exposed to a traumatic event? Do you suffer from nightmares or intrusive thoughts?
Other mental disorders	Do you suffer from any other mental disorder?

No more than minimum education according to the requirement of the country and/or a "yes" for one or more items indicate an increased CV risk and could be applied as a modifier of CV risk (see chapter 2.3.6). The management of psychosocial risk factors should be addressed according to chapter 3a.2.

Gaps in evidence

- It remains unknown whether routine screening for psychosocial risk factors contributes to fewer future cardiac events.

2.4.3 Circulating and urinary biomarkers

Key messages

- CV circulating and urinary biomarkers have either no or only limited value when added to CVD risk assessment with the SCORE system.
- There is evidence of publication bias in the field of novel biomarkers of CV risk, leading to inflated estimates of strength of association and potential added value.

Recommendations for assessment of circulating and urinary biomarkers

Recommendations	Class[a]	Level[b]	Ref[c]
Routine assessment of circulating or urinary biomarkers is not recommended for refinement of CVD risk stratification.	III	B	116, 117

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

In general, biomarkers can be classified into inflammatory (e.g. high-sensitivity C-reactive protein (hsCRP, fibrinogen), thrombotic (e.g. homocysteine, lipoprotein-associated phospholipase A2), glucose- and lipid-related markers (e.g. apolipoproteins), and organ-specific markers (e.g. renal, cardiac). However, for the purpose of overall CV risk estimation, these distinctions are generally not relevant. Also, from the perspective of risk stratification (i.e. prediction of future CV events), the question of whether a biomarker is causally related to CVD or may be a marker of preclinical disease is equally irrelevant.

Among the most extensively studied and discussed biomarkers is hsCRP. This biomarker has shown consistency across large prospective studies as a risk factor integrating multiple metabolic and low-grade inflammatory factors, with RRs approaching those of classical CV

risk factors. However, its contribution to the existing methods of CV risk assessment is probably small.[118]

Meta-analyses and systematic reviews suggest that the vast majority of other circulating and urinary biomarkers also have no or limited proven ability to improve risk classification. However, the extent to which they have been tested for their ability to add value to risk stratification varies considerably,[116, 117] with strong evidence of reporting bias.[119] Organ-specific biomarkers may be useful to guide therapy in specific circumstances (e.g. albuminuria in hypertension or DM may predict kidney dysfunction and warrant renal-protective interventions), for which we refer to section 3a.

If, despite these recommendations, biomarkers are used as risk modifiers, it is important to note that having an unfavourable biomarker profile may be associated with a somewhat higher risk, but also that a favourable profile is associated with a lower risk than calculated. The degree to which the calculated risk is affected by biomarkers is generally unknown, but almost universally smaller than the (adjusted) relative risks reported for these biomarkers in the literature.[120] Hence, in these patients particularly with a moderate risk profile, only relatively small adjustments in calculated risk are justifiable, and patients who are clearly at high or low risk should not be reclassified based on biomarkers.[121]

Gaps in evidence

- Not all potentially useful circulatory and urinary biomarkers have undergone state-of-the-art assessment of their added value in CV risk prediction on top of conventional risk factors.
- Biomarkers may be useful in specific subgroups, but this has been addressed in only a limited number of studies.
- The role of metabolomics as risk factors for CVD and to improve CV risk prediction beyond conventional risk factors should be further assessed.

2.4.4 Measurement of preclinical vascular damage

Key messages

- Routine screening with imaging modalities to predict future CV events is generally not recommended in clinical practice.
- Imaging methods may be considered as risk modifiers in CV risk assessment, i.e. in individuals with calculated CV risks based on the major conventional risk factors around the decisional thresholds.

Recommendations for imaging methods

Recommendations	Class[a]	Level[b]	Ref[c]
Coronary artery calcium scoring may be considered as a risk modifier in CV risk assessment.	IIb	B	122-127
Atherosclerotic plaque detection by carotid artery scanning may be considered as a risk modifier in CV risk assessment.	IIb	B	128-130
ABI may be considered as a risk modifier in CV risk assessment.	IIb	B	131-134
Carotid ultrasound IMT screening for CV risk assessment is not recommended.	III	A	130, 135

ABI = ankle–brachial index; CV = cardiovascular; IMT = intima–media thickness.

[a]Class of recommendation.

[b]Level of evidence.

[c]Reference(s) supporting recommendations.

Although most of the CVD may be explained by traditional risk factors, there is substantial variation in the amount of atherosclerosis. This has maintained interest in non-invasive imaging techniques to improve CV risk assessment. In individuals with calculated CV risks based on the major conventional risk factors around the decisional thresholds, some imaging techniques may be considered as risk modifiers to improve risk prediction and decision making.

2.4.4.1 Coronary artery calcium

Coronary artery calcium (CAC) is examined through electron beam or multislice CT. Calcifications indicate late stage subclinical coronary atherosclerosis.[136] Atherosclerotic coronary arteries do not necessarily always show calcifications. The extent of the calcification correlates with the extent of total coronary plaque burden.[136] CAC is not an indicator of the (in)stability of an atherosclerotic plaque.[137] In patients with ACS, the extent of CAC is more pronounced than in those without CAD.[138]

The quantification of CAC scoring is fairly consistent across studies. Most studies use the Agatston score.[139] The value of the score can be further increased if the age and sex distribution within percentiles are taken into account. A CAC score ≥300Agatston units or ≥75th percentile for age, sex, and ethnicity is considered to indicate increased CV risk.

CAC has shown a very high negative predictive value, since the Agatston score of 0 has a negative predictive value of nearly 100% for ruling out significant coronary narrowing.[122] However, studies have questioned the negative predictive value of CAC because significant stenosis in the absence of CAC is possible.[123] Many prospective studies have shown the association of CAC with CAD, and the Agatston score is an independent predictor of CAD.[124] Importantly, some studies showed that including CAC may improve CV risk prediction in addition to conventional risk factors, and also in terms of the reclassification of individuals in risk categories.[125] Thus, CAC scoring may be considered in individuals with calculated SCORE charts risks around the 5% or 10% thresholds.[126, 127]

Although recent studies also showed the presence of CAC in low-risk population, the added predictive value on CV events remains to be demonstrated. [140-142]

There are concerns regarding costs and radiation exposure. For CAC scoring the radiation exposure with the properly selected techniques is ±1mSv.

2.4.4.2 Carotid ultrasound

Population-based studies have shown correlations between the severity of atherosclerosis in one arterial territory and the involvement of other arteries.[128] Therefore, early detection of arterial disease in apparently healthy individuals has focused on peripheral arteries and in particular on the carotid arteries. Risk assessment using carotid ultrasound focuses on the measurement of the intima–media thickness (IMT) and the presence and characteristics of plaques.

The IMT is not only a measure of early atherosclerosis but also of smooth muscle hypertrophy/hyperplasia. There is a graded increase in CV risk with rising IMT,[128] and a value >0.9 mm is considered abnormal. The risk of stroke associated with IMT is non-linear, with hazards increasing more rapidly at lower IMTs than at higher IMTs. The IMT-associated risk of cardiac events is also non-linear.[129] The extent of carotid IMT is an independent predictor of CVD, but seems to be more predictive in women than in men.

The lack of standardization regarding the definition and measurement of IMT, its high variability and low intra-individual reproducibility have raised concerns. A recent meta-analysis failed to demonstrate any added value of IMT compared to the Framingham Risk Score in predicting future CVD, even in the intermediate risk group.[130] Thus, the systematic use of carotid ultrasound IMT to improve risk assessment is not recommended.

Plaque is usually defined as the presence of a focal wall thickening that it is at least 50% greater from the surrounding vessel wall or as a focal region with IMT measurement ≥1.5 mm that protrudes into the lumen.[143] Plaques may be characterized by their number, size, irregularity, and echodensity (echolucent vs. calcified). Plaques are related to both coronary and cerebrovascular events, and echolucent (as opposed to calcified) plaques increase ischaemic cerebrovascular events.[129] Many studies emphasize the greater value of measures that include plaque area and thickness, rather than IMT alone, in predicting CVD. Therefore, even though formal reclassification analyses have not been undertaken, carotid artery plaque assessment using ultrasonography may be considered to be a risk modifier in CV risk prediction in some cases.

2.4.4.3 Arterial stiffness

Arterial stiffness is commonly measured using either aortic pulse wave velocity (PWV) or arterial augmentation index. An increase in arterial stiffness is usually related to damage in the arterial wall, as has been shown in hypertensive patients.[144] Although the relationship between aortic stiffness and CVD is continuous, a PWV threshold of 12 m/s has been suggested as a conservative estimate of significant alterations of aortic function in middle-aged hypertensive patients. A meta-analysis showed that arterial stiffness predicts future CVD and improves risk classification.[144] However, the validity of this conclusion is offset by evidence of substantial publication bias.[119] The Task Force concludes that arterial stiffness may serve as a useful biomarker to improve CV risk prediction for patients close to decisional thresholds, but its systematic use in the general population to improve risk assessment is not recommended.

2.4.4.4 Ankle–brachial index

The ankle–brachial (BP) index (ABI) is an easy-to-perform and reproducible test to detect asymptomatic atherosclerotic disease. An ABI <0.9 indicates ≥50% stenosis between the aorta and the distal leg arteries. Because of its acceptable sensitivity (79%) and specificity (90%),[133] an ABI <0.90 is considered to be a reliable marker of peripheral artery disease (PAD).[131] An ABI value indicating significant PAD adds value to medical history, because 50–89% of patients with an ABI <0.9 do not have typical claudication[132] and it is present in 12–27% of asymptomatic individuals over 55 years of age.

The ABI is inversely related to CV risk.[134] but there is controversy regarding its potential to reclassify patients into different risk categories.[133, 145]

2.4.4.5. Echocardiography

Echocardiography is more sensitive than electrocardiography in diagnosing left ventricular hypertrophy (LVH) and it precisely quantifies left ventricular (LV) mass and geometric LVH patterns. Cardiac abnormalities detected by echocardiography have an additional predictive power.[146, 147] In view of the lack of convincing evidence that echocardiography improves CV risk reclassification and because of the logistical challenges in performing it, this imaging tool is not recommended to improve CV risk prediction.

Gaps in evidence

- Currently, most imaging techniques have not been rigorously tested as screening tools in CV risk assessment; more evidence on calibration, reclassification, and cost-effectiveness is still needed.
- The reduction of CVD risk in patients treated with lipid or BP lowering drugs because of reclassification with, for example, CAC or ABI remains to be demonstrated.

2.4.5 Clinical conditions affecting cardiovascular disease risk

2.4.5.1 Chronic kidney disease

Key message

- CKD is associated with an increased risk of CVD, independent of conventional CVD risk factors.

Hypertension, dyslipidaemia, and DM are common among patients with CKD. In addition, inflammatory mediators and promoters of calcification cause vascular injury, and may explain why CKD is associated with CVD even after adjustment for conventional risk factors.[148] A decreasing estimated glomerular filtration rate (eGFR) is an important sign of a gradually increasing risk for CVD-related mortality, starting below 75 mL/min/1.73 m^2 and gradually increasing to a ~ 3-fold risk in patients with values of 15 mL/min/1.73 m^2. End-stage renal disease is associated with a very high CV risk. Independent of eGFR, increased albumin excretion is also associated with CV mortality risk; the RR is ~ 2.5 in overt proteinuria.[149] Studies assessing whether the accuracy of CV risk stratification improves with the addition of eGFR levels are emerging [150], but there is no consensus on which measure of renal function (i.e. which formula, and creatinine- or cystatine-C-based) best predicts CVD.[151, 152] Based on the evidence, the Task Force decided to classify patients with severe CKD (GFR <30 mL/min/1.73 m^2) as 'very high risk' and those with moderate CKD (GFR 30–59 mL/min/1.73 m^2) as 'high risk' (see Table 5, chapter 2).

Gaps in evidence

- The contribution of various CKD markers to CVD risk stratification remains unclear.

2.4.5.2 Influenza

Key message

- There is an association between acute respiratory infections, especially those occurring at times of peak influenza virus circulation, and AMI.

Recommendation for influenza vaccination

Recommendation	Class[a]	Level[b]	Ref[c]
Annual influenza vaccination may be considered in patients with established CVD.	IIb	C	153-156

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Influenza can trigger a CV event. Studies show an increase in rates of MI during the annual influenza season. The risk of MI or stroke was more than four times higher after a respiratory tract infection, with the highest risk in the first 3 days.[153] A recent meta-analysis suggests that preventing influenza, particularly by means of vaccination, can prevent influenza triggered AMI,[156] but there is concern that some studies are biased.[153-155, 157]

Gaps in evidence

- Large-scale RCTs are needed to assess the efficacy of influenza vaccination in preventing influenza triggered AMI.

2.4.5.3 Periodontitis

Studies have linked periodontal disease to both atherosclerosis and CVD,[158, 159] and serological studies have linked elevated periodontal bacteria antibody titres to atherosclerotic disease.[160] A longitudinal study has suggested that an improvement in clinical and microbial periodontal status is related to a decreased rate of carotid artery IMT progression during a 3-year follow-up period,[161], but IMT progression does not seem to be associated with CV events.[135] Thus, if active treatment or prevention of periodontitis improved, clinical prognosis is still unclear.

2.4.5.4 Patients treated for cancer

Key messages

- Patients surviving cancer after treatment with chemotherapy or radiotherapy are at increased risk for CVD.
- The increased incidence of CVD is correlated with the (combination of) treatments given and the administered dose.
- The presence of traditional CV risk factors in cancer patients further increases CV risk.

Recommendations for patients treated for cancer

Recommendations	Class[a]	Level[b]	Ref[c]
Cardio-protection in high-risk patients* receiving type I chemotherapy should be considered for LV dysfunction prevention	IIa	B	162, 163
Optimization of the CV risk profile should be considered in cancer treated patients.	IIa	C	

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
* High-risk patients are mainly those individuals receiving high cumulative doses of type I chemotherapy and/or combined treatment with other chemotherapic agents and radiotherapy, and/or with CV uncontrolled risk factors.

Survivors of cancer represent an increasingly large population, most of whom have received chemotherapy and/or radiotherapy. Cardio-toxicity due to chemotherapy is related to a direct effect on the cell (anthracycline-like) through the generation of reactive oxygen species (ROS). It can be mediated by topoisomerase-IIβ in cardiomyocytes through the formation of ternary complexes (TopIIβ- anthracycline-DNA) inducing DNA double-strand breaks and transcriptome changes responsible for defective mitochondrial biogenesis and ROS formation. Some agents (fluorouracil, bevacizumab, sorafenib, and sunitinib can induce a direct ischemic effect not related to the premature developement of atherosclerotic lesions. Moreover, they can increase risk factors such as hypertension and accelerate atherosclerosis, especially in older patients. These effects can be irreversible (type I agents) or partially reversible (type II agents) and can develop many years after treatment exposure. Typically, anthracyclines are the prototype of type I agents and trastuzumab of type II agents.[164]
Cardio-toxicity due to chest radiotherapy can induce micro- and macrovascular injury. It can accelerate atherosclerosis and this may occur many years after the initial exposure.[165-171] Latency and severity of radiotherapy cardiotoxicity is related to multiple factors including the dose (total/per fraction), the volume of the heart irradiated, concomitant administration of other cardiotoxic drugs, and patient factors (younger age, traditional risk factors,[172] history of heart disease).

The first step, in identification of higher risk for cardio-toxicity, consists of a careful baseline assessment of CV risk factors. Primary care, cardiology and oncology should work together to deliver optimal survivorship care that addresses CVD risk factors, as well as prevalent disease. Positive health-promoting behaviour, including lifestyle factors (healthy diet, smoking cessation, regular exercise, weight control) should be strongly advised. In particular, aerobic exercise is considered as a promising non-pharmacological strategy to prevent and/or treat chemotherapy-induced cardio-toxicity.[173]

Signs or symptoms of cardiac dysfunction should be monitored before and periodically during treatment for early detection of even asymptomatic abnormalities in patients receiving potentially cardio-toxic chemotherapy and heart failure (HF) guideline recommendation should be followed if indicated.[174] Thus, pre-treatment evaluation of LV function is required.[175] A targeted approach to treat patients with early LV dysfunction in combination with global longitudinal strain abnormalities and biomarker (notably troponin) elevation has been proposed.[175, 176]

In the case of a decrease in LV function during or after chemotherapy, cardio-toxic agents should be whenever possible avoided or delayed until after discussion with the oncology team. This calls for adequate communication between oncology and cardiology.

To reduce chemotherapy type I cardiotoxicity, a variety of prophylactic treatments (including beta-blockers, ACE-inhibitors, dexrazozane and statins) has been tested and compiled in a recent meta-analysis.[163] It has been stressed that early preventive treatment is mandatory to exert a maximum effect.[177, 178] [175, 176].

Gaps in evidence

- Evidence on the effect of early preventive measures to reduce type I cardio-toxicity is inconclusive.
- The most appropriate strategy to improve risk stratification and prevent CVD in patients treated for cancer needs to be tested prospectively.

2.4.5.5 Autoimmune disease

Key messages

- Rheumatoid arthritis (RA) enhances CV risk independently of traditional risk factors, with an RR of 1.4 to 1.5 in men and women, respectively.
- There is mounting evidence that other immune diseases, such as ankylosing spondylitis or early severe psoriasis, also increase CV risk, with RRs approaching those in RA.
- Post hoc analysis of two statin trials suggests that the relative reduction in CVD incidence in autoimmune diseases is comparable to that seen in the other conditions.

Recommendations for autoimmune disease

Recommendations	Class[a]	Level[b]	Ref[c]
The use of a 1.5 factor risk multiplier for CV risk in rheumatoid arthritis should be considered, particularly if disease activity is high.	IIa	B	179
The use of a 1.5 risk multiplier for CV risk in immune inflammatory diseases other than rheumatoid arthritis may be considered on a patient-by-patient basis, depending on disease activity/severity.	IIb	C	179

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

There is now clear evidence implicating high-grade inflammation as a pathway for accelerated vascular disease.[180] Systemic inflammation appears to enhance CV risk directly and indirectly via accentuation of existing risk pathways.[180] While early small studies suggested RA increases CV risk beyond other risk markers, the recent analysis of the national QRESEARCH database in 2.3 million people provides the best available evidence for this.[47] Such evidence has now been implemented in some national risk scores[58] and European guidelines.[179]
Evidence in psoriasis is less rigorous but a recent paper demonstrates broadly comparable CV risks in RA and in early severe psoriasis.[181] Robust data for independently elevated CV risks in other autoimmune conditions are generally lacking. Hence, clinical judgment should be applied on a case-by-case basis. There is evidence from post hoc analysis of randomized trials to support a statin-associated reduction in CV risk in autoimmune conditions.[182] Finally, in all autoimmune diseases, drug interactions with anti-inflammatory and immunosuppressive drugs with, for example, statins, antiplatelet agents, and anti-hypertensives deserve attention.

Gaps in evidence

- The association between non-RA immune inflammatory disease and CVD is less clear than for RA.
- The relationship between anti-rheumatic drugs and CV risk is unknown.

2.4.5.6 Obstructive sleep apnoea syndrome

Key message

- There is evidence of a positive relationship between obstructive sleep apnoea syndrome (OSAS) and hypertension, CAD, atrial fibrillation (AF), stroke, and HF.

OSAS is characterized by recurrent partial or complete collapse of the upper airway during sleep. It affects an estimated 9% of adult women and 24% of adult men and has been associated with an RR of 1.7 for CV morbidity and mortality.[183] Repetitive bursts of sympathetic activity, surges of BP, and oxidative stress brought on by pain and episodic hypoxaemia associated with increased levels of mediators of inflammation are thought to promote endothelial dysfunction and atherosclerosis.[183] Screening for OSAS can be performed using the Berlin Questionnaire, daytime sleepiness assessed by the Epworth Sleepiness Scale and overnight oxyimetry.[184] Definitive diagnosis often requires polysomnography, usually during a night in a sleep laboratory during which multiple physiological variables are continuously recorded. Treatment options first include behavioural changes, such as avoiding alcohol, caffeine or other stimulants of wakefulness before sleep, increased physical activity, discontinuation of sedating drugs and obesity control. Continuous positive airway pressure is the gold-standard therapy and reduces CV mortality and events.[185]

Gaps in evidence

- More studies are needed to determine whether routine screening reduces (non)fatal CVD.

2.4.5.7 Erectile dysfunction

Key message

- Erectile dysfunction (ED) is associated with future CV events in men without and with established CVD.

Recommendation for erectile dysfunction

Recommendation	Class[a]	Level[b]

Assessment of CV risk factors and CVD signs or symptoms in men with ED should be considered	IIa	C

CVD = cardiovascular disease; ED = erectile dysfunction.
[a]Class of recommendation.
[b]Level of evidence.

ED, defined as the consistent inability to reach and maintain an erection satisfactory for sexual activity, is common, affecting almost 40% of men over 40 years of age (with varying degrees of severity), and increases in frequency with age. ED and CVD share common risk factors including age, hypercholesterolaemia, hypertension, insulin resistance and DM, smoking, obesity, metabolic syndrome, sedentary lifestyle, and depression. CVD and ED also share a common pathophysiological basis of aetiology and progression.[186] Numerous studies have established that ED is associated with asymptomatic CAD.[187, 188] ED precedes CAD, stroke, and PAD by a period that usually ranges from 2–5 years (average 3 years). A meta-analysis showed that patients with ED compared with subjects without ED have a 44% higher risk for total CV events, 62% for AMI, 39% for stroke, and 25% for all-cause mortality.[188] The predictive ability of ED is higher in younger ED patients despite the fact that probability of ED increases with age, and it most likely identifies a group of patients with early and aggressive CVD. Thorough history taking, including CV symptoms, presence of risk factors and comorbid conditions, assessment of ED severity, and physical examination are mandatory first-line elements of investigation. Lifestyle changes are effective in improving sexual function in men: these include physical exercise, improved nutrition, weight control, and smoking cessation. [186]

Gaps in evidence

- The benefit of ED routine screening and the most effective tool to assess it are still unclear.

2.5 Relevant groups

2.5.1 Individuals under 50 years of age

Key messages

- Some people under 50 have high relative or lifetime CV risk and should be offered lifestyle advice as a minimum.
- Some younger people will have high single CV risk factors that, of themselves, warrant intervention, such as cholesterol levels >8 mmol/L or a BP of 180/110 mmHg or higher.
- The most important group of people under 50 to identify are those with a family history of premature CVD who should be tested for familial hypercholesterolemia (FH) and treated accordingly.

Recommendation for individuals < 50 years of age

Recommendation	Class[a]	Level[b]	Ref[c]
It is recommended to screen all individuals under 50 year of age with a family history of premature CVD in a first degree relative (under 55 year of age in males, under 65 year of age in females) for familial hypercholesterolemia using a validated clinical score.	I	B	189-191

[a]Class of recommendation.
[b]Level of evidence.

[c]Reference(s) supporting recommendations.

The most powerful driver of risk in all short-term (5- or 10-year) CV risk algorithms is age. As a consequence, all standard CV risk calculators show people under 50 as low CVD risk regardless of underlying risk factors. However, some younger individuals are at very high relative risk compared to individuals at a similar age and may have high lifetime risk: they are more likely to develop CVD early and may prematurely suffer fatal or non-fatal CV events. So trying to identify who may be at such risk is an important challenge.

2.5.1.1 Assessing cardiovascular disease risk in people under 50

Information on CV risk factors should be routinely collected in all adults under 50 years of age with a first degree family history of premature (i.e. under 55 for male and 65 for female relatives) CVD. There are no data on the right age to begin collecting such information in the general population, but some guidelines advocate starting from age 40.[192] Repeating such assessments occasionally, such as every 5 years, is recommended, but there are no data to guide this interval.

People under 50 should be assessed using the standard algorithm in terms of treatment decisions. However, in the absence of a very high individual risk factor level or diagnosis of FH, their 10 year risk will never be high enough to warrant BP or lipid lowering therapy. Physicians may want to further differentiate CV risk in younger people by using a relative risk chart (see Figure 3, section 2.3.1); this might be useful in assisting people under 50 to judge their risk in relation to someone of the same age with low levels of risk factors.

Alternatively, physicians should consider using a risk age calculator (Figure 4, section 2.3.2) or a lifetime risk calculator, such as the JBS3 web-based tool (see Figure C in web addenda),[58] which might act as an educational tool in terms of how changing risk factors might change the lifetime risk score as well as illustrate long-term CVD risk.

People under 50 with a positive family history of premature CVD should be screened for FH (see section 2.4.1) by clinical criteria (or occasionally genetic testing), such as those defined by the Dutch Lipid Clinic Network criteria.[189] Alternatives are the Simon Broome Registry criteria [190] or the US MedPed Program.[191]

2.5.1.2 Management of cardiovascular disease risk in people under 50

All people under 50 with elevated CVD risk factors should be counselled on lifestyle (with emphasis on avoiding smoking, overweight and sedentary behaviour) and the relationship between risk factors and subsequent disease. There are no data on what are the most effective methods of changing health behaviours in younger people. However, smoking cessation, healthy weight maintenance, and regular aerobic activity are all important behaviours to provide advice and support with.

Younger people with very high BP levels warranting treatment should be managed the same as hypertension in older people. In younger people who are judged eligible for a statin, on the grounds of either FH or very high lipid levels, the management offered is the same as for older people. Very importantly, for all patients deemed to suffer with FH, the physician making the management decisions should arrange for FH screening for family members (see section 3a.7.9).

Gaps in knowledge

- Age to commence formal CV risk estimation.
- Whether and how to screen populations for FH.

2.5.2 Elderly

Age is the dominant driver of cardiovascular risk, and most indivuduals are already at (very) high risk at the age of 65 years (see section 2.3.1). Especially in the oldest old, cardiovascular prevention is controversial. Opponents argue that risk should not be treated when it is essentially age-driven. Proponents, on the other hand, point out that many preventive treatments are still effective at high age in terms of postponing morbidity and mortality.

The Task Force has taken the position that epidemiological evidence of absolute risk reduction in clinical trials is the main driver for recommendations in this guideline. Still, we encourage a discussion with patients regarding quality of life and life potentially gained, as well as regarding the ethical dilemmas of treating risk inherent to ageing, the total burden of drug treatment, and the inevitable uncertainties of benefit.

In this guideline, sections on treatment of the main risk factors contain recommendations or considerations specific to elderly when evidence is available.

Hypertension: Most of the elderly-specific evidence is available for BP (section 3a.9). In general, more lenient treatment targets are advocated in elderly. The hypertension literature also contains increasing evidence that biological rather than calender age is important [193].

DM: evidence supporting more lenient glycemic control targets in elderly is also available in DM (section 3a.8). The role of biological age/frailty is less well established than for BP, but nonetheless a Class IIa recommendation is given to relax glycemic targets in elderly or frail patients.

Hyperlipidemia: Few areas in CVD prevention are more controversial than the mass use of statins in elderly. As the lipid chapter points out, there is no evidence of decreasing effectiveness of statins in patients over 75 years (section 3a.7). On the other hand, cost-effectiveness of statins in these patients is offset by even small geriatric-specific adverse effects.[194] Also, evidence supporting effectiveness in the oldest old (i.e. older than 80 years is very limited. A recent trial suggested no harm of stopping statins in elderly with a limited life expectancy.[195] Taken together, the recommendations of cholesterol lowering treatment in elderly should be followed with caution and common sense, adverse effects should be monitored closely, and treatment should be reconsidered periodically.

2.5.3 Female-specific conditions

Key messages

- Several obstetric complications, in particular pre-eclampsia and pregnancy-related hypertension, are associated with higher risk of CVD later in life. This higher risk is explained, at least partly, by hypertension and DM.
- Polycystic ovary syndrome (PCOS) confers a significant risk for future development of DM.

Recommendations for female-specific conditions

Recommendations	Class[a]	Level[b]	Ref[c]
In women with a history of pre-eclampsia and/or pregnancy-induced hypertension, periodic screening for hypertension and DM should be considered.	IIa	B	196-199
In women with a history of polycystic ovary syndrome or gestational DM, periodic screening for DM should be considered.	IIa	B	200, 201 202, 203
In women with a history of giving premature birth, periodic screening for hypertension and DM may be considered.	IIb	B	204, 205

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Specific conditions that may occur in females only and may have an impact on CVD risk can be separated into obstetric and non-obstetric conditions.

2.5.2.1 Obstetric conditions

Pre-eclampsia (defined as pregnancy-related hypertension accompanied by proteinuria) occurs in 1–2% of all pregnancies. Studies suggest that pre-eclampsia is associated with an increase in CV risk by a factor 1.5 to 2.5,[196, 197] while the RR of developing hypertension is around 3,[198] and DM approximately 2.[196, 199] Because most studies did not adjust the elevated risk of future CVD for the development of conventional risk factors, it cannot be established whether the increased CV risk after pre-eclampsia occurs independent of CV risk factors. The rationale for screening these women for occurrence of hypertension and DM is, however, quite strong.

Pregnancy-related hypertension affects 10–15% of all pregnancies. The associated risk of later CVD is lower than for pre-eclampsia, but is still elevated (RR 1.9 to 2.5).[204] Also the risk for sustained or future hypertension is elevated (RR vary widely, from 2.0 to 7.2 or even higher).[198, 206]. Again, however, there was incomplete adjustment for conventional risk factors. The risk of developing DM is probably elevated also in these women, but exact estimates are not available.

There are no data to suggest that recurrent pregnancy loss is associated with an increased CV risk. A history of premature birth is possibly associated with increased risk of CVD in offspring (RR 1.5 to 2.0),[204, 205] which may partially be explained by an increased incidence of hypertension and DM.

Finally, **gestational diabetes** confers a sharply elevated risk of future DM, with up to 50% developing DM within 5 years after pregnancy.[202] Previously, oral glucose tolerance testing was advocated to screen for DM in such patients, but screening by fasting glucose or glycated hemoglobin may be preferable.[203]

2.5.2.2 Non-obstetric conditions

PCOS affects approximately 5% of all women in their fertile years. PCOS has been associated with an increased risk for future development of CVD, but larger studies produced conflicting results.[200, 207] The risk of developing hypertension is probably somewhat increased, but again the data are conflicting.[207] PCOS does seem to be associated with a higher risk of developing DM (RR 2 to 4),[200, 201] suggesting that periodic screening for DM is appropriate.

Premature menopause, better defined as primary ovarian insufficiency, occurs in roughly 1% in women aged ≤ 40 years. It has been reported to be associated with an increased risk of CVD (RR approximately 1.5),[208] but studies are sparse. There are insufficient data to draw conclusions on a possible increased risk of hypertension or DM.

Gaps in evidence

- The degree to which increased CVD risk associated with several of the female-specific conditions occurs independent of conventional CVD risk factors is unknown.
- Information on whether female-specific conditions improve risk classification in women is unknown.

2.5.4 Ethnic minorities

Key messages

- CVD risk varies considerably between immigrant groups. South Asians and sub-Saharian Africans have a higher risk while Chinese and South Americans have a lower risk.
- South Asians are characterized by a high prevalence and an inadequate management of DM.

- Current risk estimation equations do not provide adequate estimations of CVD risk in ethnic minorities.

Recommendation for ethnic minorities

Recommendation	Class[a]	Level[b]	Ref[c]
Ethnicity should be considered in CVD risk assessment.	IIa	A	209, 210

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Europe welcomes a large number of non-EU immigrants per year, mainly from India, China, North Africa and Pakistan. One out of 25 Europeans comes from outside Europe, but data regarding CVD risk or CVD risk factors among immigrants are scarce and of differing quality.[211]

First generation migrants usually display lower CVD mortality rates than natives of the host country,[212] but with time, migrants tend to approach the CVD risk in their host country.[212, 213] Relative to natives of the host country, CVD mortality risk, as well as the prevalence and management of CVD risk factors among migrants, varies according to country of origin and host country.[213-215] Given the considerable variety in CVD risk factors between immigrant groups, no single CVD risk score performs adequately in all groups and the use of ethnic-specific scores might be necessary.[209]

Immigrants from South Asia (notably India and Pakistan) present high CVD rates[216-218] and have a much higher prevalence of DM,[219, 220] while the prevalence of other CV risk factors is slightly lower than or comparable to natives of the host country.[219, 221] Interestingly, the increased prevalence of DM raises the CVD risk in South Asians in some studies[216] but not in others. Management of DM is also significantly worse, while management of high BP and hypercholesterolaemia is better among South Asians than host country natives.[222] The higher CVD risk among South Asians makes screening more cost-effective than in other immigrant groups, but risk prediction using SCORE might not be optimal.[223]

Immigrants from China and Vietnam present lower CVD risk than natives of the host country,[216], although this finding has been challenged.[217] This lower risk seems attributable to lower levels of CV risk factors[219] and higher HDL-C levels.[224]

Immigrants from Turkey have higher estimated CVD risk and higher CVD mortality rates[214] than host country natives. This seems mainly due to the higher prevalence of smoking, DM, dyslipidaemia, hypertension and obesity rates.[224-226] Management of CVD risk factors also varies according to host country: there are no differences in hypertension control compared to natives in the Netherlands,[226] but worse control in Denmark.[227]

Immigrants from Morocco present lower CVD rates than natives from the host country.[214] Possible explanations include lower BP and cholesterol levels and smoking rates,[225, 226] although a higher prevalence of DM and obesity has also been found.[226] No differences between Moroccan immigrants and Dutch natives were found regarding hypertension control.[225]

Immigrants from sub-Saharan Africa and the Caribbean present higher CVD rates than natives from the host country in some studies,[215, 216, 228] but not all.[216] African immigrants have higher DM rates[220] but smoke less[221] than natives from the host country. Management of CVD risk factors was worse than among natives in one study,[222] but not in another.[229]

Immigrants from South America have lower CVD mortality rates than natives in Spain,[230] while no difference was found in Denmark.[231] South American immigrants in Spain have a lower prevalence of CV risk factors and CVD rates than natives in Spain, but these differences decrease with increasing length of stay.[232]

Based on available mortality and prospective data,[210] the following correction factors could be applied when assessing CVD risk using SCORE *among first generation immigrants **only***.

- Southern Asia: multiply the risk by 1.4
- Sub-Saharan Africa and the Caribbean: multiply the risk by 1.3
- Western Asia: multiply the risk by 1.2
- Northern Africa: multiply the risk by 0.9
- Eastern Asia or South America: multiply the risk by 0.7

These values reflect the best estimations from available data and should be interpreted with caution, but can be used to guide CV risk management.

Gaps in evidence

- Studies focusing on CVD risk and prevalence of CVD risk factors among minorities in Europe are needed.
- Validation of the SCORE risk estimation among ethnic minorities is needed.
- Ethnicity-specific thresholds to define high risk (based on SCORE evaluation) should be identified. Alternatively, ethnicity-specific CVD risk equations should be obtained.

3a. How to intervene at the individual level: risk factor intervention

3a.1 Behaviour change

Key message

- Cognitive-behavioural methods are effective in supporting persons in adopting a healthy lifestyle.

Recommendations for facilitating changes in behaviour

Recommendations	Class[a]	Level[b]	Ref[c]
Established cognitive-behavioural strategies (eg. motivational interviewing) to facilitate lifestyle change are recommended.	I	A	233
Involvement of multidisciplinary healthcare professionals (e.g. nurses, dieticians, psychologists) to promote healthy behaviours is recommended.	I	A	234, 235
In individuals at very high CVD risk, multimodal interventions integrating education on healthy lifestyle and medical resources, physical activity, stress management and counselling on psychosocial risk factors, are recommended to promote healthy behaviour.	I	A	235, 236

CVD = cardiovascular disease.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

"Lifestyle" is usually based on longstanding behavioural patterns that are maintained by social environment. Individual and environmental factors impede the ability to adopt a healthy lifestyle, as does complex or confusing advice from caregivers. Friendly and positive interaction enhances an individual's ability to cope with illness and adhere to recommended lifestyle changes ("empowerment"). It is important to explore each patient's experiences, thoughts and worries, previous knowledge, and circumstances of everyday life. Individualized counselling is the basis for motivation and commitment. Decision-making should be shared between caregiver and patient (including also the individual's spouse and family).[234, 237] Use of the principles of effective communication [238] listed in Table 8 will facilitate treatment and prevention of CVD.

Table 8 Principles of effective communication to facilitate behavioural change

• Spend enough time with the individual to create a therapeutic relationship – even a few more minutes can make a difference.
• Acknowledge the individual's personal view of his/her disease and contributing factors.
• Encourage expression of worries and anxieties, concerns and self-evaluation of motivation for behaviour change and chances of success.
• Speak to the individual in his/her own language and be supportive of every improvement in lifestyle.
• Ask questions to check that the individual has understood the advice and has any support he or she requires to follow it.
• Acknowledge that changing life-long habits can be difficult and that sustained gradual

change is often more permanent than a rapid change.
• Accept that individuals may need support for a long time and that repeated efforts to encourage and maintain lifestyle change may be necessary in many individuals.
• Make sure that all health professionals involved provide consistent information.

In addition, caregivers can build on cognitive-behavioural strategies to assess the individual's thoughts, attitudes, and beliefs concerning the perceived ability to change behaviour, as well as the environmental context. Behavioural interventions such as "motivational interviewing" increase motivation and self-efficacy.[233]
Previous unsuccessful attempts often affect self-efficacy for future change. A crucial step is to help set realistic goals combined with self monitoring of the chosen behaviour.[234] Moving forward in small, consecutive steps is key to changing long-term behaviour.[234]
Communication training is important for health professionals. The following **"Ten strategic steps"** enhance counselling on behavioural change effectively (Table 9)[239].

Table 9: Ten strategic steps to facilitate behaviour change

1. Develop a therapeutic alliance.
2. Counsel all individuals at risk of or with manifest CVD
3. Assist individuals to understand the relationship between their behaviour and health
4. Help individuals assess the barriers to behaviour change
5. Gain commitments from individuals to own their behaviour change
6. Involve individuals in identifying and selecting the risk factors to change
7. Use a combination of strategies including reinforcement of the individual's capacity for change
8. Design a lifestyle-modification plan
9. Involve other healthcare staff whenever possible
10. Monitor progress through follow-up contact

Combining the knowledge and skills of caregivers (such as physicians, nurses, psychologists, experts in nutrition, cardiac rehabilitation, and sports medicine) into multimodal, behavioural interventions can optimize preventive efforts.[234-236] Multimodal behavioural interventions are especially recommended for individuals at very high risk.[234-236] These interventions include promoting a healthy lifestyle through behaviour change including nutrition, PA, relaxation training, weight management, and smoking cessation programmes for resistant smokers.[235, 236] They enhance coping with illness, and improve adherence and CV outcome.[240] [241] Psychosocial risk factors (stress, social isolation, and negative emotions) that may act as barriers against behaviour change should be addressed in tailored individual or group counselling sessions.[235, 236]
There is evidence that more extensive/longer interventions lead to better long-term results with respect to behaviour change and prognosis.[234] Individuals of low socio-economic status, older age, or female sex may need tailored programmes in order to meet their specific needs regarding information and emotional support. [234, 242, 243]

Gaps in evidence

- There is limited evidence to determine which interventions are the most effective in specific groups (e.g. young–old, male–female, high vs. low socio-economic status).

3a.2 Psychosocial factors

Key messages

- Treatment of psychosocial risk factors can counteract psychosocial stress, depression and anxiety, thus facilitating behaviour change, quality of life, and prognosis.
- The caregiver–patient interaction should follow the principles of patient-centred communication. Age- and sex-specific psychosocial aspects should be considered.

Recommendations for psychosocial factors

Recommendations	Class[a]	Level[b]	Ref[c]
Multimodal behavioural interventions, integrating health education, physical exercise and psychological therapy, for psychosocial risk factors and coping with illness are recommended in patients with established CVD and psychosocial symptoms in order to improve psychosocial health.	I	A	244
Referral for psychotherapy, medication or collaborative care should be considered in the case of clinically significant symptoms of depression, anxiety or hostility.	IIa	A	245, 246
Treatment of psychosocial risk factors with the aim of preventing CAD should be considered when the risk factor itself is a diagnosable disorder (e.g. depression) or when the factor worsens classical risk factors.	IIa	B	247, 248

CAD = coronary artery disease; CVD = cardiovascular disease.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Caregivers in clinical practice are in a unique position to directly support their patients regarding psychosocial risk factors in individuals with high CV risk or with established disease. Empathic, patient-centred communication helps to establish and maintain a trustful relationship and is a powerful source of emotional support and professional guidance in coping with psychosocial stressors, depression, anxiety, CV risk factors, and CVD.[249, 250] The principles of a supportive caregiver–patient interaction are[249, 250]:

- Spend enough time with the patient, listen carefully, repeat essential keywords;
- Consider age- and sex-specific psychosocial aspects;
- Encourage expression of emotions, do not trivialize psychosocial burdens and worries;
- Explain essential medical facts in his/her own language, convey hope, relief from feelings of guilt, and reinforce adaptive thoughts and actions;
- In the case of severe mental symptoms, obtain treatment preferences and perform shared-decision making regarding further diagnostic and therapeutic steps;
- Summarize important aspects of the consultation in order to signal that the patient has been understood;
- Offer regular follow-up contacts.

Specialised psychological interventions have additional beneficial effects on distress, depressiveness and anxiousness, even when added to standard rehabilitation.[244] These interventions include individual or group counselling on psychosocial risk factors and coping with illness, stress management programmes, meditation, autogenic training, biofeedback, breathing, yoga, and/or muscular relaxation.

Large and consistent effects on depression have been shown in “collaborative care”, which may involve a systematic assessment of depression, a (non-physician) care manager to perform longitudinal symptom monitoring, treatment interventions and care coordination, and specialist-provided stepped care recommendations and treatment.[246] Collaborative care for depression resulted in a 48% lower risk for developing first CAD events 8 years after

treatment compared to usual care (RR 0.52, 95% CI 0.31–0.86).[247] Internet-delivered cognitive behavioural therapy in depressed patients with high CVD risk produced small, but robust, improvement of depressive symptoms, adherence and some health behaviours.[248].

In patients with established CAD, mental health treatments for depression (psychotherapy and/or medication) have moderate efficacy for reducing cardiac events (NNT 34), but do not reduce total mortality.[245] Especially collaborative care is effective on depressive symptoms and partially also on cardiac prognosis.[251, 252] Furthermore, there is evidence that physical activity can effectively improve depression in patients with CAD.[253]

In addition to the treatment of mood symptoms, there are several other approaches to psychosocial intervention that have proved useful. Two RCTs[254, 255] have shown the favourable impact of stress management and social support groups on the prognosis of clinical CAD. Nurse-led interventions reveal beneficial effects on anxiety, depression and general well-being in CAD patients.[256, 257]

In hostile CAD patients, a group-based hostility-control intervention may lead not only to decreases in behaviourally assessed hostility levels, but also to decreased levels of depression, resting heart rate (HR), and CV reactivity to mental stress, as well as to increased social support and satisfaction with life.[258] Work reorganizations aimed at improving autonomy and increasing control at work may result in improved social support and reduction in physiological stress responses. Hence, reduction of work stress in managers and supervisors may have beneficial health effects on the target individuals and may also improve perceived social support in their subordinates.[259]

Gaps in evidence

- Evidence that treatment of clinically significant depression and anxiety alone will prevent CVD and improve outcomes is inconclusive.

3a.3 Sedentary behaviour and physical activity

Key messages

- Regular PA is a mainstay of CV prevention; participation decreases all-cause and CV mortality.
- PA increases fitness and improves mental health.
- Sedentary subjects should be encouraged to start light-intensity aerobic PA.

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended for healthy adults of all ages to perform at least 150 minutes a week of moderate intensity or 75 minutes a week of vigorous intensity aerobic PA or an equivalent combination thereof.	I	A	260-263
For additional benefits in healthy adults, a gradual increase in aerobic PA to 300 minutes a week of moderate intensity, or 150 minutes a week of vigorous intensity aerobic PA, or an equivalent combination thereof is recommended.	I	A	261, 262
Regular assessment and counselling on PA is recommended to promote the engagement and, if necessary, to support anincrease in PA volume over time.[d]	I	B	264-266
PA is recommended in low risk individuals without further assessment.	I	C	267, 268
Multiple sessions of PA should be considered, each lasting ≥ 10 minutes and evenly spread throughout the week, i.e. on 4–5 days a week and preferably every day of the week.	IIa	B	269, 270
Clinical evaluation, including exercise testing, should be considered for sedentary people with CV risk factors who intend to engage in vigorous PAs or sports.	IIa	C	267

CV = cardiovascular; PA = physical activity.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]Volume is the total weekly dose of PA

3a.3.1 Introduction

Regular PA is related to a reduced risk of many adverse health outcomes over a wide age range: all cause and CVD mortality in healthy individuals, [260, 269, 271] in subjects with coronary risk factors[271] and in cardiac patients[272]. PA has a positive effect on many risk factors, including hypertension, low-density lipoprotein cholesterol (LDL-C) and non-HDL-C, body weight and type 2 DM.[269] In healthy subjects, PA and cardiorespiratory fitness are associated with a significant reduction (20–30%) in risk of all-cause and CV mortality, in a dose–response fashion.[261, 262] This applies for both men and women and across a broad range of ages from childhood to the very elderly. A sedentary lifestyle is one of the major risk factors for CVD independently of participation in PA.[273]

3a.3.2 Physical activity prescription

Health providers should assess the PA level in any subject (how many days and minutes per day are spent on average doing PA at moderate or vigorous intensity. They should warn against inactivity, and help add PA to daily life. Subjects should be advised on appropriate types of activities, ways of progressing, and should be helped to set personal goals to achieve and maintain the benefits. To this end, individuals should be encouraged to find some activity they either enjoy and/or that they could include in their daily routines, as such activities are more likely to be sustainable. For a more effective behaviour change, clinicians should explore practical ways to overcome barriers to exercise. For this reason the link between primary care and local community-based structures for activity, recreation and sport is crucial.[264] The amount of time spent being sedentary should be minimized by active travelling

(cycling or walking), taking breaks from extended periods of sitting, and reducing screen time.[274] Brief exercise advices are more cost-effective than supervised gym–based exercise classes or instructor-led walking program [266].

3a.3.2.1 Aerobic physical activity

Aerobic PA, the most studied and recommended modality, with a beneficial dose–response effect on prognosis,[261, 262, 270] consists of movements of large muscle mass, involved in a rhythmic manner for a sustained period. It includes every day activity, such as active travel (cycling or walking), heavy household work, gardening, occupational activity, and leisure time activity or exercise such as brisk walking, nordic-walking, hiking, jogging or running, cycling, cross-country skiing, aerobic dancing, skating, rowing or swimming.

Similar to all other interventions, its prescription can be adjusted in terms of frequency, duration and intensity. However, practising PA below the lowest recommended levels should be encouraged in individuals unable to meet the minimum or in those sedentary individuals who have just started and recommended to gradually increase the level.

Intensity: moderate or vigorous aerobic exercise should be recommended. It can be expressed either in absolute or relative terms.

Absolute intensity is the amount of energy expended per minute of activity, assessed by oxygen uptake per unit of time ($mL.min^{-1}$or $L.min^{-1}$) or by metabolic equivalent (MET, which is estimated as the rate of energy expenditure while sitting at rest, by convention this corresponds to 3.5 mL O2 kg-1 min-1). [275] A list of PA intensities in MET values is available.[276] An absolute measure does not take into account individual factors such as body weight, sex, and fitness level: older persons exercising at a vigorous intensity of 6 METs, may be exercising at their maximal intensity, while a younger person working at the same absolute intensity will be exercising moderately.

Relative intensity is the level of effort required to perform an activity. Less fit individuals generally require a higher level of effort than fitter people to perform the same activity. It is determined relative to an individual's level of cardiorespiratory fitness (VO_2max) or as a percentage of a person's measured or estimated maximum heart rate (HR), which is 220 – age, (%HRmax). It also can be expressed as an index of individual rate of effort (how hard the person feels he/she is exercising), i.e. the rating of perceived exertion (RPE) or by frequency of breathing (the so-called "Talk Test"). For individuals on medication it is important to consider possible modification of HR response and to refer to other relative intensity parameters. Especially for older and deconditioned individuals, a relative measure of intensity is more appropriate. Classification for both absolute and relative intensity and examples are presented in Table 10.

Table 10 Classification of physical activity intensity and examples of absolute and relative intensity levels

Absolute intensity			**Relative intensity**		
Intensity	**MET**	**Examples**	**%HRmax**	**RPE (Borg scale score)**	**Talk Test**
Light	1.1–2.9	Walking < 4.7 km/h, light household work	50–63	10–11	
Moderate	3–5.9	Walking briskly (4.8–6.5 km/h), slow cycling (15 km/h), painting/decorating, vacuuming, gardening (mowing lawn), golf (pulling clubs in trolley), tennis (doubles), ballroom dancing,	64–76	12–13	Breathing is faster but compatible with speaking full sentences

		water aerobics			
Vigorous	≥ 6	Race-walking, jogging or running, bicycling > 15 km/h, heavy gardening (continuous digging or hoeing), swimming laps, tennis (single)	77–93	14–16	Breathing very hard, incompatible with carrying on a conversation comfortably

MET (metabolic equivalent) is estimated as the energy cost of a given activity divided by resting energy expenditure: 1 MET = 3.5 mL O2 kg-1 min-1oxygen consumption (VO_2).
RPE, rating of perceived exertion (20 value Borg score).
%HRmax, percentage of measured or estimated maximum heart rate (220 – age).
Modified from Howley.[277]

Frequency: At least 3–5 sessions per week, but preferably every day.
Duration. It is recommended to accumulate at least 30 minutes per day, 5 days/week of moderate intensity (i.e. 150 min/week), or 15 minutes per day, 5 days/week of vigorous intensity (75 min/week), or a combination of both, performed in sessions of at least 10 minutes' duration. Shorter exercise bouts (i.e. < 10 minutes) may also be appropriate especially in very deconditioned individuals.[269, 278, 279] For lipid control or body weight management, longer durations of exercise, 40 and 60–90 minutes per day respectively, have been proposed.[280]
Aerobic interval training and high intensity interval training cannot yet be broadly recommended, until further data on safety and efficacy are available.[268]

3a.3.2.2 Muscle strength/resistance physical activity

Isotonic PA stimulates bone formation and reduces bone loss, preserves and enhances muscle mass, strength, power and functional ability, with some evidence of benefit in lipid and BP control, insulin sensitivity, especially in combination with aerobic exercise.[269, 281] It should target the major muscle groups (agonist and antagonist) and include multi-joint or compound movements through the full range of motion of the joints, such as working with resistance-bands, calisthenic exercise using body weight for resistance, carrying heavy loads, and heavy gardening. For each exercise session, the suggested prescription is 2–3 sets of 8–12 repetitions at the intensity of 60–80% of the individual's one repetition maximum (1-RM; the maximum load that can be lifted one time) at the frequency of least 2 days a week. For older adults or very deconditioned individuals it is suggested to start with 1 set of 10-15 repetitions at 60-70% of 1RM.[282]

3a.3.2.3 Neuromotor physical activity

For older adults at risk of falls, neuromotor exercise helps to maintain and improve balance, and motor skills (balance, agility, coordination and gait). This includes multifaceted activities such as tai chi and yoga, and recreational activities using paddles or sport balls to challenge hand eye coordination. The optimal volume is not known.[278]

3a.3.2.4 Phases and progression of physical activity

PA sessions should include the following phases: warm-up, conditioning phase (aerobic, muscle strength/resistance, and neuromotor exercise), cool-down, and stretching/flexibility. Progressive warm-up before and cool-down after exercise may prevent injuries and adverse cardiac events. Inactive adult should start gradually, at light or moderate intensity for short periods of time (even less than 10 minute), with sessions spread throughout the week. With the improvement in exercise tolerance, each subject progresses in the level of PA, but the increases in any components (i.e frequency, duration and intensity) should be gradual, to minimize risks of muscle soreness, injury, fatigue and the long-term risk of overtraining.[278]
Following any adjustments, the individual should check for adverse effects (e.g. excessive

shortness of breath) and if there are any such effects, downward adjustments should be made.[278]

3a.3.3 Risk assessment

The risk of an adverse CV response during PA is extremely low for apparently healthy adults (5 to 17 sudden deaths per million population per year).[283] The risk of participation is outweighed by substantial health benefits conferred by PA.[269] Risk during light or moderate intensity exercise is lower than during vigorous activity[269]: thus in healthy individuals who wish to undertake moderate PA, such as a walking programme, a preliminary medical evaluation is not needed.[268]

Before starting more intensive leisure-time activities (i.e. structured or competitive activity, amateur sport, exercise and fitness training), risk assessment should be tailored to the individual's clinical (i.e. metabolic, musculoskeletal condition/disease) and cardiac risk profile, the current level of habitual PA, and the intended level of PA.[267] Individuals who exercise only occasionally seem to have an increased risk of acute coronary events and sudden cardiac death during or after exercise.[284] Sedentary subjects and those with CV risk factors should start aerobic PA at low-intensity activity and progress gradually. Clinical evaluation, including exercise testing, may be considered for sedentary people with CV risk factors who intend to engage in vigorous PA and sports. The information gathered from exercise tests may be useful in establishing a safe and effective exercise prescription. Validated self-assessment questionnaires have been proposed for sedentary individuals entering low-intensity leisure-time sport activity or starting moderate intensity activities[267] (see Table B in web addenda).

Gaps in evidence

- The lower and upper limit of aerobic PA intensity, duration and frequency to exert a beneficial effect is unknown.
- The effectiveness of PA monitoring, versus simple counselling, to optimize the motivation of patients to adhere to active lifestyle, versus simple counselling is not known
- The role and sustainability of modern technology (such as comprises wearable technology, "exergaming" and smartphone's apps) motivating people to undertake more PA has not been established

3a.4 Smoking intervention

Key messages

- Stopping smoking is the most cost-effective strategy for CVD prevention.
- There is a strong evidence base for:
    - brief interventions with advice to stop smoking,
    - all types of nicotine replacement therapy (NRT),
    - bupropion,
    - varenicline,
    - more effectiveness of drugs in combination, except for except for NRT plus varenicline
    - most effective are brief interventions plus assistance with stopping using drug therapy and follow-up support.
- Electronic cigarettes (e-cigarettes) may help in smoking cessation but should be covered by the same marketing restriction as cigarettes
- Passive secondary smoking carries significant risk, with the need to protect non-smokers.

Recommendations for smoking intervention strategies

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended to identify smokers and provide repeated advice on stopping with offers to help, by the use of follow up support, nicotine replacement therapies, varenicline, and bupropion individually or in combination.	I	A	285-288
It is recommended to stop all smoking of tobacco or herbal products, as this is strongly and independently causal of CVD.	I	B	289-293
It is recommended to avoid passive smoking	I	B	294, 295

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

3a.4.1 Introduction

Smoking is a lethal addictive disorder. A lifetime smoker has a 50% probability of dying due to smoking, and on average will lose 10 years of life,[289] contrasting with under 3 years in severe hypertension and < 1 year with mild hypertension.[290] Smoking is an established cause of a plethora of diseases and is responsible for 50% of all avoidable deaths in smokers, half of these due to CVD. Ten-year fatal CVD risk is approximately doubled in smokers. The relative risk in smokers < 50 years is even five-fold higher than in non-smokers.[291]

Slightly less than half of lifetime smokers will carry on smoking until death. Around 70% of UK smokers want to stop smoking at some time in the future,[292] with around 43% trying to stop in the past year, but only 2–3% of the population succeed in stopping.[293] Even modest and low levels of smoking confer vascular risk[296]

Although the rate of smoking is declining in Europe, it remains very common and is increasing in women, adolescents, and the socially disadvantaged.[297] Widening education-related inequalities in smoking-cessation rates have been observed in many European countries. In the EUROASPIRE IV survey among CAD patients, 16% smoked after a mean follow-up time of 16 months, and nearly half of the participants who smoked at the time of their coronary event were persistent smokers. The survey also found that evidence-based treatment for smoking cessation was underused.[6]

3a.4.2 Dosage and type

The risks associated with smoking show a dose–response relationship with no lower limit for deleterious effects.[298] Duration also plays a role, and while cigarette smoking is the most common, all types of smoked tobacco, including low-tar (“mild” or “light”) cigarettes, filter cigarettes, cigars and pipes, are harmful.[294] Smoking is deleterious regardless of how it is done, including by waterpipe. Tobacco smoke is more harmful when inhaled but smokers who claim not to inhale the smoke (e.g. pipe smokers) are also at increased risk of CVD. Smokeless tobacco is also associated with a small but statistically significant increased risk of MI and stroke.

3a.4.3 Passive smoking

Passive smoking increases the risk of CAD.[295, 299] A smoking spouse or workplace exposure increases CVD risk by an estimated 30% Major health benefits result from reduced environmental tobacco smoke, with public smoking bans in various different geographical locations leading to significant decreases in MI rates (see section 3c.4).

3a.4.4 Mechanisms by which tobacco smoking increases risk

Smoking enhances the development of both atherosclerosis and superimposed thrombotic phenomena. Smoking affects endothelial function, oxidative processes, platelet function, fibrinolysis, inflammation, lipid oxidation, and vasomotor function. In experimental studies, several of these effects are fully or partly reversible within a very short time. Plaque formation is not thought to be fully reversible and thus smokers would never be expected to reach the risk level of never-smokers concerning CVD. Nicotine replacement shows no adverse effect on outcomes in patients with cardiac disease,[300, 301]

3a.4.5 Smoking cessation

The benefits of smoking cessation have a major evidence base. Some advantages are almost immediate; others take more time. CVD risk in former smokers is in between that of current and never-smokers.

Stopping smoking after a MI is potentially the most effective of all preventive measures: a systematic review and meta-analysis showed reductions in MIs and in the composite endpoints of death/MI (RRs 0.57 and 0.74, respectively) compared with continued smoking.[302] The benefit is consistent over gender, duration of follow-up, study site, and time period. Significant morbidity reductions occur within the first 6 months.[303] Randomized trials also support smoking cessation, with risk of CVD approaching (but never equalling) the risk of never-smokers within 10–15 years.

Smoking reduction has not been shown to increase probability of future smoking cessation, but some advocate nicotine-assisted smoking reduction in smokers unable or unwilling to quit. Quitting must be encouraged in all smokers (Table 11). There is no age limit to the benefits of smoking cessation. Passive smoking should also be avoided.

Table 11 The "Five As" for a smoking cessation strategy for routine practice

A-ASK:	Systematically inquire about smoking status at every opportunity.
A-ADVISE:	Unequivocally urge all smokers to quit.
A-ASSESS:	Determine the person's degree of addiction and readiness to quit.
A-ASSIST:	Agree on a smoking-cessation strategy, including setting a quit date, behavioural counselling and pharmacological support.
A-ARRANGE:	Arrange a schedule of follow-up.

Professional support can increase the odds of stopping (RR 1.66, 95% CI 1.42–1.94).[304] An impetus for smoking cessation occurs at the time of diagnosing or (invasive) treatment of CVD. Prompting a person to try to quit, brief reiteration of CV and other health hazards, and agreeing on a specific plan with a follow-up arrangement are evidence-based interventions (see Figure D in web addenda).

Smoking cessation programmes initiated during hospital admission should continue for a prolonged period after discharge. A smoking history including daily tobacco consumption and degree of addiction (most commonly assessed by the Fagerström test[304]) may guide the degree of support and pharmacological aid. Smokers should be advised about expected weight gain of on average 5 kg and that the health benefits of tobacco cessation far outweigh the risks from weight gain.

3a.4.6 Evidence-based drug interventions

Following the failure of advice, encouragement and motivational interventions, and in addition to them, NRT, varenicline or bupropion should be offered to assist cessation.[288] All forms of NRT (chewing gum, transdermal nicotine patches, nasal spray, inhaler, sublingual tablets) are effective: in a systematic review, the RR for abstinence with NRT versus control was 1.60: NRTs increase the rate of quitting by 50 to 70%, regardless of setting.[305]

The antidepressant bupropion aids long-term smoking cessation with a similar efficacy to NRT.[306] A meta-analysis of 44 trials comparing long-term cessation rates using bupropion versus control yielded a relative success rate of 1.62 [285] Bupropion carries a known risk of seizures (reported as about 1 per 1000 users), [306] without increased risks of neuropsychiatric or heart and circulatory problems. Overall, NRT and bupropion help about 80% more people to quit than placebo; this means that for every 10 people who quit with placebo about 18 could be expected to quit with NRT or with bupropion.[288]

The partial nicotine receptor agonist varenicline at standard dose increases the chances of quitting more than two-fold compared with placebo (14 trials, 6166 people).[285] The number of people stopping smoking with varenicline is higher than with bupropion (three trials, 1622 people). Varenicline more than doubles the chances of quitting compared with placebo, so that for every 10 who quit with placebo about 28 could be expected to quit with varenicline. Varenicline helps about 50% more people to quit than nicotine patch and "other" NRT (tablets, sprays, lozenges and inhalers), and about 70% more people than nicotine gum. So for every 10 people who quit with NRT patch or with "other" NRT, about 15 could be expected to quit with varenicline, and for every 10 who quit with NRT gum about 17 could be expected to quit with varenicline.[288]

Low-dose varenicline (four trials, 1272 people) roughly doubles the chances of quitting, and reduces the number and severity of side effects. The main side effect of varenicline is nausea, but this is mostly at mild or moderate levels and usually subsides over time.[288] Though concerns have been raised, retrospective cohort studies and an RCT,[307] indicate no severe adverse events with varenicline in the setting of ACS patients, with the large EVITA trial in ACS ongoing.

Clonidine helped people to quit, but causes side effects and is therefore a second line agent. It is not clear whether mecamylamine used with NRT helps people to quit. Other treatments did not seem to help. So far, nicotine vaccines are not licensed for use anywhere in the world.[288]

Combining two types of NRT is as effective as using varenicline, and helps more people to quit than single types of NRT.[288]

3a.4.7 Electronic cigarettes

E-cigarettes are battery-operated devices that simulate combustible cigarettes by heating nicotine and other chemicals into a vapour that is inhaled. Electronic cigarettes deliver the addictive nicotine without the vast majority of tobacco chemicals, and the EMA has concluded that electronic cigarettes are less harmful than tobacco.

Evidence on the effectiveness of electronic cigarettes is limited due to the small number of trials, low event rates and wide confidence intervals.[308] However data from observational studies and randomized trial suggest that efficacy of first generation electronic cigarettes is similar to that of transdermal NRT patches[309] or the NRT inhalators.[310] Benefit may come from low nicotine delivery or just the non-nicotine behavioural components of electronic cigarette use. About 6% of former smokers who used electronic cigarettes daily relapsed to smoking after 1 month, and 6% after one year, and nearly a half of dual users of both tobacco and e-cigarettes stopped smoking after one year, indicating that electronic cigarette use might be effective in relapse prevention and smoking cessation.[311] These studies and "real world" data indicate that electronic cigarettes are moderately effective as smoking cessation and harm reduction aids, but that a significant component of that effect is due to changes in behaviour rather than in nicotine delivery. Although the long-term safety of electronic cigarettes is unknown, no safety issues have been observed in the short term (2 years). Thus, there is a debate whether e-cigarettes should be formally regulated and subject to licensing restrictions since the potential for addiction is high.

3a.4.8 Other smoking-cessation interventions

Both individual and group behavioural interventions are effective in helping smokers quit. Support from the partner and family is important. There are no reliable data that acupuncture, acupressure, laser therapy, hypnotherapy, or electrostimulation are effective for smoking cessation.

Gaps in evidence

- More efficient, safe, and cost-effective smoking cessation aids are required.

3a.5 Nutrition

Key messages

- Dietary habits influence the risk of CVD and other chronic diseases such as cancer.
- Energy intake should be limited to the amount of energy needed to maintain (or obtain) a healthy weight; that is, a BMI >20.0 and < 25.0 kg/m².
- In general, when following the rules for a healthy diet, no dietary supplements are needed.

Recommendation on nutrition

Recommendation	Class[a]	Level[b]	Ref[c]
A healthy diet is recommended as a cornerstone of CVD prevention in all individuals	I	B	312

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

3a.5.1 Introduction

Dietary habits influence CV risk, either through an effect on risk factors such as cholesterol, BP, body weight and DM, or through other effects.[312] Table 12 summarises the characteristics of a healthy diet.

Table 12 Healthy diet characteristics

• Saturated fatty acids to account for < 10% of total energy intake, through replacement by polyunsaturated fatty acids.
• Trans unsaturated fatty acids: as little as possible, preferably no intake from processed food, and < 1% of total energy intake from natural origin.
• < 5 g of salt per day.
• 30–45 g of fibre per day, preferably from wholegrain products.
• ≥200 g of fruit per day (2–3 servings).
• ≥200 g of vegetables per day (2–3 servings).
• Fish 1-2 times per week, one of which to be oily fish.
• 30 grams unsalted nuts per day
• Consumption of alcoholic beverages should be limited to 2 glasses per day (20 g/d of alcohol) for men and 1 glass per day (10 g/d of alcohol) for women.
• Sugar-sweetened soft drinks and alcoholic beverages consumption must be discouraged

Most evidence on the relation between nutrition and CVD is based on observational studies; randomized clinical trials estimating the impact of diet on endpoints are scarce. The impact of diet is studied on three levels: specific nutrients, specific foods/food groups, or specific dietary patterns, of which the Mediterranean diet is the most studied.

The nutrients of interest with respect to CVD are fatty acids (which mainly affect lipoprotein levels), minerals (which mainly affect BP), vitamins, and fibre.

3a.5.2 Fatty acids

For prevention of CVD, the types of fatty acids consumed are more important than the total fat content.

The risk of CAD is reduced by 2–3% when 1% of energy intake from **saturated fatty acids** is replaced by polyunsaturated fatty acids. The same has not been clearly shown for the replacement with carbohydrates and monounsaturated fatty acids (MUFAs). Saturated fatty acid intake should be reduced to a maximum of 10% of energy intake by replacing it with polyunsaturated fatty acids.[313]

MUFAs have a favourable effect on HDL-C levels when they replace saturated fatty acids or carbohydrates,[314] but there is little evidence that MUFAs lower CAD risk.

Polyunsaturated fatty acids lower LDL-C levels, and to a lesser extent HDL-C levels, when they replace saturated fatty acids. The polyunsaturated fatty acids can be divided into two subgroups: n-6 fatty acids, mainly from plant foods; and n-3 fatty acids, mainly from fish oils and fats. Within the subclass of n-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid (EPA/DHA) are especially important. They do not change serum cholesterol levels, and, with currently available cardio-protective therapies, it is debateable whether they exert a favourable effect on all cause, CAD mortality, and stroke mortality.[315, 316]

The **trans fatty acids**, a subclass of unsaturated fatty acids, have been shown to be especially harmful, due to their unfavourable impact on both total cholesterol (increase) and HDL-C (decrease). These fatty acids are formed during industrial processing (hardening) of fats, and are present in margarine and bakery products, for example. A meta-analysis of prospective cohort studies has shown that, on average, a 2% increase in energy intake from trans fatty acid increases CAD risk by 23%.[317] It is recommended to derive < 1% of total energy intake from trans fatty acids – the less the better.

The impact of **dietary cholesterol** on serum cholesterol levels is weak compared with that of the fatty acid composition of the diet. When guidelines are followed to lower saturated fat intake, this usually also leads to a reduction in dietary cholesterol intake. Some guidelines (including this one) on healthy diet do not therefore give specific guidelines on intake of dietary cholesterol; others recommend a limited intake of < 300 mg/day.

3a.5.3 Minerals

A meta-analysis estimated that even a modest reduction in **sodium** intake of 1 g/day reduces SBP by 3.1 mmHg in hypertensive patients and 1.6 mmHg in normotensive patients.[318] The Dietary Approaches to Stop Hypertension (DASH) trial showed a dose–response relation between sodium reduction and BP reduction.[319] In most western countries salt intake is high (around 9–10 g/day), whereas the recommended maximum intake is 5 g/day. Optimal intake levels might be as low as around 3 g/day. Although the relation between salt intake and BP remains controversial, the totality of evidence warrants salt reduction as an important way to prevent CAD and stroke. On average 80% of salt intake comes from processed foods, while only 20% is added later on. Salt reduction can be achieved by making different dietary choices (fewer processed foods, more basic foods) as well as reformulation of foods (lowering salt content) (see chapter 3c.2)

Potassium has favourable effects on BP. Main sources of potassium are fruits and vegetables. An inverse statistically significant association exists between potassium intake and risk of incident stroke (risk ratio 0.76, 95% CI 0.66 to 0.89).[320] Apart from reducing sodium intake, increasing potassium intake contributes to BP lowering.

3a.5.4 Vitamins

Many case–control and prospective observational studies have observed inverse associations between levels of **vitamin A and E** and risk of CVD. However, intervention trials have failed to confirm these observational studies. Also for the **B-vitamins** (B6, folic acid and B12) and vitamin C, trials have shown no beneficial effects.

In the bottom tertile of serum levels of **vitamin D**, CV and total mortality is 35% higher (RR 1.35, 95% CI 1.13–1.61) than in the highest tertile.[321] A 41% higher risk of CV mortality (RR 1.41, 95% CI 1.18–1.68) and 57% higher risk of all-cause mortality (RR 1.57, 95% CI 1.36–1.81) has been reported in the lowest versus highest quintile.[322] A much smaller effect was observed in RCTs: an 11% risk reduction in all-cause mortality was observed for vitamin D3 supplementation (RR 0.89, 95% CI 0.80–0.99), but not for vitamin D2 supplementation.[321] Due to lack of power it was not possible to look at CV mortality specifically. Therefore, conclusions about vitamin D supplementation (type of supplement (D2 or D3), dosage and duration) for CV prevention cannot yet be drawn.

3a.5.5. Fibre

Recent meta-analyses of prospective cohort studies show that a 7 g/day higher intake of total fibre is associated with a 9% lower risk of CAD (RR 0.91, 95% CI 0.87–0.94),[323] and a 10 g/day higher fibre intake is associated with a 16% lower risk of stroke (RR 0.84, 95% CI 0.75–0.94)[324] and a 6% lower risk of type 2 DM (RR 0.94, 95% CI 0.91–0.97).[325] There is no evidence yet for a similar association with fibre from fruits and vegetables. Although the mechanism has not been elucidated completely, it is known that a high fibre intake reduces postprandial glucose responses after carbohydrate-rich meals, and lowers total cholesterol and LDL-C levels.

3a.5.6 Foods and food groups

3a.5.6.1 Fruits and vegetables

Prospective cohort studies have shown a protective effect of consumption of fruits and vegetables on CVD, but RCTs are scarce. A meta-analysis reported a decrease of 4% (RR 0.96, 95% CI 0.92–0.99) in CV mortality for each additional serving of fruits (equivalent to 77 g) and vegetables (equivalent to 80 g) per day, while all-cause mortality did not reduce further with intakes above 5 servings.[326] A meta-analysis reported a risk reduction for stroke of 11% (RR 0.89, 95% CI 0.83–0.97) for 3–5 daily fruit and vegetables servings and of 26% (RR 0.74, 95% CI 0.69–0.79) for > 5 servings, compared with < 3 servings.[327] A meta-analysis on CAD reported a 4% decrease in CAD risk (RR 0.96, 95% CI 0.93–0.99) for each additional serving of fruits and vegetables per day.[328]

3a.5.6.2 Nuts

A meta-analysis of prospective cohort studies has shown that daily consumption of 30 grams of nuts reduces the risk of CVD by about 30% (RR 0.71, 95% CI 0.59-0.85).[329] It must be noted that the energy density of nuts is high.

3a.5.6.3 Fish

The protective effect of fish on CVD is attributed to the n-3 fatty acid content. Pooled risk estimates from prospective cohort studies show that eating fish at least once a week results in a 16% reduction in risk of CAD (RR 0.85, 95% CI 0.75–0.95) compared to eating less fish.[330] A recent meta-analysis showed that eating fish 2–4 times a week reduces the risk of stroke by 6% (RR 0.94, 95% CI 0.90–0.98) compared with eating fish less than once a week.[331] The relation between fish intake and CV risk is not linear. Especially in the range of no or very low intake, risk is increased. The public health impact of a small increase in fish consumption in the general population is therefore potentially large.

For fish oil, three randomized controlled prevention trials have been published. All three trials, in post-AMI or CAD patients who received an extra amount of 400–1000 g EPA/DHA daily, did not observe a reduction in CV events in the intervention group. A recent meta-analysis of 20 trials, mostly prevention of recurrent CV events and mostly using fish oil supplements, showed no benefit of fish oil supplementation on CV outcomes.[316]

3a.5.6.4 Alcoholic beverages

Drinking ≥ 3 alcoholic beverages per day is associated with elevated CVD risk. Results from epidemiological studies suggest a lower risk of CVD occurring with moderate (1–2 units per day) alcohol consumption compared to non-drinkers. This association appears not to be explained by special characteristics of abstainers,[332] though the potential for residual confounding and reverse causality cannot be fully excluded. Moreover, a recent Mendelian randomization study including analyses from 59 epidemiological studies has shed doubt on any beneficial effect of moderate alcohol consumption,[333] suggesting that lowest risks for CV outcomes were in abstainers, and that any amount of alcohol was associated with elevated BP and BMI.

3a.5.6.5 Soft drinks and sugar

Sugar-sweetened soft drinks are the largest single food source of calories in the US diet and are important in Europe. In children and adolescents beverages may now even account for 10–15% of the calories consumed. Regular consumption of soft drinks has been associated with overweight, metabolic syndrome, and type 2 DM. Substitution of sugar-sweetened soft drinks with artificially sweetened drinks resulted in less weight gain in children over an 18 month period.[334] Sugar-sweetened beverages also cause weight gain in adults. Regular consumption of sugar-sweetened beverages (i.e. 2 servings per day compared with 1 serving per month) was associated with a 35% higher risk of CAD in women, even after other unhealthy lifestyle and dietary factors were accounted for, whereas artificially sweetened beverages were not associated with CAD. The WHO guideline recommends a maximum intake of 10% of energy from sugar (mono- and disaccharides); that includes added sugars as well as sugars present in fruits and fruit juices.[335]

3a.5.7 Functional foods

Functional foods containing phytosterols (plant sterols and stanols) are effective in lowering LDL-C levels by on average 10%, when consumed in amounts of 2 g/day. The cholesterol-lowering effect is additional to that obtained with a low-fat diet or use of statins. Further cholesterol reduction can be obtained with higher doses of phytosterols[336]. No studies with clinical endpoints have been performed yet.

3a.5.8 Dietary patterns

Studying the impact of a total dietary pattern theoretically shows the full preventive potential of diet, because it yields a combined estimate of the impact of several favourable dietary habits. The Mediterranean diet comprises many of the nutrients and foods that have been discussed previously: high intake of fruits, vegetables, legumes, wholegrain products, fish and unsaturated fatty acids (especially olive oil), moderate consumption of alcohol (mostly wine, preferably consumed with meals), and a low consumption of (red) meat, dairy products and saturated fatty acids. A meta-analysis of prospective cohort studies has demonstrated that greater adherence to the Mediterranean diet is associated with a 10% reduction in CV incidence or mortality (pooled RR 0.90, 95% CI 0.87–0.93) and an 8% reduction in all-cause mortality (pooled RR 0.92, 95% CI 0.90–0.94).[337] An RCT in high risk individuals suggested that following a Mediterranean diet over a 5-year period, compared to a control diet, is related to a 29% lower risk of CVD (RR 0.71, 95% CI 0.56–0.90).[338]

Gaps in evidence

- The biggest challenge in dietary prevention of CVDs is to develop more effective strategies to make people change their diet (both quantitatively and qualitatively) and to maintain that healthy diet and a normal weight.
- Research into the substances in foods that underlie the protective effects is ongoing.

3a.6 Body weight

Key messages

- Both overweight and obesity are associated with an increased risk of CVD death and all-cause mortality. All-cause mortality is lowest with a BMI of 20–25 kg/m^2 (in those <60 years); further weight reduction cannot be considered protective against CVD.
- Healthy weight in the elderly is higher than in the young and middle-aged
- Achieving and maintaining a healthy weight have a favourable effect on metabolic risk factors (BP, blood lipids, glucose tolerance) and lower CV risk.

Recommendation for body weight

Recommendation	Class[a]	Level[b]	Ref[c]
It is recommended that subjects with healthy weight* maintain their weight. It is recommended that overweight and obese people achieve a healthy weight (or aim for a reduction in weight) in order to reduce BP, dyslipidaemia and risk of developing type 2 DM, and thus improve the CV risk profile.	I	A	339, 340

* BMI 20-25 kg/m^2. There is evidence that optimal weight in elderly is higher than in the young and middle-aged[340]

BP = blood pressure; CVD = cardiovascular disease; DM = diabetes mellitus.

[a]Class of recommendation.

[b]Level of evidence.

[c]Reference(s) supporting recommendations.

3a.6.1 Introduction

In many countries favourable trends in major risk factors such as blood cholesterol, BP and smoking prevalence have been observed, translating into reduced CV mortality. However, BMI has strongly increased in all countries over the past decades resulting in a concomitant increase in prevalence of type 2 DM. In the USA it has been projected that if obesity trends from 2005 to 2020 continue, obesity will increasingly offset the positive effects of declining smoking rates.[341] The main clinical complications of increasing body weight are: (1) increases in BP, dyslipidaemia, insulin resistance, systemic inflammation and prothrombotic state, and albuminuria; and (2) development of DM, CV events (HF, CAD, AF, stroke).

3a.6.2 Which index of obesity is the best predictor of cardiovascular risk?

BMI (weight (kg)/height(m^2)) can be measured easily and is used extensively to define categories of body weight (see Table C in the web addenda).[342] In addition to the amount of body fat, its distribution is important. Body fat stored in the abdomen (intra-abdominal fat) carries a higher risk than subcutaneous fat.

Several measures of body fatness are available (see Table D in the web addenda). Most data are available for BMI, waist:hip circumference ratio, and simple waist circumference. The optimal level for measurement of waist circumference is midway from the lower rib margin to the anterior superior iliac crest, in the standing position. The WHO thresholds for waist

circumference are the most widely accepted in Europe. Based on these thresholds, two action levels are recommended:
(1) Waist circumference ≥ 94 cm in men and ≥ 80 cm in women represents the threshold at which no further weight should be gained.
(2) Waist circumference ≥ 102 cm in men and ≥ 88 cm in women represents the threshold at which weight reduction should be advised.
These thresholds have been calculated based on Caucasians and it is apparent that different cut-points for anthropometric measurements are required in different races and ethnicities. A meta-analysis concluded that both BMI and waist circumference are similarly strong and continuously associated with CVD and type 2 DM.[343] Therefore, BMI generally suffices in routine practice.

3a.6.3 Does "metabolically healthy obesity" exist?

The phenotype of "metabolically healthy obesity" (MHO), defined by the presence of obesity in the absence of metabolic risk factors, has gained a lot of interest. Some studies argue that a specific subgroup of obese individuals is resistant to metabolic complications such as hypertension and insulin resistance and at increased risk. However, MHO individuals present a higher all-cause mortality compared to normal weight metabolically healthy individuals.[344, 345] Long-term results from the Whitehall study support the notion that MHO is a transient phase[346] moving towards gluco-metabolic abnormalities, rather than a specific "state".

3a.6.4 The obesity paradox in established heart disease

At the population level, obesity is associated with CVD risk. However, among those with established CAD, the evidence is contradictory. Systematic reviews of patients with CAD or undergoing percutaneous coronary intervention have suggested an "obesity paradox" whereby obesity appears protective.[339, 347] This is also the case for HF patients. However, this evidence should not be misinterpreted to recommend higher target BMIs for those with established CVD since reverse causality may be operating. Cardiorespiratory fitness might influence relationships between adiposity and clinical prognosis in the obesity paradox. Normal weight unfit individuals have a higher risk of mortality than fit individuals regardless of their BMI. Overweight and obese fit individuals have mortality risks similar to normal weight fit individuals.[348] Furthermore, the results of the EPIC study suggest that the influence of physical inactivity on mortality appears to be greater than that of high BMI.[349]

3a.6.5 Treatment goals and modalities

CVD risk has a continuous positive relationship with BMI and other measures of body fat. Because all-cause mortality appears to increase at BMI levels below 20,[340] we do not recommend such low BMI levels as treatment goals.
Although diet, exercise and behaviour modifications are the mainstay therapies for overweight and obesity, they are often unsuccessful for long-term treatment. Medical therapy with orlistat and/or bariatric surgery are additional options. A recent meta-analysis indicates that patients undergoing bariatric surgery have a reduced risk of MI, stroke, CV events and mortality compared to non-surgical controls.[350]

Gaps in evidence

- Knowledge and implementation of effective strategies to achieve weight loss and maintain a long-term healthy weight.
- Identification of the relative roles of diet, exercise, and behaviour modification in the management of overweight and obese people.
- Optimal level of BMI over the lifecourse (at higher ages and after a CV event)

3a.7 Lipid control

Key messages:

- Elevated levels of plasma LDL-C are causal to atherosclerosis.
- Reduction of LDL-C decreases CV events.
- Low HDL-C is associated with increased CV risk, but manoeuvres to increase HDL-C have not been associated with a decreased CV risk.
- Lifestyle and dietary changes are recommended for all.
- Total CV risk should guide the intensity of the intervention.
- Total cholesterol and HDL-C are adequately measured on non-fasting samples so allowing non-HDL-C to be derived

Recommendations for lipid control

Recommendations[d e]	Class[a]	Level[b]	Ref[c]
In patients at VERY HIGH CV risk, an LDL-C goal <1.8 mmol/L (<70 mg/dL), or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.[f]	I	B	351-354
In patients at HIGH CV risk, an LDL-C goal <2.6 mmol/L (<100 mg/dL), or a reduction of at least 50% if the baseline is between 2.6 and 5.1 mmol/L (100 and 200 mg/dL) is recommended.	I	B	351-354
In the remaining patients on LDL-C lowering treatment, an LDL-C goal <3.0 mmol/L (<115 mg/dL) should be considered.	IIa	C	351-354

CV = cardiovascular; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

[a]Class of recommendation.

[b]Level of evidence.

[c]Reference(s) supporting recommendations.

[d] **Non-HDL-C is a reasonable and practical alternative target** because it does not require fasting. Non HDL-C secondary targets of <2.6, <3.3 and <3.8 mmol/L (<100, <130 and <145 mg/dL) are recommended for very high, high and low to moderate risk subjects, respectively See section 3a.7.10 for more details

[e] A view was expressed that primary care physicians might prefer a single LDL-C goal of 2.6 mmol/L (100 mg/dL). While accepting the simplicity of this approach and that it could be useful in some settings, there is better scientific support for the three targets matched to level of risk

[f] This is the general recommendation for those at very high risk. It should be noted that the evidence for patients with CKD is less strong.

3a.7.1 Introduction

The crucial role of dyslipidaemia, especially hypercholesterolaemia, in the development of CVD is documented beyond any doubt by genetic, pathology, observational, and intervention studies.

In blood plasma, lipids such as cholesterol and triglycerides circulate as lipoproteins in association with various proteins (apolipoproteins). The main carrier of cholesterol in plasma (LDL-C) is atherogenic. The role of triglyceride-rich lipoproteins is currently under active investigation: chylomicrons and large very low-density lipoproteins (VLDLs) appear not to be atherogenic, but very high concentrations of these triglyceride-rich lipoproteins can cause pancreatitis. Remnant lipoproteins (total cholesterol - (LDL+HDL Cholesterol)) have recently been identified in Mendelian randomization studies as pro-atherogenic lipoproteins.

3a.7.2 Total and low-density lipoprotein cholesterol

Most cholesterol is normally carried in LDL-C. Over a wide range of plasma cholesterol concentrations, there is a strong and graded positive association between total as well as LDL-

C and risk of CVD.[355] This association applies to men and women, and to those without CVD as well as with established CVD.

The evidence that reducing plasma LDL-C reduces CVD risk is unequivocal; the results of epidemiological studies and trials with and without statins using angiographic or clinical endpoints confirm that the reduction of LDL-C is of prime concern in the prevention of CVD.[38]

Meta-analyses of many statin trials show a dose-dependent relative reduction in CVD with LDL-C lowering. Every 1.0 mmol/L reduction in LDL-C is associated with a corresponding 20–25% reduction in CVD mortality and non-fatal MI.[351]

3a.7.3 Apolipoprotein B

Apolipoprotein B (apoB, the main apoprotein of atherogenic lipoproteins) levels have also been measured in outcome studies in parallel with LDL-C.[356] Based on the available evidence, it appears that apoB is a similar risk marker to LDL-C.[357] Also, there appears to be less laboratory error in the determination of apoB than LDL-C, particularly in patients with marked hypertriglyceridaemia (>3.4 mmol/L or >300 mg/dL), but there is no evidence that apoB is a better predictor of CVD than LDL-C.[358]

3a.7.4 Triglycerides

Hypertriglyceridaemia is a significant independent CVD risk factor, but the association is far weaker than for hypercholesterolaemia.[359] The risk is associated more strongly with moderate than with very severe hypertriglyceridaemia (>10 mmol/L or >~900 mg/dL), which is, on the other hand, a risk factor for pancreatitis. There are, however, no randomized trials to provide sufficient evidence to derive target levels for triglycerides. Meta-analyses suggest that targeting triglycerides may reduce CVD in specific subgroups with high triglycerides and low HDL-C. At present, fasting triglycerides >1.7 mmol/L (>~150 mg/dL) continue to be considered as a marker of increased risk, but concentrations ≤1.7 mmol/L are not evidence-based target levels for therapy.

3a.7.5 High-density lipoprotein cholesterol

Low HDL-C is independently associated with higher CVD risk.[360] Low HDL-C may even rival hypercholesterolaemia (due to high concentrations of LDL-C) as a risk factor for CAD.[361] The combination of moderately elevated triglycerides and low concentrations of HDL-C is very common in patients with type 2 DM, abdominal obesity, insulin resistance, and those who are physically inactive. This lipid pattern is also characterized by the presence of small, dense, atherogenic LDL particles. An HDL-C level <1.0 mmol/L (<40 mg/dL) in men and <1.2 mmol/L (<45 mg/dL) in women may be regarded as a marker of increased risk. Recent Mendelian randomization studies, however, cast doubt on the *causal* role of HDL-C in CVD.[362] Physical activity and other lifestyle factors, rather than drug treatment, remain important means of increasing HDL-C levels.

3a.7.6 Lipoprotein(a)

Lipoprotein(a) (Lp(a)) is a low-density lipoprotein to which an additional protein called apolipoprotein(a) is attached. High concentrations of Lp(a) are associated with increased risk of CAD and ischaemic stroke, and Mendelian randomization studies support a causal role in CVD for Lp(a). There is no randomized intervention study showing that reducing Lp(a) decreases CVD risk.[363] At present there is no justification for screening the general population for Lp(a), but it may be considered in patients at moderate risk to refine risk evaluation or in subjects with a family history of early CVD.

3a.7.7 Apolipoprotein B/apolipoprotein A1 ratio

Apolipoprotein A1 (apoA1) is the major apoprotein of high-density lipoprotein. It is beyond doubt that the apoB:apoA1 ratio is one of the strongest risk markers.[114, 356] However, there is

insufficient evidence to support this variable as a treatment goal. As the measurement of apolipoproteins is not available to all physicians in Europe, is more costly than currently used lipid variables, and only adds moderately to the information derived from currently applied lipid parameters, its use is not recommended.

3a.7.8 Calculated lipoprotein variables

3a.7.8.1 Low-density lipoprotein cholesterol

LDL-C can be measured directly, but in most studies and in many laboratories LDL-C is calculated using the Friedewald formula [364]:

- In mmol/L: LDL-C = total cholesterol – HDL-C – (0.45 × triglycerides)
- In mg/dL: LDL-C = total cholesterol – HDL-C – (0.2 × triglycerides)

The calculation is valid only when the concentration of triglycerides is < 4.5 mmol/L (<~400 mg/dL). Similar problems may be faced when LDL-C is low (<~1.3 mmol/L or <50 mg/dL). Direct methods may be less sensitive to plasma triglyceride levels. However, recent data show that the direct methods may also be biased when triglyceride levels are high. Also, the values obtained with the different direct methods are not necessarily identical, especially for low and high LDL-C values.

3a.7.8.2 Non-high-density lipoprotein cholesterol (accurate in non-fasting samples)

Non-HDL-C comprises the cholesterol in low-density lipoprotein, intermediate-density lipoprotein, remnant and VLDL, capturing therefore all the information regarding pro-atherogenic lipoproteins. Non-HDL-C predicts CVD risk even better than LDL-C.[352] LDL-C limits may be transferred to non-HDL-C limits by adding 0.8 mmol/L (30 mg/dL). Calculated by simply subtracting HDL-C from total cholesterol, non-HDL-C, unlike LDL-C, does not require the triglyceride concentration to be < 4.5 mmol/L (< 400 mg/dL). Therefore, it is certainly a better measure than calculated LDL-C for patients with increased plasma triglyceride concentrations, but also has an additional advantage of not requiring patients to fast before blood sampling. There is evidence for a role of non-HDL-C as a treatment target.[365] As non-HDL-C is capturing the information regarding all the atherogenic apoB containing lipoproteins, we suggest that it is a reasonable alternative treatment goal while acknowledging that is has not been an endpoint in therapeutic trials.

3a.7.8.3 Remnant cholesterol

Recently the remnant cholesterol (total cholesterol minus HDL-C + LDL-C) has been shown to be causally related to atherosclerosis in Mendelian randomization studies. This parameter, however, is not suggested as a predictor or main target for therapy as further population data and clinical studies are awaited.

3a.7.9 Exclusion of secondary and familial dyslipidaemia

The presence of dyslipidaemias secondary to other conditions must be excluded before beginning treatment, as treatment of underlying disease improves hyperlipidaemia without requiring antilipidaemic therapy. This is particularly true for hypothyroidism. Secondary dyslipidaemias can also be caused by alcohol abuse, DM, Cushing's syndrome, diseases of the liver and kidneys, and several drugs (e.g. corticosteroids). Patients who could have genetic dyslipidaemias, such as FH, can be identified by extreme lipid abnormalities and/or family history. These patients should, if possible, be referred for specialist evaluation. The treatment recommendations in this guideline may not apply to these specific patients, who are dealt with in detail in the ESC/European Atherosclerosis Society guidelines on dyslipidaemias.[38, 353] An LDL-C >5.1 mmol/L (>200 mg/dL) in therapy naïve patients requires careful evaluation for possible FH. However in the presence of premature CVD or family history, possible FH should be considered also at lower LDL-C levels.

3a.7.10 Who should be treated and what are the goals?

In general, RCTs are the ideal evidence base for decisional thresholds and treatment goals. For treatment goals, this requires RCTs randomly allocating subjects to different lipid goals levels. However, most evidence in terms of treatment goals is derived from observational studies and from post-hoc analyses of RCTs (and meta-regression analyses thereof) randomly allocating different treatment strategies (and not treatment goals). Hence, recommendations reflect consensus based on large-scale epidemiological data and RCTs comparing treatment regimens, not on RCTs comparing different lipid goal levels.

In the past an **LDL-C** of 2.6 mmol/L (100 mg/dL) has been considered a treatment threshold and goal. This goal remains reasonable for most patients who have an indication for LDL-C-lowering therapy based on calculation of the CV risk (see section 2).

Evidence from trials has suggested that lowering LDL-C to ≤1.8 mmol/L (<70 mg/dL) is associated with lower risk of recurrent CVD events.[366] Therefore, an LDL-C level of 1.8 mmol/L (70 mg/dL) appears to be a reasonable goal for prevention of recurrent CV events, and in other very-high-risk subjects. A treatment goal of a LDL-C reduction of at least 50% is also recommended if the baseline LDL-C level is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL).

Non-HDL-C target values may be an alternate target if non-fasting samples are obtained and goals should be <2.6, <3.3 and <3.8 mmol/L, (<100, <130 and <145 mg/dL) in very high, high and low CV risk, respectively. In addition this is a secondary goal in people with elevated triglycerides. In the same subjects, although not generally recommended, apoB levels at <80 and <100 mg/dL can be reasonable goals for subjects with very high or high CV risk, respectively.

The benefit of cholesterol-lowering therapy depends on initial levels of risk: the higher the risk, the greater the benefit in absolute risk reduction (Table 13). There are no differences in *relative* reduction between men and women and between younger and older age or between those with and without DM.[367]

Table 13 Possible intervention strategies as a function of total cardiovascular risk and low-density lipoprotein cholesterol level

Total CV risk (SCORE) %	LDL-C lvels				
	<70 mg/dL <1.8 mmol/L	70 to <100 mg/dL 1.8 to <2.6mmol/L	100 to <155 mg/dL 2.6 to <4.0mmol/L	155 to <190 mg/dL 4.0 to <4.9 mmol/L	>190 mg/dL >4.9 mmol/L
<1	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/A
≥1 to <5	Lifestyle advice	Lifestyle advice	Lifestyle advice, consider drug if uncontrolled	Lifestyle advice, consider drug if uncontrolled	Lifestyle advice, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	IIa/A	IIa/A	I/A
>5 to <10, or high risk	Lifestyle advice	Lifestyle advice, consider drug if uncontrolled	Lifestyle advice and drug treatment for most	Lifestyle advice and drug treatment	Lifestyle advice and drug treatment
Class[a]/Level[b]	IIa/A	IIa/A	IIa/A	I/A	I/A
≥10 or very high risk	Lifestyle advice, consider drug	Lifestyle advice and concomitant drug treatment	Lifestyle advice and concomitant drug treatment	Lifestyle advice and concomitant drug treatment	Lifestyle advice and concomitant drug treatment
Class[a]/Level[b]	IIa/A	IIa/A	I/A	I/A	I/A

CV = cardiovascular;; LDL-C = low-density lipoprotein cholesterol; SCORE = Systematic Coronary Risk Estimation.

Guidance on the use of drug treatment must be interpreted in the light of the physician's judgement and knowledge with regards to his or her individual patient. Note that risk stratification is not applicable in FH, where drug treatment is recommended, and that, in this table, drug treatment may be considered at risks lower than the generic treatment thresholds indicated in section 2. Thus treatment may occasionally be considered in moderate risk (1–5%) individuals, provided that patients are well-informed of the limited absolute risk reduction, and high numbers needed to treat. In higher risk (5–10%), drug therapy is associated with somewhat larger absolute benefits, and should at least be considered. Drug therapy is strongly advised in those at very high risk (≥ 10%). If baseline LDL-C in this category is already below the target level of 1.8 mmol/L, benefit of statin therapy initiation is less certain, but may still be present.

3a.7.11 Patients with kidney disease

CKD can be characterized by mixed dyslipidaemia (high triglycerides, high LDL-C, and low HDL-C).[368] Statin therapy has a beneficial effect on CVD outcomes in CKD[369] and in some studies slows the rate of kidney function loss.[370, 371] Similar data have been observed for combination therapy of a statin with ezetimibe, but not for ezetimibe alone.[369]. For patients with end stage renal disease we recommend hypolipidaemic therapy should not be initiated. If patients with CKD already on a hypolipidaemic therapy enter end stage renal disease, the therapy may be maintained.[369]

3a.7.12 Drugs

The currently available lipid-lowering drugs include inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (statins), fibrates, bile acid sequestrants (anion exchange resins), niacin (nicotinic acid), selective cholesterol absorption inhibitors (e.g. ezetimibe), and, more recently, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Response to all therapy varies quite largely among individuals and therefore monitoring the effect on LDL-C levels is recommended.

Statins, by decreasing LDL-C, reduce CV morbidity and mortality as well as the need for coronary artery interventions.[372, 373] Statins at doses that effectively reduce LDL-C by at least 50% also seem to halt progression or even contribute to regression of coronary atherosclerosis.[374] Statins also lower triglycerides and meta-analysis evidence shows statins may also lower pancreatitis risk.[375] Therefore, they should be used as the drugs of first choice in patients with hypercholesterolaemia or combined hyperlipidaemia.

Data indicate that combination therapy with ezetimibe also brings a benefit that is in line with the Cholesterol Treatment Trialists' Collaboration (CTT) meta-analysis supporting the notion that LDL-C reduction is key to the achieved benefit independent of the approach used.[354, 376]

Increased levels of liver enzymes in plasma occur occasionally during statin therapy, and in most cases are reversible. Routine monitoring of liver enzyme values is not indicated. In addition, 5–10% of patients receiving statins complain of myalgia, but rhabdomyolysis is extremely rare. The risk of myopathy (severe muscular symptoms) can be minimized by identifying vulnerable patients and/or by avoiding statin interactions with specific drugs[377] (see Table E in web addenda). Because statins are prescribed on a long-term basis, possible interactions with other drugs deserve particular and continuous attention, as many patients will receive pharmacological therapy for concomitant conditions.[378] In practice, the management of a patient with myalgia but without a major creatinine kinase rise is based on trial and error and usually involves trial of a different statin, or the use of a very low dosage several days a week with a gradual increase.[377]

In general, the safety profile of statins is acceptable, and earlier observations that lipid-lowering treatment may contribute to an increase in non-CV mortality (e.g. cancers, suicides, depression) or mental disorders are not confirmed in a large meta-analysis.[379] Increased blood sugar and glycated haemoglobin (HbA1c) levels, i.e. increased risk of type 2 DM, occur after statin treatment and are dose dependent, in part linked to very slight weight gain, but the benefits of statins outweigh the risks for the vast majority of patients.[378-380] Patients should be reminded that adhering to lifestyle changes when prescribed a statin should lessen any modest DM risk.[380-383]

Non-statin treatment

Selective cholesterol absorption inhibitors (e.g. ezetimibe) are not usually used as monotherapy to decrease LDL-C concentrations, unless patients are intolerant to statins. They are recommended as combination therapy with statins in selected patients when a specific goal is not reached with the maximal tolerated dose of a statin.

Bile acid sequestrants also decrease total cholesterol and LDL-C but are poorly tolerated and tend to increase plasma triglyceride concentrations. They are therefore not recommended for routine use in CVD prevention.

Fibrates and niacin are used primarily for triglyceride lowering and increasing HDL-C, while *fish oils* (omega-3 fatty acids) in doses of 2–4 g/day are used for triglyceride lowering.[361, 384] The evidence supporting use of these drugs for CVD event reduction is limited and, given the strong evidence favouring statins, routine use of these drugs in CVD prevention is not recommended. When triglycerides exceed 10 mmol/L (900 mg/dL), in order to prevent pancreatitis, triglycerides must be reduced not only by drugs but also by restriction of alcohol, treatment of DM, withdrawal of oestrogen therapy, etc. In those rare patients with severe primary hypertriglyceridaemia, specialist referral must be considered.

Regarding *new therapies*, recent data from phase I–III trials show that PCSK9 inhibitors sharply decrease LDL-C up to 60%, either as monotherapy or in addition to maximal statin dose. Whether this approach results in the predicted reduction in CV events is being addressed in large outcome trials: preliminary evidence suggest that this is the case.[385-387]

3a.7.13 Drug combinations

Patients with dyslipidaemia, particularly those with established CVD, DM, or asymptomatic high-risk individuals, may not always reach treatment goals, even with the highest tolerated statin dose. Therefore, combination treatment may be needed. It must be stressed, however, that the only combination that has evidence for clinical benefit (one large RCT) is that of a statin combined with ezetimibe.[354] Based on the relatively limited body of evidence, clinicians may restrict the use of this combination to patients at high or very-high risk of CVD.

Combinations of niacin and a statin increase HDL-C and decrease triglycerides better than either of these drugs alone, but flushing is the main adverse effect of niacin, which may affect compliance. Furthermore, there is no evidence of clinical benefit for this combination [388].

Fibrates, particularly fenofibrate, may be useful, not only for decreasing high triglyceride concentrations and increasing low HDL-C, but for lowering LDL-C further when applied together with a statin. There is limited evidence for this combination in terms of reduction in CVD events. In selected cases, however, this approach may be considered such as when, during statin treatment, triglycerides remain high and/or HDL-C is very low. Other drugs metabolized through cytochrome P450 should be avoided when this combination is prescribed. Fibrates should preferably be taken in the morning and statins in the evening to minimize peak dose concentrations and decrease the risk of myopathy. Patients have to be instructed about warning symptoms (myalgia), even though such adverse effects are very rare. Gemfibrozil should not be added to a statin treatment due to the high potential for interactions.

If target levels cannot be reached even on maximal doses of lipid-lowering therapy or drug combinations, patients will still benefit from treatment to the extent by which the dyslipidaemia has been improved. In these patients, increased attention to other risk factors may help to reduce total risk.

Gaps in evidence

- Triglyceride or HDL-C values as a target for therapy
- Whether Lp(a) lowering against background statin therapy can reduce the risk of CVD
- How to increase adoption of non-HDL-C and non-fasting samples in clinical practice
- Whether functional foods and food supplements with a lipid-lowering effect can safely reduce the risk of CVD

3a.8 Diabetes Mellitus (Type 2 and Type 1)

Key messages

- The importance of multifactorial approach is very important in patients with type 2 DM
- Lifestyle management to aid weight control by sustainable dietary changes and increased PA levels should be central in the management of patients with type 2 DM.
- Intensive management of hyperglycaemia reduces the risk of microvascular complications and, to a lesser extent, risk of CVD. However, targets should be relaxed in the elderly, frail, those with long duration of DM, or those with existing CVD.
- Intensive treatment of BP in DM, with a target of 140 mmHg systolic for the majority, reduces the risk of macrovascular and microvascular outcomes. A lower SBP target of 130 mmHg further lessens risks for stroke, retinopathy and albuminuria and should be applied to selected patients.
- Lipid lowering is a key mechanism to lower CVD risk in both type 2 and type 1 DM. All patients above 40 years of age and selected younger patients at elevated risk are recommended for statin therapy as first line.

- In DM patients with existing CVD, the use of an Sodium-glucose co-transporter-2 (SGLT2) inhibitor substantially lessened CVD and total mortality and HF hospitalisation without major adverse effects. SGLT2 inhibitors should be considered early in the course of DM management in such patients.
- Recent evidence points to sizeable reductions in CVD mortality in DM patients via improvement in risk factor management, though rising worldwide DM prevalence will create increasing major challenges. More should be done to prevent DM.

Recommendations for management of diabetes

Recommendations	Class[a]	Level[b]	Ref[c]
Lifestyle changes including smoking cessation, low fat diet, high fibre diet, aerobic physical activity, and strength training are recommended.	I	A	389
Reduction in energy intake is recommended to patients to help achieve lower weight or prevent weight gain.	I	B	389
A target HbA1c for the reduction in risk of CVD and microvascular complications in DM of <7.0% (<53 mmol/mol) is recommended for the majority of non-pregnant adults with either type 1 or type 2 DM.	I	A	390, 391
For patients with a long duration of DM, the elderly, frail, or those with existing CVD, HbA1c targets should be relaxed (i.e. less stringent).	IIa	B	391
A target HbA1c of ≤ 6.5% (≤ 48 mmol/mol) should be considered at diagnosis or early in the course of type 2 DM in patients, who are not frail and do not have CVD.	IIa	B	391
When screening for DM in individuals with or without CVD, HbA1c (which can be done non-fasting) or fasting blood glucose should be used. An oral glucose tolerance test can be offered when there is still doubt.	IIa	A	392
Metformin is recommended as first-line therapy, if tolerated and not contra-indicated, following evaluation of renal function.	I	B	393
Avoidance of hypoglycaemia and excessive weight gain should be considered and individual approaches (with respect to both treatment targets and drug choices) should be considered in patients with advanced disease.	IIa	B	391, 394, 395
In patients with type 2 DM and CVD, the use of an SGLT2 inhibitors should be considered early in the course of the disease to reduce CV and total mortality.	IIa	B	396
Lipid lowering agents (principally statins) are recommended to reduce CV risk in all patients with type 2 or type 1 DM above the age of 40 years.	I	A	372, 373
Lipid lowering agents (principally statins) may be considered also in individuals below 40 years of age if at significantly elevated risk based on the presence of micro-vascular complications or of multiple CV risk factors.	IIb	A	372, 373
In DM patients at very high risk (see table 5), a LDL-C target <1.8 mmol/L (<70 mg/dL), or a reduction of at least 50% if the baseline LDL-C is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL), is recommended.[d] In DM patients with high risk (see table 5), LDL-C target <2.6 mmol/L (<100mg/dL) or a reduction of at least 50% if the baseline	I	B	397

LDL-C is between 2.6 and 5.1 mmol/L (100 and 200 mg/dL) is recommended.[d]			
BP targets in type 2 DM are generally recommended to be <140/85 mmHg, but a lower target of <130/80 mmHg is recommended in selected patients (e.g. younger patients at elevated risk for specific complications) for additional gains on stroke, retinopathy and albuminuria risk. Renin-angiotensin-aldosterone system blocker is recommended in the treatment of hypertension in DM, particularly in the presence of proteinuria or micro- albuminuria. Recommended BP target in patients with type 1 DM is <130/80 mmHg.	I	B	398, 399
The use of drugs that increase HDL-C to prevent CVD in type 2 DM is not recommended.	III	A	388
Antiplatelet therapy (e.g. with aspirin) is not recommended for people with DM who do not have CVD	III	A	400

BP = blood pressure; CV = cardiovascular; DM = diabetes mellitus; HbA1c = glycated haemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SGLT2 = Sodium-glucose co-transporter-2.

[a]Class of recommendation.

[b]Level of evidence.

[c]Reference(s) supporting recommendations.

[d] **Non-HDL-C is a reasonable and practical alternative target** because it does not require fasting. Non HDL-C secondary targets of <2.6 and <3.3 mmol/L (<100 and <130 mg/dL) are recommended for very high, and high risk subjects, respectively See section 3a.7.10 for more details

People with DM are on average at double the risk of CVD.[401] A simple DM risk questionnaire can guide which patients without CVD should be tested for DM.[402]

Keeping close to the recommended targets for BP, lipid control, glycaemia, and HbA1c is important for the prevention of CVD. Clear reductions have occurred in CVD death rates in DM consistent with better management of risk factors, though rising prevalence of DM continues to create pressures on all healthcare systems.

The targets, especially the glycaemic and in some cases lipid targets, should be less stringently implemented in older people with DM, those with longer duration of DM, those with evidence of CVD, and the frail.[403]

There is mounting evidence for a very high relative risk in younger individuals with type 2 DM (age < 40 years)[404] and additional guidance on care is needed.

Excepting for glucose management, prevention of CVD follows the same general principles as for people without DM. Achieving low BP levels and low LDL-C and total cholesterol concentrations is particularly important. Many treatment targets are more stringent for patients with DM. Typically, patients with type 2 DM have multiple CVD risk factors, each requiring treatment according to existing guidelines.

3a.8.1 Lifestyle intervention

ESC and European Association for the Study of Diabetes scientific statements advocate lifestyle management as a first measure for the prevention and management of DM.[389] Most patients with DM are obese and weight control is a central component. Several dietary patterns can be adopted where the predominance of fruits, vegetables, wholegrain cereals and low-fat protein sources is more important than the precise proportions of total energy provided by the major macronutrients. Salt intake should be restricted. Specific dietary recommendations include limiting saturated and trans fats and alcohol intake, monitoring

carbohydrate consumption, and increasing dietary fibre. A Mediterranean-type diet is acceptable, where fat sources are derived primarily from monounsaturated oils.

A combination of aerobic and resistance exercise training is effective in the prevention of the progression of DM and for the control of glycaemia. Little is known about how to promote and sustain PA; however, reinforcement by healthcare providers to patients to find sustainable ways to increase PA is crucial. Smoking increases the risk of DM, CVD and premature death, and should be strongly discouraged (see section 3a.4.5).[389, 405] Lifestyle intervention can also prevent DM development in those at elevated risk and, in turn, lowers future microvascular and macrovascular risks.[406]

3a.8.2 Cardiovascular risk

DM is not a CAD risk equivalent state at diagnosis or in those with short duration of disease.[407, 408] In general, risk levels approach CAD risk equivalence after about a decade or in those with proteinuria or low eGFR.[408-410] Emerging data suggest that patients who develop DM at a younger age have a high complication burden.[404] People with DM with existing CAD have a vascular risk well in excess of those with CAD but without DM and a substantially lower life expectancy.[411]

Statins are recommended for all those newly diagnosed with type 2 DM beyond a certain age (> 40 years is currently recommended). This recommendation reflects greater lifetime vascular risk trajectories in these individuals. However, a proportion of DM patients at 40–50 years of age may have low 10 year risk of CVD due to normal BP and lipid levels and being non-smokers, and in such cases there remains a role for physician judgement. Equally, in some patients with type 2 DM < 40 years of age with evidence of end-organ damage or significant risk factors, statins may be indicated.

3a.8.3 Glucose control

The UK Prospective Diabetes Study (UKPDS) established the importance of intensive glucose lowering with respect to CVD risk reduction, in newly diagnosed patients with DM but not treated with modern BP and lipid lowering therapies, with best evidence to support metformin, leading to its position as first line therapy. Three trials were conducted to see if CV events could be reduced further with more intensive glycaemia treatment and lower target HbA1c levels.[391, 395, 412] However, the results were surprising with unexpected increases in total and CVD deaths in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and a trend towards an increase in CVD death in the Veterans Affairs Diabetes Trial (VADT). The results prompted concerns about the safety of intensive glucose lowering and the appropriateness of pursuing tight glucose control, particularly in older people with DM and in those with existing CVD. Subsequent meta-analyses of intensive glucose control including data from UKPDS, Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive), ACCORD, Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation (ADVANCE), and VADT[413] showed significant reductions in non-fatal AMI and CAD events, but no effect on stroke or total mortality.[414, 415] The additional analyses of these trials suggested that CVD benefits for an average HbA1c reduction of around 0.9% over 5 years were far less than via usual reductions in cholesterol and BP seen with statins and available BP lowering agents. Four recent trials of newer DM therapies (DPP-4 and GLP-1)[416-419] in patients with DM and existing CVD or at high risk demonstrated non-inferiority (i.e. safety) but not superiority with respect to CVD risk. There was, however, an increase in the rate of hospitalization for HF with saxagliptin in SAVOR-TIMI 53.[418]

Very recently, the SGLT2 inhibitor, empaglaflozin demonstrated substantial reduction in CVD death (by 38%) and all-cause mortality (by 32%) as well as in hospitalisation for HF (by 35%), as compared to standard care, suggesting use of an SLGT2 inhibitor should come very early in the course of management of patients with DM and CVD. [396] The pattern of trial results whereby non-fatal MI and stroke were not reduced by active treatment as well as the

rapid separation of mortality curves suggest that the mechanism of benefit was likely to relate more to cardio-renal haemodynamic effects than to atherothrombotic actions or effects of glucose-lowering per se. More research on understanding the trial results is needed.

3a.8.4 Blood pressure

In people with type 2 DM, apart from lifestyle interventions, the reduction of BP (along with cholesterol) should be targeted as strictly as targeting glucose/HbA1c levels. BP targets should be considered regardless of overall CV risk score in patients with type 2 DM.

Hypertension is more common in patients with type 2 DM compared with the general population. A recent systematic review and meta-analysis of randomized trials of BP lowering agents in over 100,000 patients with type 2 DM confirmed that lowering BP reduces risk of all-cause mortality, CV events, CAD events, stroke, HF, retinopathy, new or worsening albuminuria, and renal failure.[420] The results were similar when trials with low risk of bias were selected. Furthermore, a systolic target < 140 mmHg lessens risk of total mortality and most separate outcomes. Further reductions in risk for albuminuria, retinopathy and stroke, but not in overall survival or aggregate clinical endpoints, were achieved with a systolic target < 130 mmHg. In people over 80 years of age, targets should be set higher, aiming for < 150/90 mmHg, unless renal impairment is present.

Combination treatment is commonly needed to lower BP effectively in DM. An angiotensin-converting enzyme inhibitor (ACE-I) or an angiotensin receptor blocker (ARB), where tolerated, should always be included as first line therapy because of the evidence of superior protective effects against initiation or progression of nephropathy.

3a.8.5 Lipid-lowering therapy

The Heart Protection Study (HPS) demonstrated that treatment with simvastatin 40 mg reduced the risk of CAD and stroke in people with DM and individuals without DM who had no prior AMI or angina pectoris.[373] Further robust support for statin benefit came from the Collaborative Atorvastatin Diabetes Study (CARDS) study, which compared 10 mg atorvastatin with placebo,[372] and from the CTT meta-analysis in DM patients.[421] There is also trial evidence to show greater CVD risk reduction with more intense statin therapy in DM patients.[397] More recent trial evidence shows clear CVD benefit of lowering LDL-C with ezetimibe on top of statin in patients with type 2 DM.[354] Emerging evidence also shows that PCSK9 inhibitors are equally efficacious in lowering LDL-cholesterol in type 2 DM patients, though results of CV outcome trials are awaited.[422] Lower treatment targets should be pursued in patients with type 2 DM who have overt CVD or CKD.

While the most common lipid abnormality in type 2 DM is raised triglyceride and low HDL-C, trials examining possible CVD benefits of lipid (mainly triglyceride) lowering with fibrates in DM have not been positive. The FDA states that the current evidence base is insufficient to support fibrates for CVD protection and that more trial evidence is needed.[423]

Prescribing of lipid lowering agents in older people with DM (> 85 years) requires special consideration because exposure to higher doses (or higher potency) may not increase life expectancy, but may increase the risk of adverse effects.

3a.8.6 Antithrombotic therapy

Patients with type 1 or type 2 DM have an increased tendency to develop thrombotic phenomena. The Antiplatelet Trialists' Collaboration meta-analysis demonstrated benefits of antithrombotic therapy (mainly aspirin) in patients with diabetes with clinically established CAD, cerebrovascular disease, or other forms of thrombotic disease, with a 25% reduction in risk of CV events.[424]

The role of aspirin in patients without CVD remains unproven. A meta-analysis of six RCTs found no statistically significant reduction in the risk of major CV events or all-cause

mortality when aspirin was compared with placebo or no aspirin in people with DM and no pre-existing CVD.[400] Further trials are ongoing.

3a.8.7 Microalbuminuria

Microalbuminuria (urinary albumin excretion from 30 to 300 mg/24 h) predicts the development of overt nephropathy in patients with type 1 or type 2 DM, while the presence of overt proteinuria (300 mg/24 h) generally indicates established renal parenchymal damage. In patients with diabetes and hypertension, microalbuminuria – even below the current threshold values – predicts CV events, and a continuous relationship between CV as well as non-CV mortality and urinary protein/creatinine ratios has been reported. Microalbuminuria can be measured from spot urine samples (due to inaccuracy in sampling, 24 h or night-time urine collection is discouraged) by indexing the urinary albumin concentration to the urinary creatinine concentration (2.5/3.5 to 25/35 mg/mmol). Patients with DM and microalbuminuria or proteinuria should be treated with an ACE-I or ARB regardless of baseline BP.

Gaps in evidence

- There is a need examine whether a type 2 DM CV risk score based on either 10-year or lifetime risk help improve targeting of preventative therapies, and lead to a reduction in CV risk or gain of lifetime years free from disease.
- Further trial data are needed to establish if the empaglaflozin outcome findings hold for other classes of SGLT2 inhibitors, and to better understand mechanisms of benefit. It would also be useful to know if SGLT2 inhibitors lessen CV mortality and HF risks in patients with DM but without CVD.
- More research on the benefits of glucagon-like peptide 1 (GLP-1) receptor agonists on CVD risk is needed and trials are due to be reported in subsequent years. Early evidence suggests no CVD benefit with short term use of DPP4 inhibitors in people at high risk for CVD, as reviewed.[425]

3a.8.8 Type 1 diabetes

Key messages

- CVD and mortality risks have come down in type 1 DM patients but remain unacceptably elevated in those with very poor glycaemic control or any evidence of kidney disease.
- Intensive management of hyperglycaemia in DM reduces the risk of macrovascular complications and premature mortality; a target of 6.6% - 7.5% (48–58 mmol/mol) HbA1c is recommended.
- Recommended BP target in the majority of patients with type 1 DM is 130/80 mmHg.
- Lipid lowering agents targeting LDL-C reduction should be recommended to the majority of patients above 40 years of age and to those younger than this with evidence of nephropathy or with multiple risk factors.

Type 1 DM is due to a lack of insulin production in the pancreas, confirmed by absent or virtually absent C-peptide levels. The average age of onset is around 14, though persons of any age can develop Type 1 DM. Type 1 DM should be suspected on any patient who progresses to insulin within first year of diagnosis. A contemporary large study in Scotland observed a relative risk for CVD events of 2.3 in men and 3 in women with type 1 DM compared to the general population,[426] suggesting CVD risks may have declined over time, commensurate with improvements in life expectancy.[427] Another report from Sweden demonstrated CVD mortality rates in type 1 DM to be twice the rates of the general population in those with HbA1c levels below 6.9% (52 mmol/mol), whereas risk was especially high (around 10-fold) in those with very poor control (≥9.7%, ≥83 mmol/mol).[428]

In the majority of studies, the risk of CVD events or mortality was highest among those with diabetic nephropathy, macroalbuminuria or CKD. Presence of proliferative retinopathy and autonomic neuropathy also signalled elevated CVD risk.

The Diabetes Control and Complications Trial (DCCT) established the importance of tight glucose control to lessen risks of both microvascular and macrovascular disease. A 27-year follow-up of this trial showed that 6.5 years of initial intensive DM therapy in type 1 DM was associated with a modestly lower all-cause mortality rate when compared with conventional therapy.[429] A glycaemic target for HbA1c of 6.5% to 7.5% (48–58 mmol/L) appears a balanced approach for long-term care of patients with type 1 DM. The use of insulin analogues, insulin pumps and continuous glucose monitoring to improve glycaemic control while minimizing hypoglycaemia, is the subject of intense research, as is the use of agents (e.g. metformin, GLP-1 agonists) commonly used in type 2 DM.

The CTT suggested lipid lowering with statins is as equally effective in type 1 patients as in type 2.[430] All patients above 40 years of age with type 1 DM should be recommended for statins unless they have a short duration of DM and no other risk factors. Younger patients with multiple risk factors or evidence of end organ damage (albuminuria, low eGFR, or proliferative retinopathy, neuropathy) should be considered for statin therapy.

A target BP of 130/80 mmHg is accepted practice in type 1 DM, with evidence of specific benefits of ACE-I or ARB on the early development and later progression of microvascular disease in younger type 1 DM. A lower target BP of 120/75–80 mmHg may be helpful in younger type 1 DM (aged < 40 years) with persistent microalbuminuria. Studies supporting improved CVD outcome in type 1 DM through BP reduction are lacking. As more patients with type 1 DM are living to older age, SBP targets may need to be relaxed (140 mmHg) in some to avoid side effects.

Current evidence suggests many patients with type 1 DM > 40 years of age continue to smoke, are still not receiving statins, and, perhaps most importantly, have very poor glucose control.[426] Further efforts to target these established risk factors are needed.

Gaps in evidence

- Further studies are needed on metformin and GLP-1 receptor agonists in (subgroups of) patients with type 1 DM to determine whether they improve glycaemic control, aid weight changes and improve clinical outcomes.
- There is a need for a CVD risk score in type 1 DM to better guide initiation of preventative therapies in younger patients.

3a.9 Hypertension

Key messages

- Elevated BP is a major risk factor for CAD, HF, cerebrovascular disease, PAD, CKD, and AF.
- The decision to start BP lowering treatment depends on BP level and total CV risk.
- Benefits of treatment are mainly driven by BP reduction per se, not by drug type.
- Combination treatment is needed to control BP in most patients.

Recommendations for management of hypertension

Recommendations	Class[a]	Level[b]	Ref[c]
Lifestyle measures (weight control, increased physical activity, alcohol moderation, sodium restriction, and increased consumption of fruits, vegetables, and low-fat dairy	I	A	338, 431-433

products) are recommended in all patients with hypertension and in individuals with high normal BP.			
All major BP lowering drug classes (i.e. diuretics, ACE-I, calcium antagonists, ARBs, and beta-blockers) do not differ significantly in their BP-lowering efficacy and thus are recommended as BP lowering treatment.	I	A	434, 435
In asymptomatic subjects with hypertension but free of CVD, CKD, and DM, total CV risk stratification using the SCORE model is recommended.	I	B	30
Drug treatment is recommended in patients with grade 3 hypertension irrespective of CV risk, as well as in patients with grade 1 or 2 hypertension who are at very high CV risk.	I	B	436
Drug treatment should be considered in patients with grade 1 or 2 hypertension who are at high CV risk.	IIa	B	436
In patients at low to moderate total CV risk and with grade 1 or 2 hypertension, lifestyle measures are recommended.	I	B	436
In patients at low to moderate total CV risk and with grade 1 or 2 hypertension, if lifestyle measures fail to reduce BP, drug treatment may be considered.	IIb	B	436
SBP <140 mmHg and DBP <90 mmHg are recommended in all treated hypertensive patients < 60 years old.	I	B	436
In patients >60 years old with SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg.	I	B	437
In fit patients <80 years old, a target SBP < 140 mmHg may be considered if treatment is well tolerated. In some of these patients a target SBP <120 mmHg may be considered if at (very) high risk and tolerate multiple BP lowering drugs.	IIb	B	437, 438
In individuals >80 years and with initial SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg, provided they are in good physical and mental conditions.	I	B	437
In frail elderly patients, a careful treatment intensity (e.g. number of BP lowering drugs) and BP targets should be considered, and clinical effects of treatment should be carefully monitored.	IIa	B	439
Initiation of BP lowering therapy with a two-drug combination may be considered in patients with markedly elevated baseline BP or at high CV risk. Combination of two drugs at fixed doses in a single pill may be considered because of improved adherence.	IIb	C	440
Beta-blockers and thiazide diuretics are not recommended in hypertensive patients with multiple metabolic risk factors,[d] due to the increased risk of DM.	III	B	441

ACE-I = angiotensin-converting enzyme inhibitor; ARBs = angiotensin receptor blockers; BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DBP = diastolic blood pressure; NNT = number needed to treat; SBP = systolic blood pressure; SCORE = Systematic Coronary Risk Estimation.

[a]Class of recommendation.

[b]Level of evidence.

[c]Reference(s) supporting recommendations.

[d]Overweight, obesity, dyslipidaemia, impaired glucose tolerance

3a.9.1. Introduction

High BP is a leading risk factor for disease burden globally, accounting for 9.4 million deaths and 7.0% of global disability-adjusted life years (DALYs) in 2010.[442] Compared to 1990, the impact of high BP has increased by about 2.1 millions deaths.[442] Overall, the prevalence of hypertension is around 30–45% in adult persons aged 18 years or older, with a steep increase with ageing.

Elevated BP is a risk factor for CAD, HF, cerebrovascular disease, PAD, CKD, and AF. The risk of death from either CAD or stroke increases progressively and linearly from BP levels as low as 115 mmHg systolic and 75 mmHg diastolic upwards,[443] although for absolute risk the curves flatten in the lower BP ranges.

3a.9.2 Definition and classification of hypertension

The definition and classification of hypertension are shown in Table 14.[11]

Table 14 Definition and classification of blood pressure levels[a]

Category	Systolic BP (mmHg)		Diastolic BP (mmHg)
Optimal	< 120	and	< 80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥ 180	and/or	≥ 110
Isolated systolic hypertension	≥ 140	and	< 90

BP = blood pressure.

[a] BP levels in untreated individuals.

3a.9.3 Blood pressure measurement

Office BP is recommended for screening and diagnosis of hypertension, which should be based on at least two BP measurements per visit and on at least two visits. If the BP is only slightly elevated, repeated measurements should be made over a period of several months to achieve an acceptable definition of the individual's "usual" BP and to decide about initiating drug treatment. If BP is more markedly elevated or accompanied by target organ damage, other CV factors, or established CV or renal disease, repeated BP measurements are required within a shorter period in order to make treatment decisions.

3a.9.4 Office or clinic blood pressure measurement

Auscultatory or oscillometric semiautomatic sphygmomanometers should be validated and checked periodically.[444] Measurement of BP at the upper arm is preferred and cuff and bladder dimensions should be adapted to the arm circumference. If feasible, automated recording of multiple BP readings in the office, with the patient seated in an isolated room, might be considered as a means to improve reproducibility and make office BP values closer to those provided by daytime ambulatory BP monitoring (ABPM) or home BP measurements

(HBPM).[445] Note that automated devices are not validated for BP measurement in patients with AF.

3a.9.5 Out-of-office blood pressure monitoring

Out-of-office BP is commonly assessed by ABPM or HBPM, usually by self-measurement; it is usually lower than office BP and the difference increases as office BP increases (Table 15).[446]

Table 15 Blood pressure thresholds for definition of hypertension with different types of BP measurement

	SBP (mmHg)	DBP (mmHg)
Office or clinic	140	90
24-hour	125–130	80
Day	130–135	85
Night	120	70
Home	130–135	85

DPB = diastolic blood pressure; SBP = systolic blood pressure.

General principles and remarks should be taken into account: (1) The procedure should be adequately explained to the patient, with verbal and written instructions; (2) Interpretation of the results should take into account that the reproducibility of out-of-office BP measurements is reasonably good for 24 h, day and night BP averages but less for shorter periods: (3) ABPM and HBPM provide somewhat different information on the subject's BP status and risk and the two methods should thus be regarded as complementary, rather than competitive; (4) Devices should have been validated and regularly calibrated, at least every 6 months.

Both ABPM and HBPM values are closely related to prognosis.[447] Night-time BP seems to be a stronger predictor than daytime BP. Out-of office measurement may be useful not only in untreated subjects but also in treated patients, with the aim of monitoring the effects of treatment and increasing compliance with drug therapy (Table 16).

Table 16 Clinical indications for the use of out-of-office blood pressure measurements (home blood pressure measurement, ambulatory blood pressure measurement)

Suspicion of white-coat or masked hypertension
High office BP in individuals without organ damage and at low total CV risk
Normal office BP in individuals with organ damage or at high total CV risk
Considerable variability of office BP over the same or different visits
Autonomic, postural, post-prandial, siesta- and drug-induced hypotension
Elevated office BP or suspected pre-eclampsia in pregnant women
Identification of true and false resistant hypertension
Specific indications for ABPM
Marked discordance between office BP and home BP
Assessment of dipping status
Suspicion of nocturnal hypertension or absence of dipping, such as in patients with sleep apnoea, CKD, or DM
Assessment of BP variability

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular.

3a.9.6 Diagnostic evaluation in hypertensive patients

Routine: *Laboratory tests*: haemoglobin, fasting plasma glucose (HbA1c if not fasting) and serum tests for total cholesterol, and HDL-C, triglycerides, potassium, uric acid, creatinine (and calculated renal function), thyrotropin (in postmenopausal women); *Urine analysis*: albumin/creatinine ratio, dipstick test, sediment, and quantitative proteinuria if dipstick test positive; *Electrocardiogram (ECG).* Echocardiography and fundoscopy can be considered. The routine measurement of additional biomarkers and/or the use of vascular imaging methods is not recommended.

3a.9.7 Risk stratification in hypertension

The decision to start pharmacological treatment depends not only on the BP level but also on total CV risk, outlined in section 2. However, even subclinical hypertensive organ damage predicts CV death independently of SCORE, and the combination may improve risk prediction, especially in subjects at moderate risk (SCORE 1–4%).[448, 449] Echocardiography is more sensitive than ECG in diagnosing LVH and in predicting CV risk, and may help in more precise stratification of the overall risk and in directing therapy.[450] Albumin/creatine ratio >30mg/g in urine is also a marker of subclinical damage in hypertensive patients.

3a.9.8 Who to treat, and when to initiate antihypertensive treatment

The decision to start antihypertensive treatment depends on the BP level and total CV risk. Lifestyle changes are recommended in all patients with suboptimal BP including masked hypertension. Prompt initiation of drug treatment is recommended in individuals with grade 3 hypertension with any level of CV risk.[434] Lowering BP with drugs is more frequently required when total CV risk is very high and should be considered when the risk is high (section 2.3.5).[434] Initiation of BP lowering drug treatment may also be considered in grade 1 or 2 hypertensive patients at low to moderate risk when BP is within this range at several repeated visits or elevated by ambulatory BP criteria, and remains within this range despite a reasonable period of time with lifestyle measures.[450] However, the NNT in this patient category is very high, and patients should be informed about this, and their preference must be considered.

Lifestyle measures only with close BP monitoring should be the recommendation in young individuals with isolated moderate elevation of brachial SBP[451] and in individuals with high normal BP who are at low or moderate risk.[450] Also in white-coat hypertensives without additional risk factors, therapeutic intervention should be limited to lifestyle changes, accompanied by close follow-up. Drug treatment may also be considered in white-coat hypertensives with a higher CV risk because of metabolic derangements or in the presence of organ damage.

3a.9.9 How to treat

3a.9.9.1 Lifestyle changes

Lifestyle interventions, weight control and regular PA alone may be sufficient for patients with high-normal and grade 1 hypertension, and should always be advised for patients receiving BP lowering drugs as they may reduce the dosage of BP lowering drugs needed to achieve BP control. The lifestyle intervention specific to hypertension is salt restriction. At the individual level, effective salt reduction is by no means easy to achieve. As a minimum, advice should be given to avoid added salt and high-salt food. As the BP-lowering effect of increased potassium has been well documented in the DASH diet (rich in fruits, vegetables, and low fat diary products with a reduced content of dietary cholesterol as well as saturated and total fat), patients with hypertension should generally be advised to eat more fruits and vegetables and to reduce intake of saturated fat and cholesterol.[450]

3a.9.9.2 Blood pressure lowering drugs

The large number of randomized trials of BP lowering therapy, both those comparing active treatment versus placebo, and those comparing different compounds, confirm that: a) the main benefits of BP lowering treatment are due to lowering of BP *per se*, and are largely independent of the drugs employed; and b) thiazide and thiazide-like diuretics (chlorthalidone and indapamide), beta-blockers, calcium antagonists, ACE-I, and ARB can adequately lower BP, and reduce risk of CV death and morbidity.[434, 435] These drugs are thus all recommended for initiation and maintenance of BP control, either as monotherapy or in combination. Some aspects should be considered for each of the BP lowering drugs groups.

The position of **beta-blockers** as first-choice BP lowering drugs has been questioned. A meta-analysis of 147 randomized trials[434] reports only a slight inferiority of beta-blockers in preventing stroke (17% reduction rather than 29% reduction with other agents), but a similar effect in preventing CAD and HF, and higher efficacy in patients with a recent coronary event. However, as beta-blockers induce weight gain, have adverse effects on lipid metabolism, and increase (compared with other drugs) the incidence of DM, they are not preferred in hypertensive patients with multiple metabolic risk factors and conditions that increase the risk of new-onset DM (such as obesity, impaired fasting glucose). However, this may not apply to vasodilating beta-blockers such as carvedilol and nebivolol, which have less or no dysmetabolic action, as well as a reduced incidence of new-onset DM compared with conventional beta-blockers.

Thiazide diuretics also have dyslipidaemic and diabetogenic effects, particularly when used in high doses. Thiazides have often been administered together with beta-blockers in trials showing a relative excess of new-onset DM.

ACE-I and **ARB** are particularly effective in reducing LVH, reducing microalbuminuria and proteinuria, and preserving renal function and delaying end-stage renal disease.

Evidence concerning the benefits of **other classes of agents** is much more limited. Alpha1-blockers, centrally acting agents (alpha2-adrenoreceptor agonists and imidazoline-receptor agonists), anti-aldosterone drugs and the renin inhibitor aliskiren effectively lower BP in hypertension, but there are no data documenting their ability to improve CV outcome. All of these agents have frequently been used as added drugs in trials documenting CV protection and can thus be used for combination treatment on top of the recommended combinations (see below).

Drugs with 24 h efficacy are preferred. Simplification of treatment improves adherence to therapy, while effective 24 h BP control is prognostically important in addition to “office” BP control. Long-acting drugs also minimize BP variability, which may offer protection against progression of organ damage and risk of CV events.

Any all-purpose ranking of drugs for general BP lowering usage is infeasible and no evidence is available that different choices should be made based on age or sex (except for caution in using ACE-I and ARB in women with child-bearing potential because of possible teratogenic effects).[452] Some agents should be considered as the preferred choice in specific conditions because they have been used in trials including patients with those conditions or because of greater effectiveness in specific types of organ damage (Table 17).[450]

Table 17 Drugs to be preferred in specific conditions

Condition	Drug
Asymptomatic organ damage	
LVH	ACE-I, calcium antagonist, ARB
Asymptomatic atherosclerosis	Calcium antagonist, ACE-I
Microalbuminuria	ACE-I, ARB
Renal dysfunction	ACE-I, ARB
Clinical CV event	
Previous stroke	Any agent effectively lowering BP

Previous MI	BB, ACE-I, ARB
Angina pectoris	BB, calcium antagonist
Heart failure	Diuretic, BB, ACE-I, ARB, mineralocorticoid receptor antagonist
Aortic aneurysm	BB
Atrial fibrillation: prevention	Consider ARB, ACE-I, BB or mineralocorticoid receptor antagonist
Atrial fibrillation: rate control	BB, non-dihydropyridine calcium antagonist
ESRD/proteinuria	ACE-I, ARB
Peripheral artery disease	ACE-I, calcium antagonist
Other	
ISH (elderly)	Diuretic, calcium antagonist
Diabetes mellitus	ACE-I, ARB
Pregnancy	Methyldopa, BB, calcium antagonist
Blacks	Diuretic, calcium antagonist

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta-blocker; BP = blood pressure; CV = cardiovascular; Diuretic = thiazide or thiazide-like; ESRD = end-stage renal disease; ISH = isolated systolic hypertension; LVH = left ventricular hypertrophy; MI = myocardial infarction.

3a.9.9.3 Combination treatment

Combination treatment is needed to control BP in most patients. The addition of a drug from another class should thus be regarded as a recommended treatment strategy unless the initial drug needs to be withdrawn because of side effects or the absence of any BP-lowering effects. The extra BP reduction from combining drugs from two different classes is approximately five times greater than doubling the dose of one drug[453] and may reduce the side effects associated with either drug. The combination of two drugs may also offer advantages for treatment initiation, particularly in patients at (very) high risk in whom early BP control may be desirable. Trial evidence of outcome reduction has been obtained, particularly for the combination of a diuretic with an ACE-I, or an ARB or calcium antagonist.[454]

Despite the trial evidence of outcome reduction, the beta-blocker/diuretic combination favours the development of DM and should thus be avoided unless required for other reasons. The combination of ACE-I and ARB is not recommended.[455] Specific benefits of such a combination in nephropathic patients with proteinuria (because of a superior anti-proteinuric effect) await confirmation in event-based trials and, if used, should be monitored closely.

In 15–20% of hypertensive patients, a combination of three drugs is needed to achieve BP control; thus a combination of three BP lowering drugs at fixed doses in a single tablet may be favoured, because reducing the number of daily pills improves adherence, which is low in patients with hypertension. The most rational combinations appear to be a blocker of the renin–angiotensin system, a calcium antagonist, and a diuretic at effective doses.

3a.9.10 Blood pressure goals

There are only a few randomized clinical trials comparing different treatment targets. Hence, recommendation on target levels largely derives from observational studies and post-hoc analyses of randomized clinical trials, which mostly compared different treatment regimens and reported achieved BP levels.

There is sufficient evidence to recommend that SBP be lowered to < 140 mmHg and diastolic BP (DBP) to < 90 mmHg in all non-elderly hypertensive patients. Evidence is missing in the elderly hypertensive patient, in whom the benefit of lowering SBP to < 140 mmHg has not been tested in randomized trials.

A DBP target < 90 mmHg is always recommended, except in patients with DM, in whom values < 85 mmHg are recommended. It should nevertheless be considered that DBP values between 80 and 85 mmHg are generally safe and well tolerated.[398, 399]
Post-hoc analyses of large-scale trials (e.g. ONTARGET, INVEST, and VALUE), although suffering from the limitation posed by comparisons of non-randomized groups, suggest that at least in high-risk hypertensive patients, there may be no advantage in lowering SBP below 130 mmHg, except perhaps for risk of stroke. A J-curve phenomenon for achieved SBP below 130 mmHg cannot be excluded,[450] mainly in patients with advanced atherosclerotic diseases and/or frailty.
The publication of the primary results of the Systolic Blood Pressure Intervention Trial (SPRINT), which compared the benefit of treatment of SBP to a target of less than 120 mmHg with treatment to a target of less than 140 mmHg, challenged the above goal recommendations in high risk patients without DM.[438] Frail elderly were underrepresented in this trial. Targeting a SBP of less than 120 mmHg, as compared with less than 140 mmHg (average values 121 mmHg and 136 mmHg, respectively at the first year), resulted in lower rates of a combined outcome of fatal and nonfatal major CV events and death from any cause. However significantly higher rates of serious adverse events, hypotension, syncope, electrolyte abnormalities and acute kidney injury or failure but not injurious falls, were observed in the intensive-treatment group. The fact that the study was open-label in a strategy close to usual care with frequent visits may have helped to adjust the antihypertensive treatment if serious side effects occurred and then minimized the risk of events. Generalizability of the findings of SPRINT to patients with DM and to frail elderly is problematic.
Based on current data, it may still be prudent to recommend lowering SBP/DBP to values within the range 130–139/80–85 mmHg and, possibly, close to lower values in this range, in all hypertensive patients.

3a.9.11 Hypertension in special groups

3a.9.11.1 Diabetes mellitus

See section 3a.8.4.

3a.9.11.2 Elderly

Large meta-analyses confirm that treatment is highly beneficial in the elderly hypertensive patient. The proportional benefit in patients aged > 60 years is no less than that of younger patients.
In patients > 60 years old with SBP ≥ 160 mmHg there is solid evidence to recommend reducing SBP to between 140 and 150 mmHg. However, in fit patients < 80 years of age, BP lowering treatment may be considered at SBP values ≥ 140 mmHg with a target SBP < 140 mmHg if treatment is well tolerated.
Evidence is now available from an outcome trial that BP lowering treatment also has benefits in patients aged ≥ 80 years. Because patients in the Hypertension in the Very Elderly Trial (HYVET) were generally in a good condition, the extent to which HYVET data can be extrapolated to more fragile octogenarians is uncertain. In individuals older than 80 years with an initial SBP ≥ 160 mmHg it is recommended to reduce SBP to between 140 and 150 mmHg, provided they are in good physical and mental condition.[439] The decision to treat should be taken on an individual basis, and patients should always be carefully monitored during treatment, with BP also measured in the standing position. In frail elderly patients, it is recommended to be careful and reach a decision based on monitoring of the clinical effects of treatment.

3a.9.12 Resistant hypertension

The definition of hypertension resistant to treatment is when a therapeutic strategy that includes appropriate lifestyle measures plus a diuretic and two other BP lowering drugs belonging to different classes at adequate doses (but not necessarily including a mineralocorticoid receptor antagonist) fails to lower SBP and DBP values to < 140 and 90 mmHg, respectively. Depending on the population examined and the level of medical screening, the prevalence of resistant hypertension has been reported to range from 5–30% of the overall hypertensive population, with figures < 10% probably representing the true prevalence. Resistant hypertension is associated with a high risk of CV and renal events.[456]
Before a patient is considered treatment resistant, consideration should be given to lack of treatment adherence, white-coat effect or high salt or alcohol intake, as well as drug intake with potential pressor effect, or the use of recreational drugs or secondary hypertension. In these patients physicians should check whether the drugs included in the existing multiple drug regimen have any BP lowering effect, and withdraw them if their effect is absent or minimal. Anti-aldosterone drugs, amiloride, or the alpha-1-blocker doxazosin should be considered as the fourth or fifth drug, if no contra-indication exists (eGFR < 45 mL/min/m^2 and/or serum potassium > 4.5 mmol/L for mineralocorticoid receptor antagonists).
In the case of ineffectiveness of drug treatment (i.e. resistant hypertension) specialist referral should be considered. Any invasive approach in these patients should be considered only for truly resistant hypertensive patients, with clinic values ≥ 160 mmHg SBP or ≥ 110 mmHg DBP and with BP elevation confirmed by ABPM.

3a.9.13 Duration of treatment and follow-up

Generally, BP lowering therapy should be maintained indefinitely. Cessation of therapy in hypertensive patients is mostly followed by the return of BP to pre-treatment levels. In some patients, in whom treatment is accompanied by an effective BP control for an extended period, it may be possible to reduce the number and dosage of drugs. This may be particularly the case if BP control is accompanied by healthy lifestyle changes. Reduction of medications should be made gradually and the patient should frequently be checked because of the risk of reappearance of hypertension.
Patient follow-up should be carried out by the healthcare team which should include physicians, nurses and pharmacists in a concerted activity, although wide variations exist in the organization of healthcare systems across Europe. In some countries the task relies more on the physicians while in others specially educated and trained nurses have a more prominent role. Once the target is reached, a visit interval of a few months is reasonable; there is no difference in BP control between 3- and 6-month intervals. The regression of asymptomatic organ damage occurring during treatment reflects the treatment-induced reduction of morbid and fatal CV events[457]; however, a cost-effectiveness analysis of which signs of organ damage should best be assessed in the follow-up has never been done.[450]

Gaps in evidence

- Drug treatment in white-coat hypertension
- If and when drug treatment should be started in the high normal BP range
- The optimal office BP values (i.e. the most protective and safe) for patients to achieve by treatment in different demographic and clinical conditions
- The optimal out-of-office (home and ambulatory) BP targets, and whether the treatment strategies based on control of out-of-office BP provide an advantage over strategies based on conventional (office) BP control

3a.10 Antiplatelet therapy

Key messages

- Antiplatelet therapy is not recommended in individuals free from CVD, due to its increased risk of major bleeding.

Recommendations for antiplatelet therapy

Recommendations	Class[a]	Level[b]	Ref[c]
In acute coronary syndromes, a $P2Y_{12}$ inhibitor for 12 months is recommended in addition to aspirin, unless there are contraindications such as excessive risk of bleeding.	I	A	458-460
$P2Y_{12}$ inhibitor administration for a shorter duration of 3–6 months after DES implantation may be considered in patients deemed at high bleeding risk.	IIb	A	461-464
$P2Y_{12}$ inhibitor administration in addition to aspirin beyond 1 year may be considered after careful assessment of ischaemic and bleeding risks of the patient.	IIb	A	465, 466
In the chronic phase (> 12 months) after MI, aspirin is recommended.	I	A	467
In patients with non-cardioembolic ischaemic stroke or TIA, prevention with aspirin only, or dipyridamole plus aspirin or clopidogrel alone is recommended.	I	A	468-470
Prasugrel is not recommended in patients with stable CAD. Ticagrelor is not recommended in patients with stable CAD without a previous ACS.	III	C	466
In patients with non-cardioembolic cerebral ischaemic events, anticoagulation is not recommended.	III	B	471, 472
Antiplatelet therapy is not recommended in individuals without CVD due to the increased risk of major bleeding.	III	B	467

MI = myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

3a.10.1 Antiplatelet therapy in individuals without cardiovascular disease

Prevention in individuals without overt CV or cerebrovascular disease was investigated using long-term aspirin versus control in a systematic review of six trials including 95,000 individuals. A risk reduction from 0.57% to 0.51% per year of serious vascular events was found by the Antithrombotic Trialists' Collaboration.[467] Major gastrointestinal and extracranial bleeds increased by 0.03% per year. Risk of vascular mortality was not changed by treatment with aspirin. In a recent Japanese study,[473] patients aged 60–85 years presenting with hypertension, dyslipidaemia, or DM were randomized to treatment with 100 mg aspirin or placebo. The 5-year cumulative primary outcome event rate (death from CV causes) was not significantly different between the groups, but treatment with aspirin significantly increased the risk of extracranial haemorrhage requiring transfusion or hospitalization (P=0.004). In individuals with multiple risk factors, clopidogrel in combination with aspirin was tested versus aspirin in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilisation, Management, and Avoidance (CHARISMA) trial and was not of significant benefit.[474] The results of the four major ongoing primary prevention trials, two in DM patients,[475, 476] one in individuals with advanced age,[477] and one in individuals with moderate CV risk,[478] are expected to become available over the next 5 years.

3a.10.2 Antiplatelet therapy in individuals with cardiovascular or cerebrovascular disease

In the acute state of cerebral ischaemia, aspirin reduced the risk of new vascular events within 2–4 weeks, by preventing four recurrent strokes and five vascular deaths per 1000 patients treated.[479]

Following an episode of ACS, dual antiplatelet therapy given for a period of 12 months is a standard treatment based on results from the CURE,[458] TRITON,[459] and PLATO[460] studies, whereas no clinical studies support use of prasugrel and ticagrelor in patients with stable CAD.

In long-term prevention after MI, stroke, or PAD, aspirin is the most studied drug. In a meta-analysis of 16 trials comprising 17,000 individuals, the Antithrombotic Trialists' Collaboration,[467] aspirin treatment was associated with serious vascular events in 6.7% of patients per year versus 8.2% of controls. The risk of total stroke was 2.08% per year versus 2.59% (P=0.002) and coronary events 4.3% per year versus 5.3% (P=0.0001). Aspirin was associated with a 10% reduction in total mortality with a significant excess of major bleeds; nevertheless, the benefits of aspirin exceeded the bleeding hazards.

In patients with prior MI, stroke, or PAD, clopidogrel showed a slight superiority with respect to aspirin; the rate of serious vascular events was 5.32% per year with clopidogrel versus 5.83% with aspirin (P=0.043). There were slightly more bleeds with aspirin.[480]

Adding aspirin to clopidogrel in high-risk patients with recent ischaemic stroke or transient ischaemic attack was associated with a non-significant difference in reducing major vascular events. However, the risk of life-threatening or major bleeding was significantly increased by the addition of aspirin[481].

On the other hand, The Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial showed that the combined treatment of clopidogrel and aspirin decreased the 90-day risk of stroke without increasing hemorrhage in comparison with aspirin alone in 5170 Chinese patients randomized within 24 hours after symptom onset of minor stroke or TIA to clopidogrel-aspirin or to the aspirin alone. Moderate or severe hemorrhage did not differ between the study [482].

In patients with prior non-cardioembolic ischaemic stroke, dual antiplatelet therapy with dipyridamole plus aspirin showed superiority over aspirin.[468] In such patients, oral vitamin K antagonists are not superior to aspirin but are associated with a higher bleeding risk.[471, 472]

In patients with ischaemic stroke, a direct comparison of dipyridamole plus aspirin versus clopidogrel alone [469] showed similar rates of recurrent stroke, including haemorrhagic stroke. There was a higher frequency of major haemorrhagic events with dipyridamole plus aspirin (4.1% vs. 3.6%).

Vorapaxar is a novel antiplatelet agent that selectively inhibits the cellular actions of thrombin through antagonism of PAR-1. In 26,449 patients who had a history of MI, ischaemic stroke, or PAD, the primary composite endpoint – CV death, MI or stroke – was significantly reduced with vorapaxar in addition to standard antiplatelet therapy, but with increased risk of moderate or severe bleeding.[483] Vorapaxar cannot be recommended systematically in patients with stable atherosclerotic disease.

Gaps in evidence

- The experience with the new antiplatelet drugs in patients with stable CAD is still limited and so is their use in combination with anticoagulant treatment.

3a.11 Adherence to medication

Key messages

- Adherence to medication in individuals at high risk and in patients with CVD is low.

- Several types of interventions are effective in improving medication adherence.
- The polypill may increase adherence to treatment and improve CV risk factor control.

Recommendations for achieving medication adherence

Recommendations	Class[a]	Level[b]	Ref[c]
Simplifying the treatment regimen to the lowest acceptable level is recommended, with repetitive monitoring and feedback. In case of persistent non-adherence, multi-session or combined behavioural interventions are recommended.	I	A	484
It is recommended that physicians assess medication adherence, and identify reasons for non-adherence in order to tailor further interventions.	I	C	485-487
The use of the polypill and combination therapy to increase adherence to drug therapy may be considered.	IIb	B	488, 489

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Adherence to medication in individuals at high risk and in patients with CVD is low, resulting in worse outcomes and higher healthcare costs.[490] One month after AMI, 25–30% of patients stop at least one drug, with a progressive decline in adherence over time. After 1 year, only 50% of patients report persistent use of statins, beta-blockers, or BP lowering therapy.[486, 487] The reasons for poor adherence are multifactorial (Table F in web addenda).[486]

Cost-related non-adherence is a relevant problem in many healthcare systems. For example, in American veterans, adherence to lipid-lowering medication decreased as co-payment increased.[491] Depression also independently doubles the risk for non-adherence.[492] Reasons for non-adherence tend to cluster; for example, complex medication regimens may be important in individuals with chronic disease or multiple risk factors. This places high demands on caregivers to provide clear advice and continuous care.[487] Physicians often fail to communicate critical elements of medication use (e.g. possible adverse effects, how long to take the medication, and the frequency or timing of dosing).[493] Thus there is a need to train physicians to identify risk factors for non-adherence and promote adherence to medication.

Several interventions are effective in improving adherence in chronic conditions.[484] Solely reducing dosage demands resulted in strong effects, but other interventions such as repetitive monitoring and feedback, multi-session information and combined behavioural interventions have shown effects ranging from minor to strong.[484] Collaboration with pharmacists or pharmacist-directed care was superior to standard care with respect to BP, total cholesterol and LDL-C levels.[494] Knowledge of one's CAC score may increase risk perception and adherence to medication.[495].

In clinical practice, physicians should assess adherence to medication, identify reasons for possible non-adherence, and promote adherence according to the following established principles:

- provide clear advice regarding the benefits and possible adverse effects of the medication, and the duration and timing of dosing;
- consider patients' habits and preferences (shared decision making);
- simplify the treatment regimen to the lowest feasible level;
- ask patients in a non-judgemental way how the medication works for them, and discuss possible reasons for non-adherence (e.g. side effects, worries);
- implement repetitive monitoring and feedback; introduce physician assistants and/or trained nurses or pharmacists whenever it is necessary and feasible;

- in case of persistent non-adherence, offer multi-session or combined behavioural interventions e.g. for patients after myocardial revascularisation in a cardiac rehabilitation (CR) setting.

3a.11.1 Polypill

Over a decade ago, Wald and Law quantified the efficacy and adverse effects of a fixed dose combination (FDC) from published trials and proposed that a FDC consisting of statin, BP lowering agents, aspirin, and folate could potentially reduce CVD by 80% in individuals above 55 years of age.[496].

A recent systematic review and meta-analysis[488] summarizes nine randomized trials (*n* = 7047) on FDCs, largely conducted in higher-risk populations and primarily designed to evaluate changes in CV risk factors and adherence. However FDCs included in the analysis were single pills of diverse composition and doses (although all contained a statin and at least one BP lowering agent) and had a range of comparators (placebo, single drug active component, or "usual care"). No convincing evidence of either benefit or risk for FDCs in terms of all-cause mortality or CV events was found. FDC therapy improved adherence (only one trial) to a multi-drug strategy by 33% (95% CI 26% to 41%) compared with usual care.

Another international study, not included in the previous meta-analysis, in 695 CAD patients randomized to test the effect of an FDC polypill containing aspirin, simvastatin and ramipril, or the three drugs separately, showed that FDC improved adherence compared to separate medications after 9 months follow-up (adherence 63% vs. 52%; *P*=0.006).[489]

The polypill should not be considered in isolation but as an integral part of a comprehensive CVD prevention strategy that includes efforts to reduce tobacco use, increase PA, and increase consumption of heart-healthy diets.[497] However, potential adverse effects of a single drug component of the FDC cannot be specifically corrected and therefore may also affect treatment adherence to the other components. Until we have the results of ongoing trials with major CVD as endpoints the polypill cannot be recommended in prevention of CVD and cannot be prescribed to all individuals.

Gaps in evidence

- There is limited evidence about which interventions to improve adherence to medication are the most effective in whom (e.g. young–old, male–female, high vs. low socio-economic status).
- The effect of the polypill as a global strategy to reduce CVD remains uncertain.

3b. How to intervene at the individual level: disease specific intervention. Atrial fibrillation, coronary artery disease, chronic heart failure, cerebrovascular disease, peripheral artery disease (web addenda)

3c. How to intervene at the population level

3c.1 Introduction (healthy lifestyle promotion)

The population level approach follows the Geoffrey Rose paradigm: small shifts in the risk of disease (or risk factor) across a whole population consistently lead to greater reductions in disease burden than a large shift in high risk individuals only. This population-wide approach has further advantages: it addresses CV health over the entire life-course and reduces health inequalities.

Individual behaviour is enacted in an environment with hierarchical levels, which encompass individual choice, family influence, cultural and ethnic grouping, workplace, health care and policy at state and global levels (e.g. EU policies and international trade agreements).

The aim of this section is to provide stakeholders with evidence-based suggestions for the most effective interventions to improve CVD risk that can be implemented at a group, community, regional, national or global level. Health care professionals play an important role in advocating evidence-based population level interventions.

Strategies such as "nudging" (to push mildly) and "default" have been proposed as tools. By changing the context to make healthy decisions default, the individual is "nudged" in the healthy direction. A task for both national and local authorities is to create social environments which provide healthier defaults.

The evidence presented here builds on recent comprehensive reviews[312, 498-500] and individual studies and summarises the "Totality of Evidence". It is rarely feasible to use an RCT to evaluate population level interventions (in contrast to individual level interventions). The guidelines committee has chosen to follow the definition of "Level of Evidence" also for population level approaches. Thus, consistent findings from several high quality studies were considered sufficient to merit strong recommendations.

3c.2 Population-based approaches to diet

Key messages

- Structural measures like product reformulation, limitations of marketing and taxes on unhealthy foods, subsidizing of costs of healthier foods, and consumer friendly nutrition labelling will improve healthy food choices.
- Healthy environments in the community, at schools and workplaces will stimulate a healthy lifestyle.

Recommendations for population-based approaches to diet

	Recommendations	Class[a]	Level[b]	Ref[c]
Governmental restrictions and mandates	Legislation on composition of foods to reduce energy density, salt and saturated fat, and (added) sugar content of foods and beverages, and to limit portion sizes is recommended.	I	B	312, 498, 499, 501-504

	Elimination of industrially produced transfats is recommended	I	A	317
	Facilitating an integrated and coherent policy and activities of the (local) governments, non-governmental organizations, food industry, retail, catering, schools, workplaces and other stakeholders to promote a healthy diet and to prevent overweight is recommended.	I	C	501, 505
	Legislation restricting marketing aimed at children of foods that are high in fats, sugar and/or salt, less healthy options, junk foods, drinks with alcohol and non-alcoholic beverages rich in sugar (e.g. on TV, internet, social media and on food packages) is recommended.	I	C	312, 498, 506, 507
Media and education	Reformulation of foods accompanied by educational information campaigns should be considered to create awareness on the nutrition quality of foods among consumers.	IIa	C	508, 509
Labelling and information	Mandatory and harmonized simplified front-of-pack nutrition labelling is recommended.	I	C	312, 499, 509
	Independently and coherently formulated criteria for nutrient profiles should be considered in support of health and nutrition claims and front-of-pack logos (e.g. traffic lights, healthy choices, key-holes).	IIa	C	312
	Mandatory nutrition labelling for non-pre-packaged foods, including in restaurants hospitals and workplaces, should be considered	IIa	C	312, 509
Economic incentives	Pricing and subsidy strategies are recommended to promote healthier food and beverage choices.	I	B	312, 498, 510, 511
	Taxes on foods and beverages rich in sugar and saturated fat, and on alcoholic drinks are recommended.	I	B	312, 498, 510, 511
Schools	At all schools, pre-schools and daycare centres a multi-component, comprehensive and coherent policy is recommended to promote a healthy diet.	I	B	312, 498, 505, 507
	Availability of fresh drinking water and healthy foods in schools, and in vending machines is recommended.	I	B	312, 498, 507
Workplaces	At all companies a coherent and comprehensive health policy and nutritional education is recommended to stimulate the health awareness of	I	B	312, 498, 499, 512

	employees.			
	Increased availability of fresh drinking water and improved nutritional quality of food served and/or sold in the workplace, and in vending machines should be considered.	IIa	C	312, 499
Community setting	Regulation of location and density of fast food and alcohol purchasing outlets and other catering establishments should be considered.	IIa	C	498-500

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Diet is a powerful determinant of obesity, hypertension, dyslipidemia, DM and CV health. Rapid reductions in CV events can be seen after changes in diet at the population level.[500, 513] Stakeholder, including health care professionals, have a shared responsibility for population-based approaches and can help to promote healthy diets and environments[498, 501] (Figure D in web addenda).[507]

Many EU countries recognize the health benefits of reducing the energy density, salt and sugar content and replacement of trans and saturated fat by unsaturated fat in foods and drinks.[312, 498, 501] These have led to successful reductions in trans fats[502] and salt,[498, 502-504] the latter likely leading to decreases in BP.[504] Mandatory upper limits harmonized across the EU will ensure that all EU consumers are equally protected.[501]

Governments can facilitate nation-wide cooperation between (local) governments, non-governmental organizations (NGOs), food industry, retail, catering, schools, workplaces and other stakeholders. The French EPODE (Ensemble Prévenons l'Obésité des Enfants) project is an example of a multi-stakeholder cooperation which can help decrease childhood obesity.[505] Similar projects are in place in Belgium, Spain, the Netherlands, Greece and Australia.

Educational tools and intervention on media may lead to reduction of childhood obesity, e.g. limiting children's exposure to advertising of unhealthy foods.[312, 498, 500, 505, 506] In 2013, the European Heart Network (EHN) published a report summarizing recent developments in relation to the marketing of unhealthy foods to children.[507] Accompanying consumer awareness campaigns on healthy foods,[508] and nutrition labelling can be effective. Consumers understand different systems of labelling and their use has a positive impact on sales.[509] EHN calls for a simplified, colour-coded, front-of-pack scheme indicating high, medium and low levels of nutrients.[312, 498, 500] This scheme can be applied to all foods and could be expanded to certain restaurants.[312] Labelling also stimulates reformulation of foods.[507] Thereby it has the potential to improve dietary intake and reduce diet-related chronic diseases.

Pricing strategies can also lead to a decline in sales of unhealthy foods and increase of sales of fruits and vegetables. Modelling studies have demonstrated that food taxes could improve energy and nutrient intake, BMI and health.[498, 510, 511] An increasing number of countries have introduced taxes on unhealthy foods and drinks e.g. fat tax in Denmark (10–15% decrease in consumption; now repealed) and junk food tax in Hungary (sales declined by 27%).[507] Consideration should be given to balanced economic incentives: subsidy and taxes to counteract any unbalanced effect on the socially disadvantaged.

To tackle obesity, every school and workplace should have a policy to promote a healthy environment and provide healthy foods and meals.[498, 507] Health education ideally should be part of the school curriculum. Workplace dietary modification interventions alone and in combination with nutrition education or environmental changes have shown improvements in consumption of fruits and vegetables and/or fat.[512]

In the community, planning of location and density of fast food outlets, and good access to supermarkets, is needed, especially in deprived areas.[498 499, 500]

Gaps in evidence

- Scientific evidence of the impact of food and nutrition policy instruments on outcome measures such as food intake and CV health is largely lacking.
- Cost-effective studies of the impact of different policy options are also limited.

3c.3 Population-based approaches to physical activity

Key messages

- Sedentary lifestyle and physical inactivity affects more than half of the population worldwide.
- Regular PA is recommended in all men and women as a lifelong part of lifestyle with at least 150 minutes moderate activity per week or at least 75 minutes of vigorous activity per week or an equivalent combination thereof. Any activity is better than none, more activity is better than some.
- Population-based interventions are effective in promoting PA.
- Early childhood education in PA and movement should start at pre-school/ kindergarten.
- Daily PA at school should be at least 30 minutes, preferably 60 minutes every day at school.
- Good neighbourhoods and safe environment enhances and encourages PA in everyday life.

Recommendations for population-based approaches to physical activity

	Recommendations	**Class[a]**	**Level[b]**	**Ref[c]**
Governmental restrictions and mandates	Consideration of PA when planning new landscaping/buildings or towns is recommended.	I	C	312, 514-516
Media and education. See also section 3c.2 for multi-component interventions	Sustained, focused, media and educational campaigns, using multiple media modes (e.g. apps, posters, flyers and signage) may be considered to promote PA.	IIb	C	499
	Short term community-based educational programmes and wearable devices promoting healthy behaviours, such as walking should be considered.	IIa	C	517; 518, 519
Labelling and information	Point-of-decision prompts should be considered to encourage use of stairs.	IIa	B	519, 520
	Exercise prescription for health promotion by physicians, especially GPs, similar to drug prescription should be considered.,	IIa	C	520, 521
Economic incentives	Increased fuel (gasoline) taxes should be considered to increase active transport/commuting	IIa	C	515, 521
	Tax incentives for individuals to purchase exercise equipment or health club/fitness memberships may be considered.	IIb	C	515, 521

	Sustained individual financial incentives may be considered for increased activity/fitness or weight loss.	IIb	C	515, 516, 521
	Tax incentives to employers to offer comprehensive worksite wellness programmes with nutrition, PA, and tobacco cessation/prevention components may be considered.	IIb	C	515, 521
Schools. See also section 3c.2 for multi-component interventions	Increased availability and types of school playground spaces and equipment for exercise activity and sports are recommended.	I	C	515, 522
	Regular classroom PA breaks during academic lessons should be considered.	IIa	B	514
	Increasing active commuting to school should be considered e.g. a walking school bus programme with supervised walking routes to and from school for safety.	IIa	C	515, 517
	Increased number and duration of PA classes, with revised PA curricula to implement at least moderate activity and trained teachers in exercise and sports may be considered.	IIb	B	514, 516
Workplace. See also section 3c.2 for multi-component interventions	Comprehensive worksite wellness programmes should be considered with nutrition and PA components.	IIa	B	515, 523-525
	Structured worksite programmes that encourage PA and provide a set time for PA during work hours should be considered. Improving stairway access and appeal, potentially in combination with "skip-stop" elevators that skip some floors should be considered.	IIa	C	
	Promoting worksite fitness centres should be considered.	IIa	C	520
Community settings	Health care providers should consider inquiring about PA in every medical encounter and adding it to the record. In addition, they should consider to motivate the individual and promote PA.	IIa	C	515, 523
	Improved accessibility of recreation and PA spaces and facilities (e.g. building of parks and playgrounds, increasing operating hours, use of school facilities during non-school hours), improved walkability should be considered.	IIa	C	515, 523
	Improved neighbourhood aesthetics (to increase activity in adults) should be considered.	IIa	C	515, 523

GPs = general practitioners; PA = physical activity.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

In most countries the majority of adults and children do not achieve the minimum activity levels recommended by health organizations: every person should engage in moderate

exercise for at least 150 minutes per week and/or vigorous activity for at least 75 minutes per week or an equivalent thereof.[260, 523] For population-based prevention, the statement of "seven best investments"[515] gives the universal and comprehensive advice to promote PA.[515]
Specific national guidelines developed for PA include frequency, intensity, time (duration), and type of activity (the FITT acronym) which can influence legislative initiatives, such as "active cities" with bicycle lanes and walking paths and re-allocation of road space.
Focused media and educational campaigns can initiate physical activities.[522] Recent campaigns from sports medicine societies endorsed PA prescriptions from the GP (www.efsma.eu). The PA should be assessed at every medical encounter.
A simple strategy for increasing daily exercise is to encourage the use of stairs rather than the elevator or escalator, along with signage directing people to the stairs and health promotion materials endorsing the positive effects of stair climbing.[519]
Interestingly, an increase in fuel prices may reduce car driving and increase active commuting for those who live within reasonable walking or biking distances with exception of diseased or disabled persons.[499]
PA education should be started in pre-school/kindergarten and continued for all levels of primary and secondary education. For school education, a multicomponent intervention should focus on improving life-long PA by trained teachers. At least 3 hours per week, better 60 minutes daily, sports or PA should be performed during school time.[514] Regular activity also improves cognitive competence for learning.[516, 524] This activity can be supplemented by active commuting to school and supervised walking routes to and from school with less reliance on buses.[517]
Workplaces may offer different opportunities for PA promotion. Some larger companies offer a fitness centre on company grounds without fees for employees. Workplace-based interventions may increase regular physical exercise for employees but results demonstrate that a high proportion of workers do not participate.[525] Therefore, supervisors and managers should endorse workplace interventions by encouraging employees to undertake PA .
Improved accessibility to recreation and exercise facilities with increased operating hours and utilizing community resources such as school playgrounds may increase regular PA in all age groups and reduce socio-economic inequality in access.[520]

Gaps in evidence

- Sustainability and long-term outcomes of population-based actions to promote PA.

3c.4 Population-based approaches to smoking and other tobacco products

Key messages

- Adolescence is the most vulnerable period for uptake of smoking with lifelong consequences.
- High taxes on all tobacco products is the most effective policy measure to reduce smoking uptake by the young.
- Restrictions on smokeless tobacco due to strong evidence of harm.
- Restrictions on electronic cigarettes due to uncertainty regarding safety and effect
- Plain packaging is effective to reduce tobacco consumption.
- Restrictions on advertising, promotion and sponsorship by the tobacco industry.
- A goal would be to make a common European decision to achieve a smoking-free Europe from 2030.

Recommendations for population-based approaches to smoking and other tobacco products

Risk factor	Recommendations	Class[a]	Level[b]	Ref[c]
Governmental restrictions and mandates	Banning smoking in public places is recommended to prevent smoking and to promote smoking cessation.	I	A	498
	Banning smoking in public places, outside public entrances, workplaces, in restaurants and bars is recommended to protect people from passive smoking.	I	A	499, 526
	Prohibit sales of tobacco products to adolescents are recommended.	I	A	498
	Banning of tobacco vending machines is recommended.	I	A	498
	Restrictions on advertising, marketing and sale of smokeless tobacco are recommended.	I	A	527-530
	Complete ban on advertising and promotion of tobacco products are recommended.	I	B	499
	Reduced density of retail tobacco outlets in residential areas, schools and hospitals is recommended.	I	B	499
	Harmonization of border sales and tax free sales of all tobacco products is recommended.	I	B	498
	Restrictions on advertising, marketing and sale of electronic cigarettes should be considered.	IIa	A	531, 532
Media and education	Telephone and internet based lines for cessation counselling and support services are recommended.	I	A	499
	Media and educational campaigns as part of multicomponent strategies to reduce smoking and increase quit rates, reduce passive smoking and use of smokeless tobacco are recommended	I	A	499
	Media and educational campaigns concentrating solely on reducing smoking, increasing quit rates, reducing passive smoking and the use of smokeless tobacco should be considered	IIa	B	498 499
Labelling and information	Cigarette package pictorial and text warnings are recommended.	I	B	498 499
	Plain packaging is recommended.	I	B	498, 499
Economic incentives	Higher taxes and prices on all tobacco products are recommended.	I	A	498, 499
Schools	Banning smoking in school, pre-school and child care to protect from passive smoking is recommended.	I	A	498
	Promotion and teaching of a healthy lifestyle	IIa	B	499

	including tobacco free life should be considered in all schools.			
Workplaces	Workplace specific bans on smoking to reduce passive smoking and increase quit rates are recommended.	I	A	[498] [499]
	Workplace policy on healthy choices including tobacco cessation/prevention is recommended.	I	A	[499]
Community settings	It is recommended that health personnel, caregivers and school personnel set an example by not smoking or using tobacco products at work.	I	A	[498] [499]
	It is recommended to advise pregnant women to be tobacco-free during pregnancy.	I	A	[527]
	It is recommended to advise parents to be tobacco-free when children are present.	I	A	[498], [499]
	It is recommended to advise parents to never smoke in cars and private homes.	I	A	[498] [499]
	Residence-specific restrictions on smoking should be considered.	IIa	B	[499]

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

The WHO Framework Convention on Tobacco Control recommends smoke-free laws: protecting people from tobacco smoke and banning smoke in public places, warning about the dangers of tobacco, raising taxes on tobacco, and enforcing advertising bans.[526] Children and low socio-economic groups are sensitive to population-based tobacco intervention. Passive smoking increases CVD risk,[498, 499] more so in women than in men.[533] All smoking, including smoking a waterpipe, is deleterious. Smokeless tobacco (in Europe usually snus, a moist powder tobacco placed under the upper lip) increases the risk of fatal CVD events [528-530], and use of snus during pregnancy increases the risk of stillbirth.[534] There is no evidence that snus increases smoking cessation more than nicotine replacement products or medication. Many smokers use electronic cigarettes (e-cigarettes) to quit. There are many unanswered questions about their safety, efficacy for harm reduction and cessation, and impact on public health. They should be subjected to the same restrictions as tobacco or pharmaceutical products.[531, 532] International legislation should be harmonized to prevent a new tobacco epidemic.[498]
Multi-component strategies are best. Advertising bans reduce tobacco consumption, and mass media campaigns reduce smoking uptake by teenagers and increase adult quitting.[498] Media and educational campaigns in schools reduce smoking and promote smoking cessation. Editors should increase the coverage of tobacco and health in the media.[535] Telephone or internet-based cessation-support reduces tobacco use.[499]
Packs with pictorial and text warnings raise awareness of tobacco dangers.[498] Plain and standardized packaging without brand labels enhances the effectiveness.
Higher taxes reduce tobacco consumption and quitting, particularly among youth and lower socio-economic groups.[498, 499]
School-based smoking bans should be implemented.[499] Smoking bans at workplaces reduce exposure to passive smoking, decrease smoking, and increase quitting rates.[498] Tobacco outlet density around homes, hospitals and schools should be reduced. Pregnant women should avoid tobacco, and parents should be tobacco-free when children are present. Health

personnel, caregivers and teachers must set an example by not using tobacco products at work.

Gaps in evidence

- Effect of school-based smoking restrictions.
- Effect of plain packaging.
- Health harm of electronic cigarettes.
- More evidence on environmental smoking is needed as smoke particles may remain in rooms for many years.

3c.5 Alcohol abuse protection

Key messages

- Excessive alcohol intake is associated with increased CV mortality and alcohol ranks as the second-leading cause of DALYs lost in high-income countries.
- The interventions for addressing the harmful use of alcohol are cost-effective with good return, i.e. increasing alcoholic beverage excise taxes, restricting access to alcoholic beverages, and implementing comprehensive restrictions and bans on advertising and promotion of alcoholic beverages.

Recommendations for protecting against alcohol abuse

	Recommendations	Class[a]	Level[b]	Ref[c]
Governmental restrictions and mandates	Regulating physical availability of alcoholic beverages is recommended, including minimum legal purchase age, restrictions on outlet density and time and place of sales, public health oriented licensing systems, and governmental monopolies of retail sales .	I	B	536-540 536, 537
	Drink-driving countermeasures are recommended such as lowered blood alcohol concentration limits and “zero tolerance”, random breath testing and sobriety check points.	I	B	538, 541
	Implementing comprehensive restrictions and bans on advertising and promotion of alcoholic beverages is recommended.	I	C	536
Media and education	Educational information campaigns may be considered to create awareness on the hazardous effects of alcohol.	IIb	B	536, 542
Labelling and information	Labelling alcohol with information on caloric content and health warning messages of the harmful effects of alcohol may be considered.	IIb	B	536, 542
Economic incentives	Taxes on alcoholic beverages are recommended.	I	B	537
Schools	At every school, pre-school and day care a multi-component, comprehensive and coherent education may be considered to prevent alcohol abuse.	IIb	B	536, 542
Workplaces	At every company a coherent and comprehensive health policy and nutritional education on stimulating the health of employees are recommended, including limiting excessive alcohol intake.	I	B	498

Community setting	Support and empower primary care to adopt effective approaches to prevent and reduce harmful use of alcohol are recommended.	I	B	[543]
	Enacting management policies relating to responsible serving of alcoholic beverages should be considered to reduce the negative consequences of drinking.	IIa	B	[538, 542]
	Planning of location and density of alcohol purchasing outlets and other catering establishments should be considered.	IIa	C	

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

At the population level, alcohol consumption is associated with multiple health risks that clearly outweigh any potential benefits. In 2012, about 3.3 million deaths, or 5.9% of all global deaths, and 139 million DALYs, or 5.1% of the global burden of disease and injury, were attributable to alcohol consumption. The highest numbers of deaths are from CVDs, with 33.3% of the alcohol-attributable deaths due to CVDs.[538] Ischaemic heart disease mortality is 65% higher in men heavy drinkers and more than double in women heavy drinkers.[544]

The relationship between alcohol consumption and CAD and cerebrovascular diseases is complex. It depends on both the level and the pattern of alcohol consumption. Low alcohol consumption, ranging from 1–3 alcohol units per day (a unit equates to about 80 mL of wine, 250 mL of normal strength beer, and 30–50 mL of spirits), in some segments of the population is associated with the lowest all-cause mortality, largely due to lower coronary mortality.[545]

SBP and DBP levels increase as alcohol consumption increases above 3 units per day and similarly, the risk of cardiac arrhythmias, cardiomyopathy, sudden death, and haemorrhagic stroke.[546] The pattern of alcohol use has an effect on CVD risk; binge drinking is associated with a higher risk of sudden death and stroke.[547]

The following strategies and interventions have the highest level of effectiveness to prevent the harmful use of alcohol: age limits for sale and serving,[539] drink-driving strategies,[541] government retail monopolies for sale and reducing the hours of sale of alcohol,[540] banning alcohol advertising, promotion, and sponsorship of events,[536] increase in retail price.[537, 542]

Labelling alcohol with information on caloric content and health warning messages of the harmful effects of alcohol has been shown to have a limited effect [542].

Alcohol regulations in policies on workplaces, educational centres, and schools are effective.[536]

Brief intervention in primary care to prevent alcohol abuse has been shown to be effective.[543]

In the community, excessive alcohol intake can be limited by restrictions in the number and opening hours of outlets, and by increasing the minimum age for sales and servings.[498]

Gaps in evidence

- Better quality evidence is needed with regard to potential confounding in studies on the effects of alcohol consumption.

3c.6 Healthy environment

Air pollution contributes to the risk of respiratory and CV diseases.[548] Important sources of fine particles in the EU are motorized road traffic, power plants, and industrial and residential

heating using oil, coal or wood. Up to a third of Europeans living in urban areas are exposed to levels exceeding EU air quality standards. In particular, young and old individuals and subjects with a high risk of CVD are more prone to the detrimental effects of air pollution on the circulation and the heart.

The EU Commission released a policy package to be implemented by the year 2030 with measures to reduce harmful emissions from traffic, energy plants and agriculture. Further efforts to reduce air pollution should be stimulated and taken by national governments, e.g. through appropriate and effective legislation. Patient organisations and health professionals have an important role to play in supporting educational and policy initiatives and provide a strong voice in the call for action at the governmental level.[548]

The media can inform the population on the quality of the air (e.g. by apps) and by providing smog alerts. Information on patients' behaviour during smog is warranted. Economic incentives like reduced taxes on electrical and hybrid cars can contribute to the improvement of the air quality. New houses and schools can preferably be built in areas remote from highways and polluting industries.

4a. Where to intervene at the individual level

The question of "where" prevention should take place requires only a simple answer: everywhere! Prevention of CVD should be valued and implemented at all levels of society and in all healthcare settings. This should include increased spending on prevention in healthcare and on actions that make communities healthier. All clinicians should also consider prevention and promotion of healthy lifestyles as a professional responsibility with individual patients and by supporting policies that promote healthier lifestyles. Patients should also be empowered and have the knowledge and support to make informed decisions, and to demand robust prevention efforts from healthcare groups and society.

4a.1 Clinical settings and stakeholders

4a.1.1 Cardiovascular disease prevention in primary care

Key messages

- The prevention of CVD should be delivered in all healthcare settings including primary care.
- Where appropriate, all health professionals should assess CV risk factors to determine individual total CV risk score.
- GPs and nurses should work together as teams to provide the most effective multidisciplinary care.

Recommendation for cardiovascular disease prevention in primary care

Recommendation	Class[a]	Level[b]
It is recommended that GPs, nurses and allied health professionals within primary care deliver CVD prevention for high-risk patients.	I	C

[a]Class of recommendation.
[b]Level of evidence.

The physician in general practice is the key person to initiate, coordinate, and provide long-term follow-up for CVD prevention. In most countries GPs deliver > 90% of consultations and provide most public health medicine, including preventive care and chronic disease

monitoring. In the case of CVD prevention they have a unique role in identifying individuals at risk of CVD and assessing their eligibility for intervention based on their risk profile. How to maximise attendance rates and adherence, particularly in those who are at highest risk, remains an issue.

As mentioned in section 2.2, a systematic approach is recommended to risk assessment, giving priority to persons with a priori higher risk (such as family history of premature CVD, presence of hypertension, etc); opportunistic screening to persons below the age of 40 years without CV risk factors is not recommended.

Intensive and structured intervention in general practice contributes to the prevention of recurrent CV events and reduces hospital admission in CAD patients.[549]

The successful implementation of CVD prevention guidelines relies heavily on GPs providing risk factor evaluation, intervention, and patient education. However, CV targets in general practice are often not achieved. The EUROASPIRE III survey (primary prevention arm) showed that the lifestyle of people being treated as high CV risk – defined as patients treated with BP and lipid lowering drugs as well as anti-diabetes drugs - showed much persistent smoking and a high prevalence of both obesity and central obesity. BP, lipid, and glucose control is poor with most patients not achieving the targets defined in the prevention guidelines. [5]

Surveys done among GPs and physicians in several European regions found that most were aware of the European guidelines on CVD prevention, but that only 36–57% were using the guidelines in practice, and less than half performed comprehensive risk assessments. The main barrier was time, but GPs also cited that there were too many guidelines, unrealistic targets for risk factor control, a preference for using their own experience, and lack of knowledge regarding comprehensive risk assessment.[550-553]. Online resources, mobile apps, pocket guidelines and summary cards may contribute as a means to overcome the implementation challenge.

Evidence for an effective role for nurses in primary care exists. A study of nurse-coordinated preventive cardiology programmes for primary prevention of CVD compared to routine practice – conducted in a matched, paired-cluster RCT in six pairs of general practices in six European countries – showed more high-risk patients achieved the lifestyle and risk factor targets in the nurse-coordinated arm compared with usual care.[554]

In 2009, a randomized trial in the Netherlands on CVD risk management and preventive care found that practice nurses achieved results equal to GPs after 1 year follow-up.[555]). A clinical trial (n = 525) in the USA has also shown that advanced practice nurses working with community health workers can achieve significant improvements in CV risk factors (BP, cholesterol, DM control) in underserved inner-city populations compared to enhanced usual care, and was cost-effective.[556]

Gaps in evidence

- Further research is needed in order to explore what is the best strategy to improve implementation of CVD prevention guidelines in general practice, taking into account heterogeneity among countries in terms of health systems and local resources.

4a.1.2 Acute hospital admission setting

Recommendations for CVD prevention strategies in the acute hospital admission setting

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended to implement strategies for prevention in CVD patients, including lifestyle changes, risk factor	I	A	302, 557

management and pharmacological optimization, after an acute event before hospital discharge to lower risk of mortality and morbidity.			

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

The importance of starting appropriate prevention before hospital discharge cannot be over-emphasised, as prevention treatment tends to decrease rather than increase post-hospitalization, with proportions of patients on appropriate therapy declining over time and patients not reaching risk factor targets.[297, 558]
The acute care team should: (1) emphasize the importance of the preventive measures directly to the patient, because failure to do so may suggest that these measure are valueless; and (2) interact with the other health professionals, e.g. physicians, nurses, to ensure that prevention strategies initiated during hospitalization are sustained and supported in other settings.
Thus patients while in acute care should receive appropriate interventions to optimize prevention strategies. These include full clinical assessment to guide optimization of medical therapy, individualised behavioural education for risk factor modification, and referral to exercise-based CR.
Education should be person-centred with full participation of patients and carers, providing explanations for each intervention, while early mobilization and physical conditioning programmes should vary according to the individual's clinical status.

4a.1.3 Specialized prevention programmes

Recommendations for specialized prevention programmes

Recommendations	Class[a]	Level[b]	Ref[c]
Participation in a CR programme for patients hospitalized for an acute coronary event or revascularization, and for patients with HF, is recommended to improve patient outcomes	I	A	559, 560
Preventive programmes for therapy optimisation, adherence and risk factor management are recommended for stable patients with CVD to reduce disease recurrence	I	B	561-564
Methods to increase referral to and uptake of CR should be considered such as electronic prompts or automatic referrals, referral and liaison visits, structured follow-up by physicians, nurses or therapists, and early starts to programmes after discharge.	IIa	B	561, 562
Nurses and allied health professional led programmes should be considered to deliver CVD prevention across healthcare settings	IIa	B	554-556, 565

CR=cardiac rehabilitation. CVD= cardiovascular disease; HF = heart failure.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Specialized prevention programmes are delivered as CR or other prevention programmes for all patients with CVD or at high risk for CVD. The core components and goals of CR have been standardized,[566] but the structure, length and type of the programme offered differs

widely by country, affected by national guidelines and standards, legislation, and payment factors.[567]

CR is a comprehensive programme involving exercise training, risk factor modification, education and psychological support. An overview of six Cochrane systematic reviews of CR (148 RCTs, *n* = 98,093) concluded that for low to moderate risk patients with HF, or who are post-MI or revascularization, exercise-based CR decreased hospital admissions and improved health-related quality of life (HRQoL) compared to usual care, and may reduce mortality longer-term.[559] A limitation of current reviews is the inclusion of trials prior the modern treatment, differing patients groups, and heterogeneous programmes of CR. Thus more research is needed to determine the optimal intervention. A number of recent controlled cohort studies have found a survival benefit for patients receiving CR compared to no CR. An on-going meta-analysis of CR in the modern era may provide more definitive results regarding patients programmes and outcomes. At present the benefit of CR appears to be both through direct physiological effects of exercise training, and CR's effects on risk factors, behaviours and mood.[559] CR also provides an opportunity for social support and to screen patients for psychosocial risk factors.

Referral and participation in CR varies widely across countries: many CR programmes do not include unstable patients, patients with HF, devices or PAD, and referral and retention of women and older, higher risk patients remain sub-optimal.[567, 568] Referrals to CR can be increased through electronic prompts or automatic referrals, while patient uptake may be improved by structured follow-up by nurses or therapists and early starts to programmes after discharge.[561, 562, 569]

Nurse-led programmes can also deliver effective preventive programmes in patients with CVD. The EUROACTION trial used a 16-week family centred approach that led to healthier lifestyle changes in activity and diet, and more effective control of risk factors in patients and their partners compared to usual care.[554] The Randomised Evaluation of Secondary Prevention by Outpatient Nurse Specialists (RESPONSE) trial randomized patients after ACS to usual care or to nurse-coordinated prevention intervention of outpatient visits over 6 months: at 1 year patients in the intervention group had better control of risk factor, fewer readmissions and emergency department visits, and a predicted relative risk of mortality (using SCORE) 17% lower than the control group.[565]

4a.1.4 Alternative rehabilitation models

Key message

- Home-based rehabilitation with and without tele-monitoring holds promise for increasing participation and supporting behavioural change.

CR has predominantly been implemented in hospitals or in community centres with trained staff. Home-based rehabilitation programmes have the potential to increase patient participation by offering greater flexibility and options for activities. A systematic review of 12 trials (*n* = 1978 patients) of home versus centre-based rehabilitation found no difference in outcomes, adherence or in cost between the two in the short-term and up to 24 months.[570] The majority of studies recruited low-risk, predominantly male patients and activities were self-regulated with intermittent support usually by telephone. Home-based rehabilitation thus offers an alternative for some patients, although relatively few programmes in Europe offer it.[567].

4a.1.4.1 Tele-rehabilitation

Tele-rehabilitation, i.e. the use of electronic communication and information technologies to provide and support remote clinical care after an acute event, has been found more effective than usual care in achieving behavioural change, and as equally effective as a CR

programme.[561, 571] Simple tele-monitoring including ECG transmission by telephone in patients with CVD has been found to be safe and acceptable to patients, and to result in improvements in physical capacity.[572] Recent studies are also using smartphone applications for monitoring and delivery of content and support with improvements in uptake, adherence and completion of rehabilitation in younger patients.[573]
Thus tele-rehabilitation could further widen participation to more patients, and provide monitoring and greater individualized behavioural support, but large-scale randomized trials are needed.

4a.1.5 Maintaining lifestyle changes

Maintaining healthy behaviours after a specialized prevention programme is problematic for many patients.
Specialized prevention programmes and patient consultations should use a patient-centred approach that focuses on the patient's priorities and goals and incorporates lifestyle changes within the context of the patient's life. Behavioural change of personal value to the individual is more likely to be maintained (see section 3a.1).
Longer term support for behaviour change may be needed and community maintenance programmes may be useful. In the Global Secondary Prevention Strategies to Limit Event Recurrence After MI (GOSPEL) trial, 3241 patients were randomized post-CR programme to an intensive multi-factorial intervention over 3 years, or usual care. Patients in the intervention group received monthly exercise and counselling sessions for 6 months, then every 6 months for 3 years. Compared to usual care, the intervention group had improved PA, diet, and total cholesterol maintained throughout the study. The intervention significantly decreased several combined end points, such as CV mortality plus non-fatal MI and stroke by 33%, cardiac death plus non-fatal MI by 36%, and non-fatal MI by 48% compared to usual care [574].

Gaps in evidence

- The optimal CR programme in the era of modern cardiology, and the incremental benefits of various components of CR programmes, especially for under-served patient groups.
- Alternative and cost-effective models of CR are needed to ensure participation globally, including low and middle-income countries.

4a.2 How to monitor preventive activities

Key message

- Standards of performance in CVD prevention may serve as vehicles to accelerate appropriate translation of scientific evidence into clinical practice.

Recommendation for monitoring preventive strategies

Recommendation	Class[a]	Level[b]
Systematically monitoring the process of delivery of cardiovascular disease prevention activities as well as outcomes may be considered.	IIb	C

[a]Class of recommendation.
[b]Level of evidence.

Candidates for measures of performance are some of those processes of care that are recommended by the Guideline either as Class I, which identifies recommended procedures/treatments, or Class III, which identifies procedures/treatments that are not recommended.

The development of standards of performance involves identification of a set of measures that target a specific patient population observed over a particular time period. Thus, these performance measures are aimed at any clinician or healthcare professional who sees adult subjects (age 18 years and older) at risk for CVD. Table 18 provides examples of prevention of CVD performance measurement. Detailed specification for each performance measure including the numerator, denominator, period of assessment, method of reporting, and sources of data, should be developed at the local level. An optimal target of 100% is recommended for all standards. If this is not achievable an interim local target could be set.

Table 18 Examples of prevention of cardiovascular disease performance measurement

• Subjects identified as tobacco users who received cessation intervention.
• Subjects for whom sedentary habits have been recorded and are counselled to increase PA.
• Subjects for whom unhealthy diet/nutritional habits have been recorded and are counselled to improve diet.
• Subjects for whom weight and BMI and/or waist circumference is documented above normal limits and are counselled on weight management.
• Subjects >40 years old with at least one lipid profile performed within the past 5 years.
• Patients <60 years old and with hypertension (not DM) who had a recorded BP reading at their most recent visit of <140/90 mm Hg
• Patients with DM who had a recorded HbA1c <7.0% (<53 mmol/mol) at the most recent visit.
• Patients with a qualifying event/diagnosis who have been referred to an in-patient CR or out-patient CR programme before hospital discharge.

BMI = body mass index; BP = blood pressure; CR = cardiac rehabilitation; HbA1c = glycated haemoglobin; PA = physical activity.

4b. Where to intervene at the population level

Key message

- Governmental and non-governmental organisations (NGOs) such as heart foundations and other health promoting organisations can be a powerful force in promoting a healthy lifestyle and healthy environments in CVD prevention.

4b.1 Government and public health

Recommendations for population-based interventions to promote CV health are described in section 3c. These preventive strategies to address unhealthy diets, smoking and physical inactivity must take place at different levels. At each level, different clusters of stakeholders are concerned and responsible for the interventions[498]:

- International level (e.g. WHO, World Trade Organization, EU);
- National level (e.g. government departments, health authorities, health promoting agencies, consumer organizations, health NGOs, industries);
- Regional and local level (e.g. local governmental departments, communities, schools, workplaces, health professionals, catering sector, retailers, NGOs).

At the EU level as well as at the level of national governments, legislation should be developed on, for example, the nutritional composition of foods, nutrition labelling, smoke-free policies and environments, restrictions on marketing of unhealthy foods, alcohol and

tobacco products, and environments that encourage PA in everyday life.[312] Also policy measures to reduce air pollution should be developed. Both levels also may use economic instruments like taxes and subsidies to support strategies on food and nutrition, tobacco and alcohol. It is not necessarily exclusively the responsibility of governments to ensure the availability of and accessibility to PA opportunities and healthy foods: this should be a joint effort by government, industry and businesses. Health authorities should monitor improvements and if voluntary efforts by the industry prove inadequate, governments must intervene.

4b.2 Non-governmental organizations

NGOs are important partners to healthcare workers in promoting CV prevention and advocates for the development and maintenance of public health policies.

Several Brussels based NGOs aim at improving CV health of the public and patients, including EHN, health and medical professionals (ESC, European Chronic Disease Alliance (ECDA), and consumer organizations (Bureau Européen des Unions de Consummateurs (BEUC).

CV patients' organizations provide their patient members with the opportunity to obtain support from their peers. They produce patient information in the form of booklets and web-based materials and promote CR.

Stakeholders such as NGOs and health professionals (e.g. cardiologists, internists and GPs) have a responsibility in agenda setting and monitoring interventions, and can initiate mass media campaigns to improve health.

In creating healthy and active environments, especially in schools, workplaces and the community, stakeholders such as teachers and parent organizations, the catering sector, employers organizations, trade unions, sport clubs and fitness centres, organizations promoting cycling, walking, public transport, or involved in urban planning and mobility, can play a role. An example is the French EPODE-project aimed at reducing overweight in children [505].

Figure list

1. SCORE chart: 10-year risk of fatal CVD in populations at **high** CVD risk based on the following risk factors: age, sex, smoking, systolic blood pressure, total cholesterol. CVD = cardiovascular disease; SCORE = Systematic Coronary Risk Estimation.
2. SCORE Chart: 10-year risk of fatal CVD in populations at **low** CVD risk based on the following risk factors: age, sex, smoking, systolic blood pressure, total cholesterol. CVD = cardiovascular disease; SCORE = Systematic Coronary Risk Estimation.
3. Relative risk chart. Conversion of cholesterol: mmol/L➔ mg/dL: 8 = 310, 7 = 270, 6 = 230, 5 = 190, 4 = 155.
4. SCORE chart (for use in high risk European regions) illustrating how the approximate risk age can be read off the chart. SCORE = Systematic Coronary Risk Estimation.

Web Figures

A. Predicted vascular deaths avoided over 5 years from reductions in LDL-C with statin treatment at different levels of CVD risks

B. Lifetime risk calculator based on the JBS3 web-based tool

C. Modified World Health Organization (WHO) smoking cessation algorithm.

D. How can governments support healthy food preferences?

Table list

Web Table

Abbreviation list

ABI	ankle–brachial (blood pressure) index
ABPM	ambulatory blood pressure monitoring
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE-I	angiotensin-converting enzyme inhibitor
ACS	acute coronary syndromes
ADVANCE	Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation
AF	atrial fibrillation
AMI	acute myocardial infarction
apoA1	apolipoprotein A1
apoB	apolipoprotein B
ARB	angiotensin receptor blocker
BEUC	Bureau Européen des Unions de Consummateurs
BMI	body mass index (weight(kg)/height(m^2)
BP	blood pressure
CAC	coronary artery calcium
CAD	coronary artery disease
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk for Ischaemic Events
CARDS	Collaborative Atorvastatin Diabetes Study
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilisation, Management, and Avoidance
CI	confidence interval
CKD	chronic kidney disease
CR	cardiac rehabilitation
CT	computed tomography
CTT	Cholesterol Treatment Trialists' Collaboration
CURE	Clopidogrel vs. Placebo in Patients with ACS without ST-segment elevation
CV	cardiovascular
CVD	cardiovascular disease
DALYs	disability-adjusted life years
DASH	Dietary Approaches to Stop Hypertension
DBP	diastolic blood pressure
DCCT	Diabetes Control and Complications Trial
DHA	docosahexaenoic acid
DM	diabetes mellitus
DPP-4	dipeptidyl peptidase-4 inhibitors
eGFR	estimated glomerular filtration rate
ECDA	European Chronic Disease Alliance
ECG	electrocardiogram
ED	erectile dysfunction
EHN	European Heart Network
EMA	European Medicines Agency

EPA	eicosapentaenoic acid
EPIC	European Prospective Investigation into Cancer and Nutrition
EPODE	Ensemble Prévenons l'Obésité des Enfants
ESC	European Society of Cardiology
EU	European Union
FDA	Food and Drug Administration (USA)
FDC	fixed dose combination
FH	familial hypercholesterolaemia
GLP-1	glucagon-like peptide 1
GP	general practitioner
GOSPEL	Global Secondary Prevention Strategies to Limit Event Recurrence After Myocardial Infarction
HbA1c	glycated haemoglobin
HBPM	home blood pressure measurements
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HF-ACTION	Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training
HOPE	Heart Outcomes Prevention Evaluation
HPS	Heart Protection Study
HRQoL	health-related quality of life
HR	heart rate
hsCRP	high-sensitivity C-reactive protein
HYVET	Hypertension in the Very Elderly Trial
ICD	International Classification of Diseases
IMT	intima–media thickness
INVEST	International Verapamil-Trandolapril Study
LDL-C	low-density lipoprotein cholesterol
Lp(a)	lipoprotein(a)
LV	left ventricle/left ventricular
LVH	left ventricular hypertrophy
MET	metabolic equivalent
MHO	metabolically healthy overweight/obesity
MI	myocardial infarction
MUFA	monounsaturated fatty acids
NGO	non-governmental organization
NHS	National Health Service (UK)
NICE	National Institute for Health and Care Excellence
NNT	number needed to treat
NRI	net reclassification index
NRT	nicotine replacement therapy
OASIS	Organization to Assess Strategies in Acute Ischemic Syndromes
ONTARGET	ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial
OSAS	obstructive sleep apnoea syndrome
PA	physical activity

PAD	peripheral artery disease
PLATO	Ticagrelor vs. Clopidogrel in Patients with ACS with and without ST-segment elevation
PCOS	polycystic ovary syndrome
PCSK9	proprotein convertase subtilisin/kexin type 9
PROactive	Prospective Pioglitazone Clinical Trial in Macrovascular Events
PROGRESS	Perindopril Protection Against Recurrent Stroke Study
PROCAM	Prospective Cardiovascular Munster Study
PWV	pulse wave velocity
RA	rheumatoid arthritis
RCT	randomized controlled trial
RESPONSE	Randomised Evaluation of Secondary Prevention by Outpatient Nurse Specialists
RM	repetition maximum
ROS	reactive oxygen species
RPE	rating of perceived exertion
RR	relative risk
SBP	systolic blood pressure
SGLT2	Sodium-glucose co-transporter-2
SNP	single nucleotide polymorphism
SCORE	Systematic Coronary Risk Estimation
SPARCL	Stroke Prevention by Aggressive Reduction in Cholesterol Levels
TIA	transient ischaemic attack
TRITON	Prasugrel vs. Clopidogrel in Patients with ACS
UKPDS	United Kingdom Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial
VALUE	Valsartan Antihypertensive Long-Term Use Evaluation
VLDL	very low-density lipoprotein
$\dot{V}O_2$	oxygen uptake
WHO	World Health Organization

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2016 European Guidelines on cardiovascular disease prevention in clinical practice – Web addenda

The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice

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Web Contents

3b. How to intervene at the individual level: disease specific intervention. Atrial fibrillation, coronary artery disease, chronic heart failure, cerebrovascular disease, peripheral artery disease

3b.1 Atrial Fibrillation

Key message

- Hypertension in atrial fibrillation (AF) patients doubles risk of cardiovascular complications and must be treated in all grades

Recommendations for atrial fibrillation

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended to assess stroke risk by CHA_2DS_2-VASc score or $CHADS_2$ score, bleeding risk (HAS-BLED) and consider antithrombotic therapy	I	A	(1, 2)
In patients ≥ 65 years or diabetes screening by pulse palpation, followed by ECG if irregular pulse, to detect atrial fibrillation is recommended	I	B	(1, 2)

ECG = electrocardiogram.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

3b.1.1 Prevention of cardiovascular complication in atrial fibrillation

AF is the most common arrhythmia with an estimated lifetime risk of 25%. AF is associated with increased risk of death, stroke, heart failure (HF), thromboembolism, cognitive dysfunction, hospitalizations and reduced quality of life.(3) AF is associated with about a two-fold increased risk of AMI. Twenty per cent of strokes are caused by AF and the stroke risk is about 60% higher in women than in men. AF can be readily detected. It is recommended that in patients 65 years or older or in diabetes, opportunistic screening by pulse palpation for at least 30 seconds is performed, followed by an ECG in those with an irregular pulse.(1, 2)

Management of AF patients is aimed at preventing severe CVD complications associated with AF and relies on antithrombotic therapy with vitamin K antagonist therapy or non-vitamin K antagonist oral anticoagulants. Recommendations for antithrombotic therapy should be based on risk factors for stroke and thromboembolism in addition to risk of bleeding. Stroke risk assessment with the CHA_2DS_2-VASc score or $CHADS_2$ score include the most common stroke risk factors. A bleeding risk assessment with HAS-BLED score is recommended for all AF patients. Residual high risk of death in anticoagulated AF patients remains a CVD prevention issue. Regarding rate and rhythm control in AF patients, we refer to the Guidelines for the Management of Atrial Fibrillation.(1, 2)

3b.1.2 Prevention of cardiovascular disease risk factors in atrial fibrillation patients

Many classic CVD risk factors are risk factors for AF, particularly age, smoking, sedentary habits, obesity, hypertension and diabetes.(4) Hypertension and AF often coexist and lead to doubling of all

CVD complications and mortality in AF patients. Other clinical conditions associated with AF occurrence are hyperthyroidism, obstructive sleep apnoea, chronic kidney disease, inflammation, uric acid, major surgery, alcohol and coffee consumption, high endurance physical activity.(3) BP measurement in AF patients should be performed with a standard auscultatory BP monitor, because automated BP monitors are inaccurate in measuring BP in AF patients. Antihypertensive treatment may contribute to reduce the risk in these high risk patients, in addition to antithrombotic therapy. The main goal is BP reduction per se, and there is insufficient data to recommend specific drugs. (5) However, ACE-I and ARBs should be considered first choice in AF patients,(1) followed by beta-blockers and mineralocorticoid antagonists. Obesity and diabetes in AF patients increase CVD risk by creating a pro-thrombotic state. Diabetes is included in the score for stroke risk assessment, while obesity is not. It is not known which obesity intervention is most cost effective in AF patients. Lifestyle risk interventions in AF patients have largely targeted physical activity which should probably be encouraged, but studies have not shown the effect of physical activity on CVD in AF patients.(6) Presence of ischaemic heart disease and smoking increases the CVD risk despite antithrombotic therapy. Smoking cessation is therefore crucial. Less evidence is available on the effects of statins on major CVD outcomes in AF patients. These patients should be treated according to the SCORE recommendations and not merely because they have AF.

3b.1.3 Lone atrial fibrillation

In AF subjects < 65 years, without heart disease or hypertension (“lone AF”) and without risk factors implying antithrombotic therapy, AF is not associated with increased risk of stroke or death and antithrombotic therapy is not recommended. Lone AF is a diagnosis of exclusion. The risk of stroke in young patients with lone AF increases with advancing age or development of hypertension, underlining the importance of regular re-assessment of risk factors over time. (1, 2)

3b.2 Coronary artery disease

Key message

- Prevention is crucial for short- and long-term outcome in CAD, and it should be started as soon as possible, with a multidimensional approach that combines feasibility and efficacy. An appropriate discharge planning should be considered.

Recommendations for managing coronary artery disease

	Recommendations	Class[a]	Level[b]	Ref[c]
Patient assessment	Clinical history taking, including the conventional risk factors for the development of CAD (such as for example glycaemic state) with revision of the clinical course (uncomplicated or complicated) of ACS is recommended.	I	A	(7-9)
	Physical examination is recommended,	I	C	(9)
	The ECG is predictive of early risk: It is recommended to obtain a 12-lead ECG and to have it interpreted by an experienced physician. It is recommended to obtain an	I	B	(9-11)

	additional 12-lead ECG in case of recurrent symptoms or diagnostic uncertainty.			
	Additional ECG leads (V3R, V4R, V7–V9) are recommended if on-going ischemia is suspected when standard leads are inconclusive.	I	C	
	A resting transthoracic echocardiogram is recommended in all patients for: a) exclusion of alternative causes of angina; b) regional wall motion abnormalities suggestive of CAD; c) measurement of LVEF for d) evaluation of diastolic function.	I	B	(9-11)
	Chest X-ray should be considered in patients with suspected heart failure.	IIa	C	
	Arrhythmic burden assessment (ventricular arrhythmias, AF and other supraventricular tachy-arrhythmias, and bradycardia, AV block, and intra-ventricular conduction defects) is recommended.	I	A	(7-9, 12, 13)
	Ambulatory monitoring should be considered in patients in whom arrhythmias are suspected	IIa	C	
	Exercise stress testing should be considered to evaluate the efficacy of medical treatment or after revascularization, or to assist prescription of exercise after control of symptoms.	IIa	B	(9, 14)
	Exercise capacity and ischaemic threshold assessment should be considered by exercise maximal stress test (ergospirometry if available) to plan the exercise training programme.	IIa	B	(9, 14)
	An imaging stress test is recommended in patients with resting ECG abnormalities which prevent accurate interpretation of ECG changes during stress.	I	B	(13)
	An imaging stress test should be considered to assess the functional severity of intermediate lesions on coronary arteriography.	IIa	B	(13)
Physical activity counselling	In the presence of exercise capacity > 5 METs without symptoms, return to routine physical activity is recommended; otherwise, the patient should resume physical activity at 50% of maximal exercise capacity and gradually increase. Physical activity should be a combination of activities like walking, climbing stairs, cycling and supervised medically prescribed aerobic exercise training.	I	B	(9, 15, 16)
Exercise training	In low risk patients, at least 2 hours/week aerobic exercise at 55–70% of the maximum work load (METs) or heart rate at	I	B	(9, 17-

	the onset of symptoms (≥ 1500 kcal/week) are recommended. In moderate to high risk patients, an individualised programme is recommended, that starts with < 50% maximum workload (METs), resistance exercise at least 1 hour/week, 10 – 15 repetitions per set to moderate fatigue . *(refer also to section 3a.3).*			19)
Diet / nutritional counselling	Caloric intake is recommended to be balanced by energy expenditure (physical activity) to achieve and maintain healthy BMI Diet poor in cholesterol and saturated fat is recommended. *(refer also to section 3a.5).*	I	C	(9, 15, 20)
Weight control management	Normal-weight CAD patients should be advised to avoid weight gain. On each patient visit, it is recommended to consistently encourage weight control through an appropriate balance of physical activity, caloric intake, and formal behavioural programmes when indicated to achieve and maintain a healthy BMI If waist circumference is ≥ 80 cm in women or ≥ 94 cm in men, it is recommended to initiate lifestyle changes and consider treatment strategies as indicated *(refer also to section 3a.6).*	I	B	(9, 15, 20-23)
Lipid management	According to lipid profile, statin therapy is recommended. *(refer also to section 3a.7)*	I	B	(9, 20, 21)
	Annual control of lipids, glucose metabolism and creatinine are recommended.	I	C	
BP monitoring	A structured approach is recommended *(refer to section 3a.9).*	I	B	(9, 20, 24)
Smoking cessation	A structured approach is recommended *(refer to section 3a.4).*	I	B	(9, 20)
Psychosocial management	Psychosocial risk factor screening should be considered (refer to *section* 2.4.2)	IIa	B	(9, 16, 20)
	Multimodal behavioural interventions is recommended (refer to *section* 3a.2)	I	A	(9, 16, 20)

ACS = acute coronary syndrome; BMI = body mass index; BP = blood pressure; LVEF = left ventricular ejection fraction; MET = metabolic equivalent; PCI – percutaneous coronary intervention.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Acute manifestation of CAD, associated complications and successive management and surveillance should be administered according to guidelines. (7, 8, 10-14, 25) Beyond that, survivors need a structured support to restore their quality of life and to maintain or improve functional capacity.(20) A comprehensive professional lifestyle intervention based on behavioural models of change with different strategies, from the more basic, family-based to the more structured and complex modalities, according to CV risk assessment and concomitant diseases, is recommended. (9, 10, 20). Risk factor management in terms of effective risk factor control, physical activity advice, psychosocial supports and appropriate prescription of and adherence to cardio-protective drugs are integral parts,(15-17, 21-24, 26, 27) to help patients regain as full a life as possible. In short, CAD patients are at high risk and preventive measures are keystone.

The prescription and adherence to behavioural recommendations in the immediate post-event care of CAD patients should have as high a priority as other preventive medications and invasive strategies, and justify an investment in establishing programmes that systematically enhance early lifestyle modification and prevention. In a large cohort of CAD patients from several countries enrolled in the Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS) 5 randomized clinical trial,(26) adherence to behavioural advice (diet, physical activity, and smoking cessation) after acute manifestation of CAD was associated with a substantially lower risk of recurrence. Benefits were seen early (< 6 months), and each behaviour modification was additive. Hence, clinical assessment, risk factor control and behavioural policies should start as soon as possible, in the acute setting . Unfortunately, large proportions of patients still do not achieve the lifestyle, risk factor, and therapeutic targets,(28) and attendance at preventive programmes is still low.(29) To properly connect the acute and post-acute phase and to favour continuity of care and prevention, the discharge planning is fundamental, as it selects and arranges the best next care setting and healthcare services, promotes patient and family preventive and education issues, and organizes follow-up. A dedicated discharge letter can contribute to implementation(30): beyond primary and secondary diagnosis, procedures and clinical progress description, preventive concepts and recommendations oriented to general and individual risk factor control, lifestyle intervention, medicine reconciliation, and follow-up arrangements should be clearly announced.

Gaps in evidence

- Although in CAD patients, prevention strategies have been demonstrated in observational studies, the best comprehensive tactic, setting and timing **are** still to be defined.

3b.3 Chronic heart failure

Key message

- CVD prevention in HF patients should start as soon as possible, and requires a multi-faceted integrated tactic.

5984 **Recommendations for chronic heart failure**

	Recommendations	Class[a]	Level[b]	Ref[c]
	The control of fluid status throughout the assessment of symptoms and signs is recommended	I	B	(11, 31)
Patient assessment	Identification of precipitating CV and non-CV factors is recommended.	I	B	(11, 31, 32)
	Transthoracic echocardiography is the method of choice for assessment of myocardial systolic and diastolic function of both left and right ventricles.	I	A	(11,31, 33)
	12-lead ECG is recommended in all patients with HF in order to determine heart rhythm, heart rate, QRS morphology and duration, and to detect other relevant abnormalities. This information is needed to plan and monitor treatment.	I	C	
	The following diagnostic tests are recommended for initial assessment of a patient with newly diagnosed HF in order to evaluate the patient‘s suitability for particular therapies, to detect reversible/treatable causes of HF and co-morbidities interfering with HF: blood testing (natriuretic peptides, complete blood count -haemoglobin/hematocrit, WBC and platelet counts- potassium, sodium- creatinine -with estimated GFR-, C-reactive protein, uric acid, liver function tests fasting glucose, HbA1c, fasting lipid profile, TSH, ferritin, TSAT = iron/TIBC),	I	B	(11, 31, 33)
	Additional laboratory tests should be considered in patients admitted due to acute HF based on clinical indications	IIa	C	
	Chest radiograph (X-ray) is recommended in patients with HF to detect/exclude alternative pulmonary or other diseases, which may contribute to dyspnoea. It may also identify pulmonary congestion/oedema and is more useful in patients with suspected HF in the acute setting.	I	C	
	Exercise testing (ergospirometry if available) should be considered in patients with HF to prescribe adequate exercise training program and to discriminate the origin of unexplained dyspnea	IIa	C	(34)
	Exercise testing (ergospirometry if available) may be considered in patients with HF to detect reversible myocardial ischaemia	IIb	C	33
	Exercise testing (ergospirometry if available) is recommended in patients with HF as a part of the evaluation of patients for heart transplantation and/or	I	C	

	mechanical circulatory support			
	Other imaging and non- imaging diagnostic tests should be considered in selected clinical situations.	IIa	B	(11, 31, 32)
Physical activity counselling is recommended.		I	B	(11, 31, 32),
Exercise training	Aerobic exercise training is recommended.	I	A	(35, 36)
	High intensity interval training may be considered in selected patients.	IIb	B	(37)
	Respiratory training should be considered.	IIa	B	(17, 38)
	Resistance training may be considered.	IIb	C	(17, 38)
Weight control, cachexia and obesity management is recommended *(refer also to section 3a.6).*		I	C	(11, 31, 32)
Diet/nutritional counselling should be considered *(refer also to section 3a.5).*		IIa	C	(11, 31, 32)
Psychosocial management	Psychosocial screening should be considered (*refer to section 2.4.2*)	IIa	C	(11, 31, 32)
	Psychosocial management is recommended (*refer to section 3a.2*)	I	A	(11, 31, 32)
Self-care management should be considered.		IIa	B	(11, 32)
Home care monitoring should be considered.		IIa	B	(11, 32)

CV = cardiovascular. HbA1c = glycated haemoglobin; HF=heart failure;; TIBC = total iron-binding capacity; TSAT = transferrin saturation; TSH = thyroid-stimulating hormone; WBC=white blood cells.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

HF is a common, disabling and deadly disease, that leads to frequent hospital admissions due to CV events (39): HF patients are at high risk, and they deserve special attention throughout a multifaceted and multidisciplinary intervention, to start as soon as possible during (26) and after (31) hospital admission in order to develop a life-long structured prevention course. In-hospital, clinical management and risk assessment are decisive,(11, 32) and selection of a test in daily practice should consider availability, local expertise, advantages/disadvantages, and, in the case of several questions to address, which test could best answer several of them. CV prevention extends also to physical activity counselling, psychological support, and patient/caregiver management education. (31) Clinical stage may impact recommendations for preventive measures, as advanced HF might be associated with low BP and lipid profile, concomitant CV and non-cardiovascular diseases (such as atrial fibrillation,

ventricular arrhythmia, non-revascularizable CAD, previous stroke/TIA, diabetes, anaemia, iron deficiency, COPD, renal failure, liver dysfunction, sleep apnoea, cognitive impairment, depression, *etc*), and future strategies (device therapy, heart transplantation and mechanical circulatory support) that advocate specialized interventions.(11)

Although congestion management is critical to improving symptoms and readmission risk, management extends beyond diuresis alone, and prevention of adverse CV events requires reducing cardiac injury, inhibiting maladaptive systemic responses, and controlling relevant co-morbidities. Lifesaving HF therapies should be prescribed as recommended. (11) While the patient's condition and clinical progress are informative, monitoring systems that rely less on patient input are attractive.(40) Since most readmissions for HF exacerbations are attributable, at least in part, to poor self-care, non-adherence to medications and diet counsels, and failure to act upon escalating symptoms, effective self-care is essential for CV prevention. (41)

Before leaving the hospital, several issues should be considered, and discussed with the patient and carers. A discharge plan should be organized to build up an appropriate management strategy aiming to prevent CV readmissions: congestion should be absent and a stable oral diuretic regimen established for at least 48 hours (11). Long-term disease-modifying therapy should be optimized as much as possible and appropriate education provided to the patient and family/caregivers. Pre- and post-discharge management should follow the standards of care and goals of treatment suggested by ESC guidelines.(11)

Exercise training (ET) should be prescribed in out-patients as a fundamental preventive action in stable HF. (35, 36) Since HF patients experience exercise intolerance due to several maladaptive changes even on optimal HF medical therapy, (42, 43) exercise training dominates symptoms and impacts outcome. The HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial showed a 7% reduction in all-cause mortality and all-cause hospitalization, even after adjustment for pre-specified predictors of mortality. (36) However, adherence is crucial (44) and exercise intensity should be a balance between efficacy and safety. (45) ET protocols vary in most trials (see also section 3a.3), even though moderate-vigorous intensity exercise (50–60% peak $\dot{V}O_2$) is frequently employed, leading to an average 17% improvement in peak oxygen consumption. (46) In selected stable patients, "high intensity interval training" may yield even greater improvements in peak $\dot{V}O_2$.(37) Before commencing any ET programme, clinical stability and functional evaluations are warranted (17, 38), and a comprehensive flowchart has been proposed.(38)

Prevention recommendations and intervention modalities in HF with preserved left ventricular ejection fraction HF are similar to that of HF with reduced ejection fraction; in particular exercise training therapy has shown to be effective as should be recommended. (47-49)

Gaps in evidence

- Biomarkers may guide therapy in HF hospitalized patients, but further evidence is needed.

3b.4 Cerebrovascular disease

Key message

- CV risk management in patients with previous TIA or ischaemic stroke is generally comparable to that in patients with other ischaemic complications of atherosclerosis. However, treatments may differ between stroke types (ischaemic stroke, intracerebral haemorrhage, subarachnoid haemorrhage, or cerebral venous sinus thrombosis) and causes.

Recommendations for cerebrovascular disease

Recommendations	Class[a]	Level[b]	Ref[c]
In patients with TIA or stroke, it is recommended to investigate the cause of the event and a cardiovascular disease prevention program tailored to type and cause of stroke (specific guidelines are available).	I	A	(2, 50-53)

TIA = transient ischaemic attack.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

CV risk management in patients with previous TIA or ischaemic stroke is generally comparable to that in patients with other ischaemic complications of atherosclerosis. However, treatment may differ between stroke types (ischaemic stroke, intracerebral haemorrhage, subarachnoid haemorrhage, or cerebral venous sinus thrombosis) and causes (e.g., cardio-embolism, large artery atherosclerosis, or small vessel disease as the most important of many potential causes of ischaemic stroke). Details can be found in recent practice guidelines. (2, 50-53) This paragraph will discuss some aspects specific to patients with TIA or stroke.

In patients with TIA or stroke included in the randomised HPS or SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trials, either 40 mg of simvastatin or 80 mg of atorvastatin reduced the long-term risk of major CV events, but only atorvastatin reduced the risk of recurrent stroke. (54, 55) Most of the included patients had had an ischaemic brain event, and the number of patients with prior intracerebral or subarachnoid haemorrhage included in statin trials was too small to recommend either starting a statin or to withdraw any statin the patient is using at the time of the haemorrhage.(51) This also applies to patients with TIA or ischaemic stroke of cardioembolic origin. Despite earlier suggestions of the opposite, there is no evidence that the use of statins is associated with an increased risk of intracerebral haemorrhage.(56) There are insufficient data on the effects of other statins or other cholesterol-lowering treatments in patients with TIA or stroke, and there are also no relevant data supporting the benefit of aiming for a specific LDL-C target in this population.(50)

Starting BP reduction in the first 48 hours after stroke onset generally does not improve outcome, (57, 58) probably except in patients who had a spontaneous intracerebral haemorrhage within the previous 6 hours and who have a systolic blood pressure of 150 mm Hg or above. In these patients, intensive blood pressure lowering (with a target systolic level of <140 mm Hg reached within 1 hour) likely has a modest benefit. (59)

In patients with stroke or TIA that has occurred more than 1 week earlier, the use of BP-lowering drugs reduces the risk of CAD or (recurrent) stroke. (60) The optimal drug regimen in this population is uncertain because just a few strategies have been tested in sufficiently large trials. The evidence of

benefit is largest for diuretics alone or diuretics in combination with an ACE-I (50, 61) . In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), the relative reduction in the risk of recurrent stroke with the combination of indapamide and perindopril was independent of the baseline BP (62) and the risk reduction was larger with larger reductions in SBP. (63) However, data are limited and the evidence is not conclusive. For this reason, it appears reasonable to base the choice of a specific drug and BP target on individual patient characteristics as described elsewhere in this guideline.

In patients with TIA or ischaemic stroke of presumed atherosclerotic origin, the combination of aspirin 30–300 mg daily and dipyridamole 200 mg twice daily is associated with a larger reduction in the risk of a major CV event than aspirin alone. (64) Clopidogrel 75 mg once daily is as effective as the combination of aspirin and dipyridamole, but is associated with fewer side effects. (65) Patients with TIA or ischaemic stroke of presumed cardioembolic origin or stenosis of the carotid or vertebral artery should be treated according to the relevant guidelines. (2, 50)

There is a marked lack of evidence on CVD prevention in patients with unruptured intracranial aneurysms and on secondary prevention after intracerebral haemorrhage during treatment with oral anticoagulation or subarachnoid haemorrhage, and randomized trials for these conditions are warranted.

Gaps in evidence

- For patients with cryptogenic stroke, it is uncertain whether non-vitamin K antagonist oral anticoagulants reduce the risk of future CV events more than antiplatelet drugs.
- The optimal secondary prevention strategy after subarachnoid haemorrhage is uncertain.

3b.5 Peripheral artery disease

Key message

- PAD is asymptomatic in a large cohort of patients.
- Preventive treatment is identical with coronary and carotid prevention treatment, but specific studies for PAD population and specific treatment targets are lacking

Recommendations for peripheral artery disease

Recommendations	Class[a]	Level[b]	Ref[c]
In all PAD patients BP values controlled to values below 140/90 mmHg are recommended.	I	A	(66-68)
Antiplatelet therapy is recommended	I	A	(69)
Statin therapy is recommended	I	A	(70)
ACE-I therapy is recommended in patients with symptomatic PAD in patients with hypertension.	I	A	(66)
Exercise training is recommended in all patients with PAD	I	A	(71)

It is recommended that all patients with PAD who smoke should be advised to stop smoking.	I	B	(72)
ACE-I therapy is should be considered in patients with symptomatic PAD without hypertension.	IIa	A	(66)
Beta-blockers should be considered	IIa	B	(73)

ACE-I = Ace-inhibitors; BP = blood pressure; CAD = coronary artery disease; LDL-C = low-density lipoprotein cholesterol; PAD = peripheral artery disease.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

The primary non-invasive test for the diagnosis of lower extremity PAD is the ankle–brachial index (ABI). In healthy persons, the ABI is > 1.0. Usually an ABI < 0.90 is used to define PAD. The actual sensitivity and specificity have been estimated, respectively, at 79% and 96% (74). For diagnosis in primary care, an ABI < 0.8 or the mean of three ABIs < 0.90 had a positive predictive value of ≥ 95%; an ABI > 1.10 or the mean of three ABIs > 1.00 had a negative predictive value of ≥ 99% (75).

The German Epidemiologic Trial on Ankle Brachial Index Study Group included 6880 patients ≥ 65 years of age and demonstrated that 21% of the cohort had either asymptomatic or symptomatic PAD (76).

The level of ABI also correlates with PAD severity, with high risk of amputation when the ABI is < 0.50. An ABI change > 0.15 is generally required to consider worsening of limb perfusion over time, or improving limb perfusion after revascularization.

Smoking is an important risk factor for PAD. In the general population smoking increased the risk of PAD between two- and six-fold (72).

Statins reduce the risk of mortality, CV events, and stroke in patients with PAD with and without CAD (70). The Antithrombotic Trialists' Collaboration meta-analysis (69) combined data from 42 randomized studies of 9706 patients with intermittent claudication and/or peripheral arterial bypass or angioplasty. The incidence of vascular death, non-fatal MI, and non-fatal stroke at follow-up was significantly decreased, by 23%, by antiplatelet drugs with respect to placebo. The efficacy of clopidogrel compared with aspirin was studied in the randomized Clopidogrel versus Aspirin in Patients at Risk for Ischaemic Events (CAPRIE) trial, including a subgroup of 6452 patients with PAD.(77) At 1.9-years follow-up, the annual combined incidence of vascular death, non-fatal MI, and non-fatal stroke in the PAD group was 3.7% and 4.9%, respectively, in the clopidogrel and aspirin groups, with a significant 23.8% decrease with clopidogrel, with no major differences in terms of safety .

Treatment with ACE-I has shown a beneficial effect beyond a BP decrease in high-risk groups. In the Heart Outcomes Prevention Evaluation (HOPE) trial, ramipril significantly reduced cardiovascular events by 25% in patients with symptomatic PAD without known low ejection fraction or heart failure. (66) The ONTARGET trial showed equivalence of telmisartan to ramipril in these patients (67).

Importantly, beta-blockers are not contraindicated in patients with PAD. A meta-analysis of 11 randomized controlled studies found that beta-blockers did not adversely affect walking capacity or symptoms of intermittent claudication in patients with mild to moderate PAD(73).

Symptoms can be treated conservatively or invasively. In patients with PAD, training therapy is effective in improving symptoms and increasing exercise capacity. In meta-analyses (71) compared with usual

care or placebo, exercise significantly improved maximal walking time, with an overall improvement in walking ability. The types of exercise varied from strength training to polestriding and upper or lower limb exercises, generally supervised sessions, at least twice a week. Cilostazol, naftidrofuryl and pentoxyfilline improve pain-free distanc. For other options please refer to ESC Guidelines on the diagnosis and treatment of peripheral arterial disease.(70)

Gaps in evidence

- There are few studies specific for the PAD population. Most of the data comes from CAD patients with concomitant PAD. More specific data on the PAD population are needed

Web Figures

A. Predicted vascular deaths avoided over 5 years from reductions in LDL-C with statin treatment at different levels of CVD risks [Jackson R, Kerr A, Wells S. Vascular risk calculators essential but flawed clinical tools? Circulation. 2013 May 14;127(19):1929-31]

B. Lifetime risk calculator based on the JBS3 web-based tool

C. Modified World Health Organization (WHO) smoking cessation algorithm.

D. How can governments support healthy food preferences?

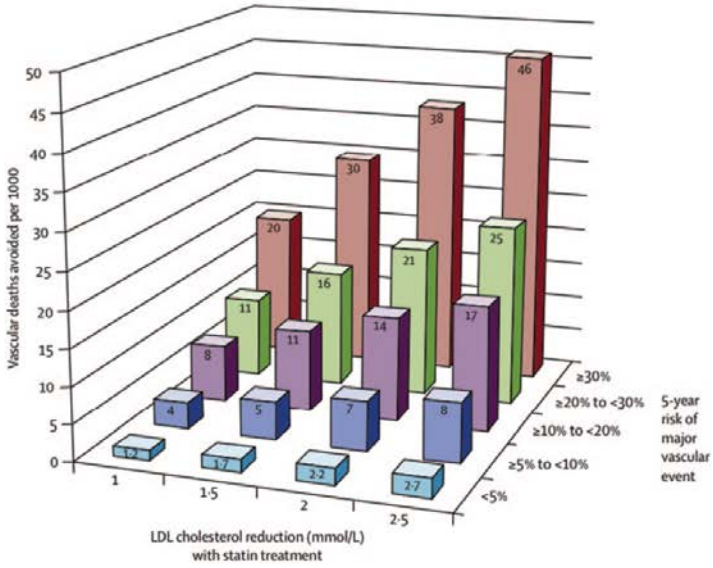


Figure. Predicted vascular deaths avoided over 5 years from reductions in low-density lipoprotein (LDL) cholesterol with statin treatment at different levels of cardiovascular disease risk.[1]

Figure A Predicted vascular deaths avoided over 5 years from reductions in LDL-C with statin treatment at different levels of CVD risks [Jackson R, Kerr A, Wells S. Vascular risk calculators essential but flawed clinical tools? Circulation. 2013 May 14;127(19):1929-31]

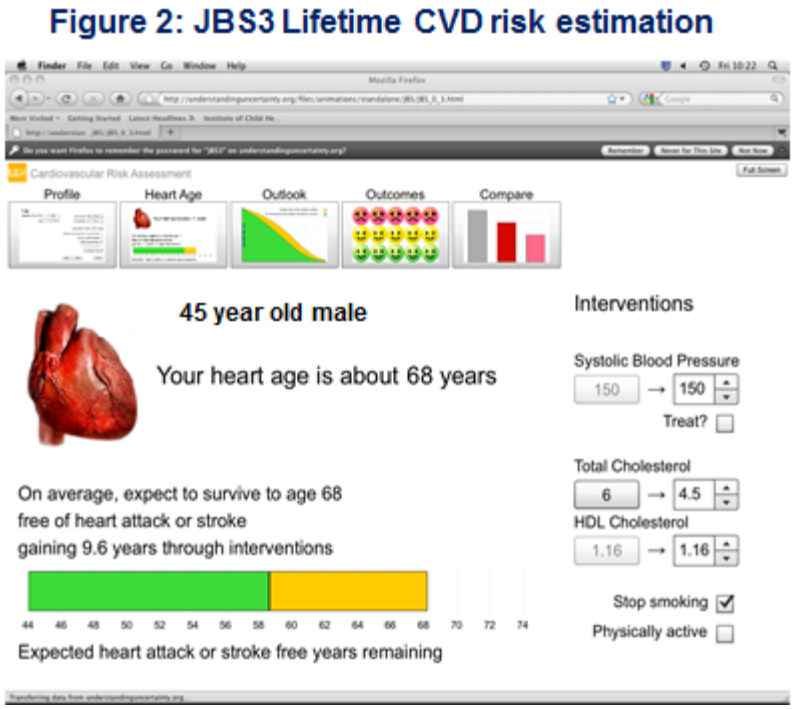
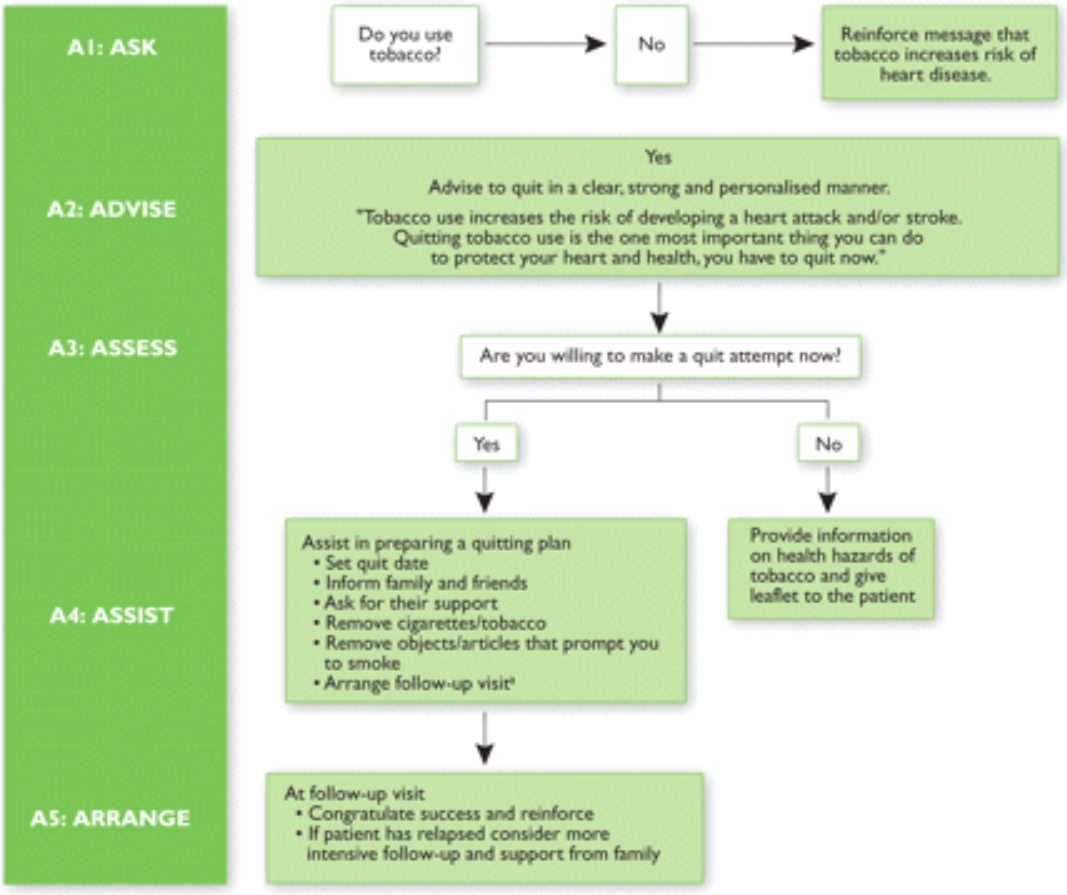


Figure B Lifetime risk calculator based on the JBS3 web-based tool.



[a]Ideally second follow-up visit is recommended within the same month and every month thereafter for 4 months and evaluation after one year. If not feasible, reinforce counselling whenever the patient is seen for blood pressure monitoring.

Taken with permission from WHO CVD risk management package.

Figure C. Modified World Health Organization (WHO) smoking cessation algorithm.

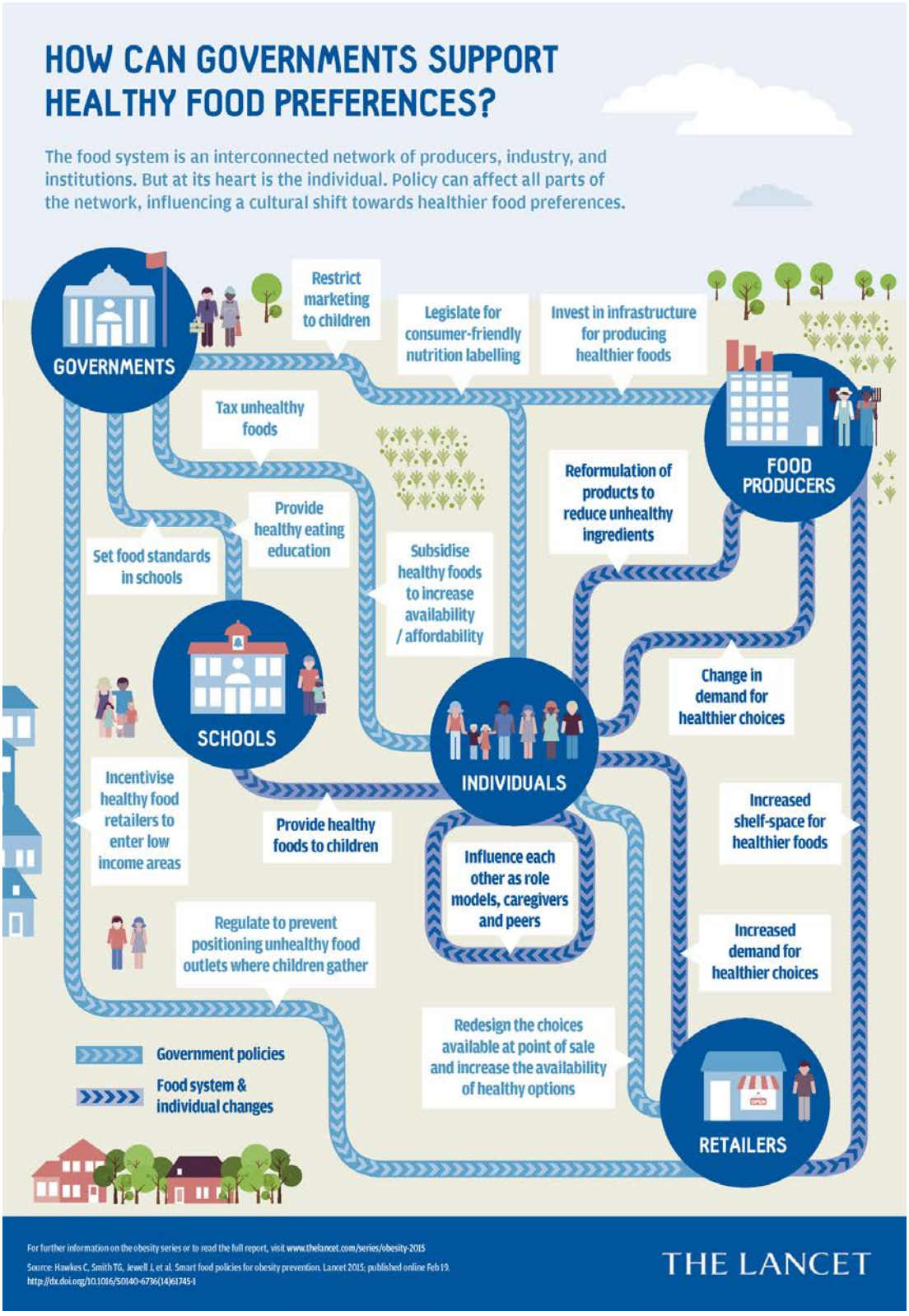


Figure D. How can governments support healthy food preferences?

Web Tables

A. Table for different risk factor combinations for more accurate estimation of risk ages
B. Self-assessment questionaires PAR-Q & YOU
C. World Health Organization classification of body weight according to body mass index in adults
D. Measures of general obesity and abdominal adiposity
E. Selected drugs that may increase risk of myopathy and rhabdomyolysis when used concomitantly with statin (CYP3A4 inhibitors/substrates or other mechanisms)
F. Reasons for medication non-adherence according to the World Health Organization

Table A. Table for different risk factor combinations for more accurate estimation of risk ages.

		WOMEN												MEN										
		Non-Smokers					Smokers					Age		Non-Smokers					Smokers					
	180	78	80	>80	>80	>80	**180**	>80	>80	>80	>80	>80		**180**	>80	>80	>80	>80	>80	**180**	>80	>80	>80	>80	>80
	160	73	75	76	78	80	**160**	>80	>80	>80	>80	>80	**65**	**160**	76	79	>80	>80	>80	**160**	>80	>80	>80	>80	>80
	140	69	70	72	74	76	**140**	76	78	80	>80	>80		**140**	70	73	75	78	>80	**140**	>80	>80	>80	>80	>80
	120	65	66	68	69	71	**120**	72	73	75	77	79		**120**	65	67	70	72	75	**120**	75	77	>80	>80	>80
	180	72	73	75	76	78	**180**	79	>80	>80	>80	>80		**180**	76	78	>80	>80	>80	**180**	>80	>80	>80	>80	>80
	160	68	69	70	72	74	**160**	75	76	78	80	>80	**60**	**160**	70	72	75	78	80	**160**	80	>80	>80	>80	>80
	140	64	65	66	68	70	**140**	70	72	73	75	77		**140**	65	67	69	72	75	**140**	74	77	80	>80	>80
Systolic Blood	**120**	60	61	63	64	66	**120**	66	68	69	71	73		**120**	60	62	64	67	69	**120**	69	71	74	77	80
Pressure	**180**	66	67	68	70	71	**180**	72	74	75	77	79		**180**	69	71	74	76	79	**180**	79	>80	>80	>80	>80
(mmHg)	**160**	62	63	64	66	67	**160**	68	69	71	73	74	**55**	**160**	64	66	68	71	74	**160**	73	76	79	>80	>80
	140	58	59	61	62	64	**140**	64	65	67	69	70		**140**	59	61	63	66	68	**140**	68	70	73	76	79
	120	55	56	57	59	60	**120**	61	62	63	64	66		**120**	55	57	59	61	64	**120**	63	65	68	70	73
	180	59	60	62	63	64	**180**	65	66	68	69	71		**180**	62	64	67	69	72	**180**	71	74	77	80	>80
	160	56	57	58	59	61	**160**	62	63	64	66	67	**50**	**160**	58	60	62	64	67	**160**	66	68	71	74	77
	140	53	54	55	56	58	**140**	58	59	61	62	64		**140**	54	56	58	60	62	**140**	61	64	66	68	71
	120	50	51	52	53	55	**120**	55	56	57	59	60		**120**	50	52	54	56	58	**120**	57	59	61	64	66
	180	53	54	55	56	57	**180**	58	59	60	62	63		**180**	56	58	60	62	64	**180**	64	66	68	71	74
	160	50	51	52	53	54	**160**	55	56	57	59	60	**45**	**160**	52	54	55	57	60	**160**	59	61	63	66	68
	140	48	48	49	50	52	**140**	52	53	54	55	57		**140**	48	50	52	54	56	**140**	55	57	59	61	64
	120	45	46	47	48	49	**120**	49	50	51	52	54		**120**	45	47	48	50	53	**120**	51	53	55	57	59
	180	47	48	49	50	51	**180**	51	52	53	54	55		**180**	49	51	52	54	56	**180**	56	58	60	62	65
	160	45	46	46	47	48	**160**	49	49	50	51	53	**40**	**160**	46	47	49	51	53	**160**	52	54	56	58	60
	140	43	43	44	45	46	**140**	46	47	48	49	50		**140**	43	44	46	47	49	**140**	48	50	52	54	56
	120	40	41	42	43	44	**120**	44	45	45	46	48		**120**	40	41	43	44	46	**120**	45	47	49	51	52
		4	**5**	**6**	**7**	**8**		**4**	**5**	**6**	**7**	**8**			**4**	**5**	**6**	**7**	**8**		**4**	**5**	**6**	**7**	**8**
		Total Cholesterol (mmol/l)												**Total Cholesterol (mmol/l)**										

Table B. Self-assessment questionaires PAR-Q & YOU

Physical Activity Readiness Questionnaire - PAR-Q (revised 2002)

PAR-Q & YOU

(A Questionnaire for People Aged 15 to 69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

YES	NO	
☐	☐	**1. Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?**
☐	☐	**2. Do you feel pain in your chest when you do physical activity?**
☐	☐	**3. In the past month, have you had chest pain when you were not doing physical activity?**
☐	☐	**4. Do you lose your balance because of dizziness or do you ever lose consciousness?**
☐	☐	**5. Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?**
☐	☐	**6. Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?**
☐	☐	**7. Do you know of any other reason why you should not do physical activity?**

If you answered

YES to one or more questions

Talk with your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want — as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

DELAY BECOMING MUCH MORE ACTIVE:

- if you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better; or
- if you are or may be pregnant – talk to your doctor before you start becoming more active.

PLEASE NOTE: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed Use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

No changes permitted. You are encouraged to photocopy the PAR-Q but only if you use the entire form.

NOTE: If the PAR-Q is being given to a person before he or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

"I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction."

NAME _____

SIGNATURE _____ DATE _____

SIGNATURE OF PARENT or GUARDIAN (for participants under the age of majority) _____ WITNESS _____

Note: This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.

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Link: http://www.csep.ca/cmfiles/publications/parq/par-q.pdf)

Table C World Health Organization classification of body weight according to body mass index in adults

Adults (> 18 years of age)	BMI (kg/m^2)
Underweight	< 18.5
Normal	18.5–24.9
Overweight	25–29.9
Obese	≥ 30
Class 1	30–34.9
Class 2	35–39.9
Class 3	≥ 40

BMI = body mass index.

6211 **Table D** Measures of general obesity and abdominal adiposity
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A. Measures of general obesity – body mass index
B. Measures of abdominal adiposity – waist circumference – waist:hip ratio – waist:height ratio
C. Direct measures of fat mass – bioelectrical impedance analysis – skinfold thicknesses
D. Measures of general obesity and abdominal adiposity – dual-energy X-ray absorptiometry – ultrasound – computed tomography – magnetic resonance imaging

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Table E. Selected drugs that may increase risk of myopathy and rhabdomyolysis when used concomitantly with statin (CYP3A4 inhibitors/substrates or other mechanisms)

CYP3A4 Inhibitors/substrates	**Others**
Cyclosporine, tacrolimus, sirolimus	Digoxin
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	Fibrates (gemfibrozil)
Azole antifungals (fluconazole, itraconazole, ketoconazole, posaconazole)	Niacin
Calcium antagonists (mibefradil, diltiazem, verapamil)	
Nefazodone	
HIV protease inhibitors (amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir)	
Hepatitis C drugs (boceprevir, telaprevir)	
Danazol	
Amiodarone	
Grapefruit juice	
Sildenafil	
Warfarin	

Table F. Reasons for medication non-adherence according to the World Health Organization

Category of non-adherence	Example
Health system	Poor quality of provider–patient relationship; poor knowledge on medication and/or low acceptance of guidelines; poor communication (e.g. limited, complex or confusing advice); lack of access to healthcare; lack of continuity of care.
Condition	Asymptomatic chronic disease (lack of physical cues); co-morbid mental health disorders (e.g. depression).
Patient	Physical impairments (e.g. vision problems or impaired dexterity); cognitive impairment; psychological/behavioural factors (e.g. lack of motivation, low self–efficacy, impulsivity); younger age.
Therapy	Complexity of regimen; side-effects.
Socioeconomic	Low literacy; high medication costs; poor social support.

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