JOINT SOCIETIES GUIDELINES

European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (Version 2012)

The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by Representatives of Nine Societies and by Invited Experts)

Joep Perk · Guy De Backer · Helmut Gohlke · Ian Graham · Željko Reiner · W. M. Monique Verschuren · Christian Albus · Pascale Benlian · Gudrun Boysen · Renata Cifkova · Christi Deaton · Shah Ebrahim · Miles Fisher · Giuseppe Germano · Richard Hobbs · Arno Hoes · Sehnaz Karadeniz · Alessandro Mezzani · Eva Prescott · Lars Ryden · Martin Scherer · Mikko Syvänne · Wilma J. M. Scholte Op Reimer · Christiaan Vrints · David Wood · Jose Luis Zamorano · Faiez Zannad ·
Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)

J. Perk (✉)
School of Health and Caring Sciences,
Linnaeus University,
Stagneliusgatan 14,
SE-391 82 Kalmar, Sweden
e-mail: joep.perk@lnu.se

G. De Backer · H. Gohlke · I. Graham · W. M. M. Verschuren · P. Benlian · C. Deaton · S. Ebrahim · G. Germano · R. Hobbs · A. Mezzani · E. Prescott · L. Ryden · W. J. M. S. Op Reimer · C. Vrints · D. Wood · J. L. Zamorano · F. Zannad
European Society of Cardiology (ESC),
Sophia Antipolis, France

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Ž. Reiner
European Atherosclerosis Society (EAS),
Göteborg, SWEDEN

C. Albus
International Society of Behavioural Medicine (ISBM),
Ulm, Germany

G. Boysen
European Stroke Organisation (ESO),
Basel, Switzerland

R. Cifkova
European Society of Hypertension (ESH),
Prague, Czech Republic

M. Fisher
European Association for the Study of Diabetes (EASD),
Düsseldorf, Germany

R. Hobbs · A. Hoes · M. Scherer
European Society of General Practice/Family Medicine
(ESGP/FM/WONCA),
Lubljana, Slovenia

S. Karadeniz
International Diabetes Federation Europe (IDF-Europe),
Brussels, Belgium

M. Syvänne
European Heart Network (EHN),
Brussels, Belgium

Abbreviations and acronyms

ABI	ankle–brachial index
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
AGREE	Appraisal of Guidelines Research and Evaluation
AHA	American Heart Association
apoA1	apolipoprotein A1
apoB	apolipoprotein B
CABG	coronary artery bypass graft surgery
CARDS	Collaborative AtoRvastatin Diabetes Study
CCNAP	Council on Cardiovascular Nursing and Allied Professions
CHARISMA	Clopidogrel for High Athero-thrombotic Risk and Ischemic Stabilisation, Management, and Avoidance
CHD	coronary heart disease
CKD	chronic kidney disease
COMMIT	Clopidogrel and Metoprolol in Myocardial Infarction Trial
CRP	C-reactive protein

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CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events
CVD	cardiovascular disease
DALYs	disability-adjusted life years
DBP	diastolic blood pressure
DCCT	Diabetes Control and Complications Trial
ED	erectile dysfunction
eGFR	estimated glomerular filtration rate
EHN	European Heart Network
EPIC	European Prospective Investigation into Cancer and Nutrition
EUROASPIRE	European Action on Secondary and Primary Prevention through Intervention to Reduce Events
GFR	glomerular filtration rate
GOSPEL	Global Secondary Prevention Strategies to Limit Event Recurrence After MI
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HbA$_{1c}$	glycated haemoglobin
HDL	high-density lipoprotein
HF-ACTION	Heart Failure and A Controlled Trial Investigating Outcomes of Exercise TraiNing
HOT	Hypertension Optimal Treatment Study
HPS	Heart Protection Study
HR	hazard ratio
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 SR/Trandolapril
JTF	Joint Task Force
LDL	low-density lipoprotein
Lp(a)	lipoprotein(a)
LpPLA2	lipoprotein-associated phospholipase 2
LVH	left ventricular hypertrophy
MATCH	Management of Atherothrombosis with Clopidogrel in High-risk Patients with Recent Transient Ischaemic Attack or Ischaemic Stroke
MDRD	Modification of Diet in Renal Disease
MET	metabolic equivalent
MONICA	Multinational MONItoring of trends and determinants in CArdiovascular disease
NICE	National Institute of Health and Clinical Excellence
NRT	nicotine replacement therapy
NSTEMI	non-ST elevation myocardial infarction
ONTARGET	Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial
OSA	obstructive sleep apnoea

PAD	peripheral artery disease
PCI	percutaneous coronary intervention
PROactive	Prospective Pioglitazone Clinical Trial in Macrovascular Events
PWV	pulse wave velocity
QOF	Quality and Outcomes Framework
RCT	randomized clinical trial
RR	relative risk
SBP	systolic blood pressure
SCORE	Systematic Coronary Risk Evaluation Project
SEARCH	Study of the Effectiveness of Additional Reductions in Cholesterol and
SHEP	Systolic Hypertension in the Elderly Program
STEMI	ST-elevation myocardial infarction
SU.FOL.OM3	SUpplementation with FOlate, vitamin B6 and B12 and/or OMega-3 fatty acids
Syst-Eur	Systolic Hypertension in Europe
TNT	Treating to New Targets
UKPDS	United Kingdom Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial
VALUE	Valsartan Antihypertensive Long-term Use
VITATOPS	VITAmins TO Prevent Stroke
VLDL	very low-density lipoprotein
WHO	World Health Organization

1 What is Cardiovascular Disease Prevention?

1.1 Introduction

Atherosclerotic cardiovascular disease (CVD) is a chronic disorder developing insidiously throughout life and usually progressing to an advanced stage by the time symptoms occur. It remains the major cause of premature death in Europe, even though CVD mortality has fallen considerably over recent decades in many European countries. It is estimated that >80 % of all CVD mortality now occurs in developing countries.

CVD causes mass disability: within the coming decades the disability-adjusted life years (DALYs) estimate is expected to rise from a loss of 85 million DALYs in 1990 to a loss of ~150 million DALYs globally in 2020, thereby remaining the leading somatic cause of loss of productivity [1].

CVD is strongly connected to lifestyle, especially the use of tobacco, unhealthy diet habits, physical inactivity, and psychosocial stress [2]. The World Health Organization (WHO) has stated that over three-quarters of all CVD mortality may be prevented with adequate changes in lifestyle. CVD prevention, remaining a major challenge for the general population, politicians, and healthcare workers alike, is

defined as a co-ordinated set of actions, at public and individual level, aimed at eradicating, eliminating, or minimizing the impact of CVDs and their related disability. The bases of prevention are rooted in cardiovascular epidemiology and evidence-based medicine [3].

The aim of the 2012 guidelines from the Fifth Joint Task Force (JTF) of the European Societies on Cardiovascular Disease Prevention in Clinical Practice is to give an update of the present knowledge in preventive cardiology for physicians and other health workers. The document differs from 2007 guidelines in several ways: there is a greater focus on new scientific knowledge. The use of grading systems [European Society of Cardiology (ESC) and Grading of Recommendations Assessment, Development, and Evaluation (GRADE)] allows more evidence-based recommendations to be adapted to the needs of clinical practice.

The reader will find answers to the key questions of CVD prevention in the five sections: what is CVD prevention, why is it needed, who should benefit from it, how can CVD prevention be applied, and when is the right moment to act, and finally where prevention programmes should be provided.

A literature search of clinical guidelines aimed at cardiovascular risk assessment in clinical practice identified >1900 publications [4]. When these were evaluated using the Appraisal of Guidelines Research and Evaluation (AGREE) instrument, only seven achieved the level considered 'considerable rigour'. Too much guidance and too little impact? The gap between state-of-the-art knowledge and its implementation in clinical practice remains wide, as shown in recent surveys such as EUROASPIRE III [5]. Family doctors may be flooded with recommendations in the wide field of family medicine. Finding time to read and implement the many guidelines can be an overwhelming task in a busy primary care centre or a regional hospital clinic.

The Task Force behind the 2012 recommendations has chosen to limit the size to the level of the executive summary of previous JTF publications. All relevant reference material is available on the dedicated CVD Prevention Guidelines page of the ESC Website (www.escardio.org/guidelines). A one-page summary of all strong recommendations according to the GRADE system will be provided, which may stimulate implementation; and a pocket version will be available for daily clinical use.

1.2 Development of Guidelines

The first joint recommendations (1994) reflected the need for a consensus statement from the ESC, the European Atherosclerosis Society, and the European Society of Hypertension, and advocated the principle of total risk assessment for primary prevention. A revision was published in 1998 by the second JTF involving these three societies

joined by the European Society of General Practice/Family Medicine, the European Heart Network (EHN), and the International Society of Behavioural Medicine.

Appreciating that an even broader field of expertise was required, the third JTF was extended to include eight societies: the European Association for the Study of Diabetes and the International Diabetes Federation Europe joined. The third JTF widened the guidance from coronary heart disease (CHD) to CVD and introduced the concept of total CVD risk assessment using the database of the Systematic Coronary Risk Evaluation Project (SCORE).

Special risk charts based on SCORE were produced for both low-and high-risk countries and gained wide acceptance throughout Europe. The concept of primary and secondary prevention was replaced by the recognition that atherosclerosis was a continuous process. Priorities were proposed at four levels: patients with established disease, asymptomatic individuals at high risk of CVD mortality, first-degree relatives of patients with premature CVD, and other individuals encountered in routine clinical practice.

In the 2007 update, the fourth JTF reflected consensus from nine scientific bodies as the European Stroke Initiative joined the group. From the ESC, the European Association for Cardiovascular Prevention & Rehabilitation contributed with scientists from the fields of epidemiology, prevention, and rehabilitation. Novelties were an increased input from general practice and cardiovascular nursing, being key players in the implementation of prevention. Lifestyle counselling was given greater importance and there was a revised approach to CVD risk in the young, using a SCORE-based relative risk chart.

The present update from the fifth JTF reflects the consensus on the broader aspects of CVD prevention from the nine participating organizations. For more detailed guidance, reference is made to the specific guidelines from the participating societies, which are in full congruence with this publication.

The partner societies co-operate in the Joint Societies Implementation Committee, which aims to stimulate dissemination of the guidelines, acceptance at national levels, and the formation of national alliances to translate the recommendations into clinical practice. The programme 'Call for Action' was one of the efforts of this committee [6].

Implementation has been well accepted at the European Union (EU) political level after the launch of the European Heart Health Charter in the European Parliament in June 2007 [6]. This public health statement has been endorsed by a majority of the EU member states, defining the characteristics of people who tend to stay healthy as:

- No use of tobacco.
- Adequate physical activity: at least 30 min five times a week.
- Healthy eating habits.

- No overweight.
- Blood pressure below 140/90 mmHg.
- Blood cholesterol below 5 mmol/L (190 mg/dL).
- Normal glucose metabolism.
- Avoidance of excessive stress.

1.3 Evaluation Methods

Good guidelines are a major mechanism for improving the delivery of healthcare and improving patient outcomes [7]. Guidelines based on credible evidence are more likely to be implemented in clinical practice [8]. The present guidelines follow the quality criteria for development of guidelines, which can be found at www.escardio.org/knowledge/guidelines/rules.

In short, experts from the nine organizations performed a comprehensive review and a critical evaluation of diagnostic and therapeutic procedures, including assessment of the risk–benefit ratio. The level of evidence and the strength of recommendation of particular treatment options were weighed and graded according to the ESC recommendations (Tables 1 and 2).

Statements from the writing panel disclosing conflicts of interest are available on the ESC website. Changes in conflicts of interest that arose during the writing period were notified.

The preparation and publication of the fifth JTF report was supported financially by the ESC without any involvement of the pharmaceutical industry. Once the document had been finalized by the fifth JTF experts it was submitted for extensive independent external review. Following this revision and after acceptance by the ESC Committee for Practice Guidelines and the co-operating organizations in the fifth JTF, the document was published.

1.4 Combining Evaluation Methods

An important novelty in reviewing quality of evidence and making recommendations is the use of both the ESC-recommended method of evaluation and the GRADE rating system [9]. In contrast to the 2007 guidelines, the JTF has chosen to provide guidance with both systems so that readers acquainted with the former method and those preferring GRADE will find their individually adapted but still congruent guidance in the combined recommendation tables.

The JTF introduced GRADE as it uses a transparent and rigorous process to assess the quality of evidence in terms of whether further research would or would not change confidence in the estimate of intervention effects or diagnostic accuracy [10]. Specific quality indicators are: study limitations; inconsistency of findings; indirectness of evidence; imprecision; and publication bias (Table 3). These are applied to each outcome of critical importance for decision-making in the judgement of the guideline group (e.g. reduction in clinical events is usually critical; changes in biochemical values are not usually critical). Judgements are then made on these indicators to rate evidence quality from high (i.e. further research is unlikely to change confidence in the estimate of effect), to moderate, low, and very low (i.e. any estimate of effect is very uncertain). This judgement is made on quality of evidence for the critical outcomes and not those that are not critical for decision-making.

The value of this new approach is that systematic review or randomized control trial (RCT) evidence that is biased, inconsistent, or imprecise may be downgraded from high-to moderate-or low-quality evidence. Similarly, observational data from cohort or case–control studies may be upgraded from moderate or low (as is typical in the old levels-of-

Table 1 Classes of recommendations

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Table 2 Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

evidence approach) to high if bias is unlikely, and findings are consistent and precise. This is very helpful in assessing evidence for CVD prevention where RCTs of health behaviours are difficult to conduct and may be misleading.

GRADE also distinguishes quality of evidence and strength of recommendation [9]. Strong evidence does not automatically lead to a strong recommendation. Recommendations are based on the quality of the evidence, the degree of uncertainty about the balance of benefits and harms of the intervention, uncertainty about the values and preferences of patients, and uncertainty about whether the intervention is a wise use of resources. Rather than have a range of classes of recommendation (e.g. Class I–Class III), GRADE only uses two categories—strong or weak (i.e. discretionary, conditional). The implications of a strong recommendation are: most informed patients would choose the recommended intervention (and request discussion if not offered); clinicians would ensure that most patients should receive the intervention; and the recommendation would be adopted as policy in organized healthcare systems. In contrast, for weak recommendations, some patients would want the intervention but many would not; clinicians would help patients make choices dependent on their values and preferences; policy makers would require debate among various stakeholders to decide on the role of the intervention.

The GRADE approach can be applied to diagnostic strategies in the same way with a few minor changes to the

Table 3 Quality of evidence used in GRADE [9]

Study limitations	Non-concealment of allocation; non-blinding of outcome assessment; high losses to follow-up; no intention-to-treat analysis.
Inconsistent findings	Variability due to differences in patients studied, intervention, outcomes assessed.
Indirectness of evidence	Head-to-head comparisons are direct; intervention A vs. control and B vs. control is indirect in assessing A vs. B.
Imprecision	Small patient numbers resulting in wide confidence intervals.
Publication bias	Typically trials showing no effect of intervention are not published or are published in local non-indexed journals.

quality criteria used [9], and may also be used in conjunction with appraisals of resource use and cost-effectiveness [10]. However, as resources are valued differently across Europe, it is not feasible in these guidelines to make judgements about the appropriateness of resource use for the interventions and diagnostic strategies considered here.

2 Why is Prevention of Cardiovascular Disease Needed?

Key messages

- Atherosclerotic CVD, especially CHD, remains the leading cause of premature death worldwide.
- CVD affects both men and women; of all deaths that occur before the age of 75 years in Europe, 42 % are due to CVD in women and 38 % in men.
- CVD mortality is changing, with declining age-standardized rates in most European countries, which remain high in Eastern Europe.
- Prevention works: >50 % of the reductions seen in CHD mortality relate to changes in risk factors, and 40 % to improved treatments.
- Preventive efforts should be lifelong, from birth (if not before) to old age.
- Population and high-risk preventive strategies should be complementary; an approach limited to high-risk persons will be less effective; population education programmes are still needed.
- Despite gaps in our understanding, there is ample evidence to justify intensive public health and individual preventive efforts.
- There is still substantial room for improvement in risk factor control, even in individuals at very high risk.

2.1 Scope of the Problem

'Coronary heart disease (CHD) is now the leading cause of death worldwide; it is on the rise and has become a true pandemic that respects no borders'. This statement from 2009 on the website of the WHO [11] does not differ much from the warning issued in 1969 by its Executive Board: 'Mankind's greatest epidemic: CHD has reached enormous proportions striking more and more at younger subjects. It will result in coming years in the greatest epidemic mankind has faced unless we are able to reverse the trend by concentrated research into its cause and prevention' [12]. The second major CVD—stroke—is another substantial cause of death and disability. For these reasons, the fifth JTF guidelines refer to the total burden of atherosclerotic CVD.

The choice of total burden of atherosclerotic CVD may give the impression that nothing has changed over the past

40 years, but this is not true. On the contrary, the epidemic has been and still is extremely dynamic and is influenced by both changes in cardiovascular risk factors and in increased opportunities for targeted interventions to prevent and treat CVD. This results in ups and downs of cardiovascular morbidity and mortality over relatively short periods with wide variability across the globe, including developing countries where the major proportion of all events occurs nowadays. In different parts of the world, the dynamics of the epidemic vary greatly in pattern, magnitude, and timing [13]. In Europe, the burden remains high: CVD remains a major cause of premature deaths and loss of DALYs—a composite of premature death and living with the disease. It is not widely appreciated that CVD is the main cause of premature death in women: CVD was responsible for 42 % of all deaths below 75 years of age in European women and for 38 % of all deaths at <75 years in men [14]. However, a decline in age-standardized CHD and CVD mortality has been observed in many European countries between the 1970s and 1990s, with the earliest and most prominent decrease in the more affluent countries, illustrating the potential for prevention of premature deaths and for prolonging healthy life expectancy. In several eastern European countries, however, CVD and CHD mortality remains high [15].

Policy makers need to know whether major contributors to morbidity and mortality such as CVD are tracking up or down. A valid and actual description of the epidemic by place, time, and personal characteristics is continuously needed to guide and support health policies.

At present there is no standardized source of Europe-wide CVD morbidity data. Results from the Multinational MONItoring of trends and determinants in CArdiovascular disease (MONICA) project indicated a heterogeneous trend in CHD incidence in the 1980s to 1990s in Europe [16]. This pattern may have changed, and results from recent reports do suggest that mortality and morbidity from CHD is levelling, especially in younger adults [17, 18]. One should also realize that because of an ageing population and a reduced case fatality of acute coronary events, the total number of people living with CHD increases. The majority of these patients develop the disease at an advanced age, leading to a compression of morbidity in the very old of the community and to a prolonged life expectancy in good health. The Global Health Observatory database of the WHO (http://apps.who.int/ghodata/?vid=2510) provides data on present mortality rates from CVD in the world.

2.2 Prevention of Cardiovascular Disease: a Lifelong Approach

Prevention of CVD ideally starts during pregnancy and lasts until the end of life. In daily practice, prevention efforts are typically targeted at middle-aged or older men and women with established CVD (i.e. secondary prevention) or those at high risk of developing a first cardiovascular event [e.g. men and women with combinations of smoking, elevated blood pressure (BP), diabetes or dyslipidaemia (i.e. primary prevention)]; CVD prevention in the young, the very old, or those with just a moderate or mild risk is still limited, but can result in substantial benefit. Prevention is typically categorized as primary or secondary prevention, although in CVD the distinction between the two is arbitrary in view of the underlying, gradually developing atherosclerotic process. Since the instruction by Geoffrey Rose decades ago, two approaches towards prevention of CVD are considered: the population strategy and the high-risk strategy [19].

The population strategy aims at reducing the CVD incidence at the population level through lifestyle and environmental changes targeted at the population at large. This strategy is primarily achieved by establishing ad-hoc policies and community interventions. Examples include measures to ban smoking and reduce the salt content of food. The advantage is that it may bring large benefits to the population although it may offer little to the individual. The impact of such an approach on the total number of cardiovascular events in the population may be large, because all subjects are targeted and a majority of events occur in the substantial group of people at only modest risk.

In the high-risk approach, preventive measures are aimed at reducing risk factor levels in those at the highest risk, either individuals without CVD at the upper part of the total cardiovascular risk distribution or those with established CVD. Although individuals targeted in this strategy are more likely to benefit from the preventive interventions, the impact on the population level is limited, because people at such high risk are few. For a long time the population strategy has been considered to be more cost-effective than the high-risk approach but since the introduction of highly effective lipid lowering drugs, improvement in smoking cessation programmes and lower costs of antihypertensive drugs, the effectiveness of the high risk approach has increased [20]. There is consensus that the largest preventive effect is achieved when these are combined.

Importantly, evidence that increased cardiovascular risk starts developing at a (very) young age has accumulated over past decades. Even exposure to risk factors before birth may influence the lifetime risk of CVD [21], as has been illustrated from studies in the offspring of women who were pregnant during the Dutch famine in the Second World War [22]. Although children are at very low absolute risk of developing CVD, those at a relatively high risk compared with their peers remain at increased risk of experiencing a cardiovascular event later in life because of 'tracking' of risk factors (i.e. those at the high end of the distribution of a risk factor in early life tend to stay in the upper part of the

distribution) [23]. Thus a healthy lifestyle in the young is crucial, although ethical and other reasons prohibit the provision of strong levels of evidence based on randomized trials for the benefits in terms of reduced incidence of CVD from, for example, school programmes on health education or smoking cessation actions. Also, the limited attention on CVD prevention in the elderly has proven unjustified. Studies have shown that preventive measures (i.e. BP lowering and smoking cessation) are beneficial up to advanced age [24, 25]. These facts exemplify that prevention of CVD should be a lifelong effort, albeit that the beneficial effects in terms of, for example, a lower incidence of fatal or non-fatal cardiovascular events or improvement in quality of life, should always be weighed against the potential harm that specific measures may cause (including side effects of drugs and psychological effects of labelling healthy subjects as patients) and against related costs.

2.3 Prevention of Cardiovascular Disease Pays Off

In order to interpret the dynamics of the CVD epidemic, it is important to differentiate the effect of a reduced case fatality and changes related to preventing clinical events. Some authors credit the greater use of evidence-based medical therapies such as thrombolysis, aspirin, angiotensin-converting enzyme (ACE) inhibitors, percutaneous coronary intervention (PCI), and coronary artery bypass graft (CABG) surgery [26, 27], while others credit improved management of major risk factors such as smoking, hypertension, and dyslipidaemia [28].

The MONICA project, performed during the 1980s and 1990s, showed that only part of the variation in the time trends of coronary event rates could be predicted by trends in risk factors [16]. The relationship between changes in risk factor scores and changes in event rates was substantial. and the changes in risk factors explained almost half the variation in event rates in men but less in women.

Moreover, there was a significant association between treatment change and case fatality. Thus it was concluded that both primary prevention and treatment of cardiovascular events influence mortality. In many MONICA centres there were quite substantial changes, up or down, in CVD events within time periods as small as 10 years. The only reasonable explanation is that both environmental changes, especially related to lifestyle, and improved management are important.

Another approach to understanding the changes in CVD mortality and incidence rates is by applying models such as the IMPACT mortality model [29]. Based on information on changes in coronary risk factors and in treatment as obtained from the results of RCTs regarding the effectiveness of different treatment modalities, it estimates the expected influence on CHD mortality by age and gender. This model has been applied in different countries; the results from these studies are rather consistent and similar to what has been observed in other studies of the same subject, as summarized in Fig. 1. Beneficial reductions in major risk factors—in particular smoking, BP, and cholesterol—accounted for more than half of the decrease in CHD deaths, although they were counteracted by an increase in the prevalence of obesity and type 2 diabetes; ~40 % of the decline in CHD death rates is attributed to better treatments of acute myocardial infarction, heart failure, and other cardiac conditions. Results from clinical trials and natural experiments also show that a decline in CHD mortality can happen rapidly after individual or population-wide changes in diet or smoking [31].

The potential for prevention based on healthy lifestyles, appropriate management of classical risk factors, and selective use of cardioprotective drugs is obvious. The human and economic arguments in favour of CVD prevention were recently estimated by the National Institute for Health and Clinical Excellence (NICE) [32] as overwhelmingly positive, and many committees from other countries have almost the same views [33]. According to the report of NICE, implementation of the population approach may bring numerous benefits and savings:

- Narrowing the gap in health inequalities.
- Cost savings from the number of CVD events avoided.
- Preventing other conditions such as cancer, pulmonary diseases, and type 2 diabetes.
- Cost savings associated with CVD such as medications, primary care visits, and outpatient attendances.
- Cost savings to the wider economy as a result of reduced loss of production due of illness in those of working age, reduced benefit payments, and reduced pension costs from people retiring early from ill health.
- Improving the quality and length of people's lives.

2.4 Ample Room for Improvement

Within the scope of the comprehensive programme on CVD prevention of the ESC, surveys are carried out to document how well the guidelines are implemented in clinical practice. These surveys are called EUROASPIRE; the results from the hospital arm of EUROASPIRE III [33] (2006–2007) in 8966 patients with established CHD from 22 European countries show that large proportions of patients still do not achieve the lifestyles, risk factor levels, and therapeutic targets set in 2003 by the third JTF. The proportions of patients who were at goal for the different recommendations and for risk factor management are given in Table 4; ideally, 100 % of patients should reach the goals, but in practice fewer than half tend to reach the targets.

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Fig. 1 Percentage of the decrease in deaths from coronary heart disease attributed to treatments and risk factor changes in different populations (adapted from Di Chiara et al [30].)
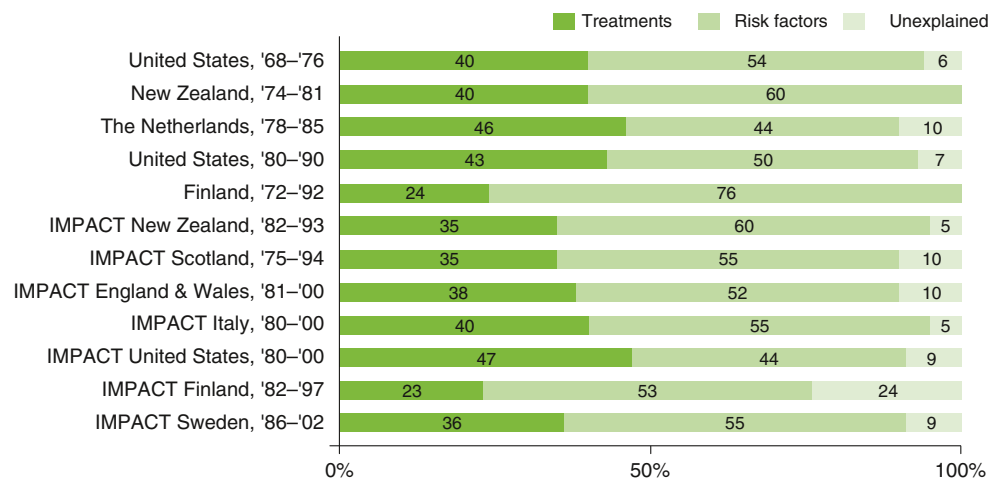
Moreover, the changes between EUROASPIRE I (1996) and EUROASPIRE III reveal that the proportion of smokers did not change and BP control has not improved despite increased use of antihypertensive drugs, while the number of patients with (central) obesity continues to increase. On the other hand, lipid control has improved significantly [5]. In EUROASPIRE III, asymptomatic high-risk subjects have been included in the primary prevention arm; the adherence to the recommended lifestyles and the proportions at goal for blood pressure, lipids, and blood glucose are even worse [34].

These findings call for comprehensive and multidisciplinary programmes involving both patients and their families. The efficacy and safety of such programmes have been demonstrated in the EUROACTION project—an ESC demonstration project showing that the recommended lifestyle changes and the targeted management of cardiovascular risk factors are achievable and sustainable in daily clinical practice, in both primary and secondary care [35].

Remaining gaps in the evidence

- Our understanding of the reasons for changes in the behaviour of both populations and individuals remains incomplete.
- The mechanisms whereby such changes in behaviour translate into changes in disease patterns are also incompletely understood.
- Auditing and studying the most effective preventive measures is therefore challenging.
- More research into prevention of CVD is needed, starting early in life or even during fetal development.
- It is uncertain whether CVD is merely deferred by preventive efforts or if it of can be avoided completely.
- There is an ongoing need for a valid and accurate description of CVD morbidity and mortality throughout the world.

Table 4 Guideline recommendations vs. achievements in patients with established coronary heart disease in EUROASPIRE III

Guideline recommendations	Proportions at goal
Smoking cessation among smokers	48
Regular physical activity	34
BMI <25 kg/m²	18
Waist circumference <94 cm (men) <80 cm (women)	25 12
Blood pressure <140/90 mmHg	50
Total cholesterol <4.5 mmol/L (175 mg/dL)	49
LDL cholesterol <2.5 mmol/L (100 mg/dL)	55

Among patients with type 2 diabetes:
   Fasting glycaemia <7.0 mmol/L (125 mg/dL)
   HbA₁c <6.5%
	27
	 35

BMI = body mass index; HbA_{1c} = glycated haemoglobin; LDL = low-density lipoprotein

3 Who Should Benefit from It?

3.1 Strategies and Risk Estimation

Key messages

The detailed SCORE charts with integrated HDL-cholesterol values can be found on http://www.escardio.org/guidelines-surveys/esc-guidelines/Pages/cvd-prevention.aspx in the related material section.

- In apparently healthy persons, CVD risk is most frequently the result of multiple interacting risk factors.
- A risk estimation system such as SCORE can assist in making logical management decisions, and may help to avoid both under-and overtreatment.

- Certain individuals are at high CVD risk without needing risk scoring and require immediate intervention for all 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 lifestyle efforts.
- While women appear to be at lower CVD risk than men, this is misleading as risk is deferred by ~10 years rather than avoided.
- All risk estimation systems are relatively crude and require attention to qualifying statements.
- Additional factors affecting risk can be accommodated in electronic risk estimation systems such as HeartScore (www.heartscore.org).
- The total risk approach allows flexibility: if perfection cannot be achieved with one risk factor, risk can still be reduced by trying harder with others.

Recommendations regarding risk estimation

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
Total risk estimation using multiple risk factors (such as SCORE) is recommended for asymptomatic adults without evidence of CVD	I	C	Strong	[36]
High-risk individuals can be detected on the basis of established CVD, diabetes mellitus, moderate to severe renal disease, very high levels of individual risk factors, or a high SCORE risk, and are a high priority for intensive advice about all risk factors.	I	C	Strong	[36, 37]

CVD = cardiovascular disease
[a]Class of recommendation
[b]Level of evidence
[c]References

3.1.1 Introduction

The encouragement of the use of total risk estimation as a crucial tool to guide patient management has been a cornerstone of the guidelines since the first edition [38]. This is because clinicians treat whole people (and not individual risk factors), whose cardiovascular risk usually reflects the combined effects of several risk factors that may interact, sometimes multiplicatively. Having said that, the implication that total risk assessment, while logical, is associated with improved clinical outcomes when compared with other strategies has not been adequately tested.

Although clinicians often ask for threshold values at which to trigger an 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. This issue is dealt with in more detail in these guidelines, as is the issue of how to advise younger persons at low absolute but high relative risk, and the fact that all elderly people will eventually be at high risk of death and may be overexposed to drug treatments.

The priorities suggested in this section are to assist the physician in dealing with individual people and patients. As such, they acknowledge that individuals at the highest levels of risk gain most from risk factor management. However, as noted elsewhere, the majority of deaths in a community come from those at lower levels of risk, simply because they are more numerous [19].

3.1.2 Strategies

Cardiovascular risk in the context of these guidelines means the likelihood of a person developing an atherosclerotic cardiovascular event over a defined time period.

'Total risk' implies an estimate of risk made by considering the effect of the major factors: age, gender, smoking, BP, and lipid levels. The term has become widely used; however, 'total risk' is not comprehensive because the effects of other risk factors are not considered except as qualifying statements.

The importance of total risk estimation before management decisions are made is illustrated in Table 5 and Fig. 2. The figure shows that the effect of the lipid levels on risk is modest in women who are at otherwise low risk, and that the risk advantage of being female is lost by the combination of smoking and mild hypertension. Table 5 shows that a person with a cholesterol concentration of 8 mmol/L (310 mg/dL) can be at 10 times lower risk than someone with a cholesterol concentration of 5 mmol/L (190 mg/dL) if the latter is a male hypertensive smoker. RCTs of single risk factors do not give sufficient data to address these issues fully. While audits such as EUROAS-PIRE [5, 38, 39] suggest inadequate risk factor management in very-high-risk subjects, it is also likely that, in the context of low-risk subjects who have not had a vascular event, there is the potential for substantial overuse of drugs by inappropriate extrapolation of the results of trials conducted mostly in high-risk men to low-risk individuals. In general, women and old and young subjects have been under-represented in the classic drug trials that have informed guidelines to date.

It is essential for clinicians to be able to assess risk rapidly and with sufficient accuracy to allow logical management decisions. This realization led to the development of the risk chart used in the 1994 and 1998 guidelines [38, 40]. This chart, developed from a concept pioneered by Anderson et al [41], used age, sex, smoking status, total cholesterol, and systolic blood pressure (SBP) to estimate the 10-year risk of a first fatal or non-fatal CHD event. There were several problems with this chart, outlined in the fourth JTF guidelines on prevention [37], which led to the presently recommended risk estimation system, SCORE.

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Table 5 Impact of combinations of risk factors on SCORE 10-year risk of fatal cardiovascular disease

Sex	Age (years)	CHOL (mmol/L)	SBP (mmHg)	Smoke	Risk %[a]
F	60	8	120	No	2
F	60	7	140	Yes	5
M	60	6	160	No	8
M	60	5	180	Yes	21

CHOL = cholesterol; SBP = systolic blood pressure

[a] SCORE risk at 10 years; 5 mmol/L = 190 mg/dL, 6 mmol/L = 230 mg/dL, 7 mmol/L = 270 mg/dL, 8 mmol/L = 310 mg/dL

3.1.3 Risk Estimation

When do I assess total risk?

As noted in the 'priorities' section, persons with established CVD are already at very high risk of further events and need prompt intervention on all risk factors, while in apparently healthy persons total risk should be assessed by using the SCORE system.

While the ideal scenario would be for all adults to have their risk of CVD assessed, this may not be practicable for many societies. This decision must be made by individual countries and will be resource dependent. It is recommended that risk factor screening including the lipid profile may be considered in adult men >40 years old and in women >50 years of age or post-menopausal [42].

Most people will visit their family doctor at least once over a 2-year period giving an opportunity for risk assessment. General practice databases may be useful to store risk factor data, and to flag high-risk persons. It is suggested that total risk assessment be offered during a consultation if:

- The person asks for it.
- One or more risk factors such as smoking, overweight, or hyperlipidaemia are known.

- There is a family history of premature CVD or of major risk factors such as hyperlipidaemia.
- There are symptoms suggestive of CVD.

Special efforts should be made to assess risk in the socially deprived who are more likely to carry a heavy burden of risk factors [43].

The 2003 guidelines [44] used the SCORE chart for risk estimation [45], which was based on data from 12 European cohort studies; it included 205 178 subjects examined at baseline between 1970 and 1988 with 2.7 million years of follow-up and 7934 cardiovascular deaths. The SCORE risk function has been externally validated [46].

Risk charts such as SCORE are intended to facilitate risk estimation in apparently healthy persons. Patients who have had a clinical event such as an acute coronary syndrome (ACS) or stroke automatically qualify for intensive risk factor evaluation and management.

SCORE differs from earlier risk estimation systems in several important ways, and has been modified somewhat for the present guidelines. Details of these modifications follow.

The SCORE system estimates the 10-year risk of a first fatal atherosclerotic event, whether heart attack, stroke, aneurysm of the aorta, or other. All ICD (International Classification of Diseases) codes that could reasonably be assumed to be atherosclerotic are included. Most other systems estimate CHD risk only.

The choice of CVD mortality rather than total (fatal + 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. Striking changes in both diagnostic tests and therapies have occurred since the SCORE cohorts were assembled. Critically, the use of mortality permits re-calibration to allow for time trends in CVD mortality. Any risk estimation system will overpredict in countries in which mortality has fallen

Fig. 2 Relationship between total cholesterol/HDL cholesterol ratio and 10-year fatal CVD events in men and women aged 60 years with and without risk factors, based on a risk function derived from the SCORE project
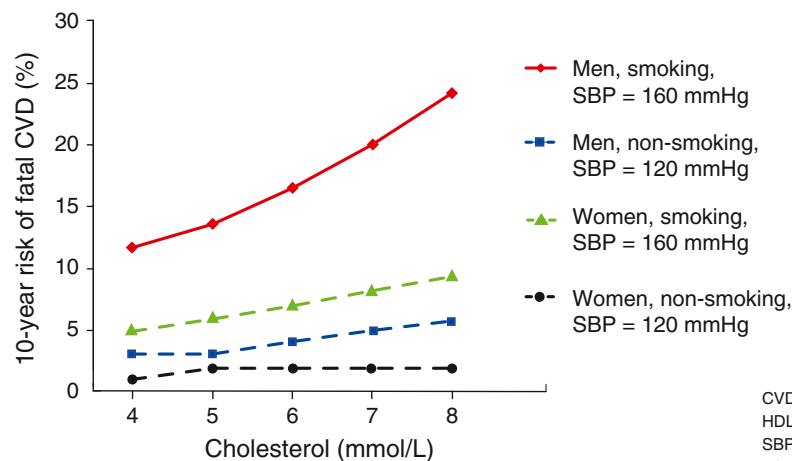
CVD = cardiovascular disease; HDL = high-density lipoprotein; SBP = systolic blood pressure; TC = total cholesterol.

and underpredict in those in which it has risen. Re-calibration 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 CVD mortality charts were produced, and have been re-calibrated for a number of European countries. Calibrated country-specific versions for Cyprus, Czech Republic, Germany, Greece, Poland, Slovakia, Spain, and Sweden, and country-specific versions for Bosnia and Herzegovina, Croatia, Estonia, France, Romania, Russian Federation, and Turkey can be found at www.heartscore.org. Nevertheless it is essential to address the issue of total risk.

In the 2003 guidelines [44], a 10-year risk of CVD death of ≥5 % was arbitrarily considered high risk. Yet this implies a 95 % chance of not dying from CVD within 10 years, less than impressive when counselling patients. The new nomenclature in the 2007 guideline was that everyone with a 10-year risk of cardiovascular death ≥5 % has an increased risk. Clearly the risk of total fatal and non-fatal events is higher, and clinicians naturally wish for this to be quantified. The biggest contributor to the high-risk SCORE charts is the Finnish contribution to MONICA, FINRISK, which has data on non-fatal events defined according to the MONICA project [47]. Calculating total event rates from FINRISK suggests that, at the level (5 %) at which risk management advice is likely to be intensified, total event risk is ~15 %. This three-fold multiplier is somewhat smaller in older persons in whom a first event is more likely to be fatal. An examination of the Framingham estimates of risk of total CVD events results in similar conclusions: a 5 % SCORE risk of CVD death equates to a 10–25 % Framingham risk of total CVD, depending upon which of the several Framingham functions is chosen. Again the lower end of the range applies to older persons.

In summary, the reasons for retaining a system that estimates fatal as opposed to fatal+ non-fatal CVD are:

- Death is a hard and reproducible endpoint; a non-fatal event is variable and depends upon definitions, diagnostic criteria, and diagnostic tests, all of which may vary over time. Thus, the '20 % total CVD (or CHD)' risk used to denote high risk in many guidelines is likely to be variable, unstable over time, and hard to validate.
- A high risk of CVD death automatically indicates a higher risk of total events.
- The multiplier to convert fatal to total CVD is similarly unstable and is often less than clinicians expect, since follow-up is terminated in all current systems with the first event, and subsequent fatal or non-fatal events are not counted.

- The use of fatal CVD as the endpoint allows accurate re-calibration to other countries and cultures to adjust for time trends in mortality and in risk factor prevalence, an important consideration given the cultural diversity within Europe.

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. A particular problem relates to young people with high levels of risk factors: a low absolute risk may conceal a high relative risk requiring advice for intensive lifestyle measures. In the 2003 guidelines [44], it was suggested to extrapolate risk to age 60 to stress that a high absolute risk would occur if preventive action was not taken. This part of the text has been rephrased, and a relative risk chart added to the absolute risk charts to illustrate that, particularly in younger persons, lifestyle changes can reduce risk substantially as well as reducing the increase in risk that will occur with ageing. A new approach to this problem in these guidelines is cardiovascular risk age, which is explored later in this section.

Another problem relates to old people. In some age categories the majority, especially of men, will have estimated cardiovascular death risks exceeding the 5–10 % level, based on age (and gender) only, even when other cardiovascular risk factor levels are relatively low. This could lead to excessive use of drugs in the elderly. This issue is dealt with later in this section.

The role of high-density lipoprotein (HDL) cholesterol in risk estimation has been systematically re-examined using the SCORE database [48, 49]. This work has shown that HDL cholesterol can contribute substantially to risk estimation if entered as an independent variable. For example, HDL cholesterol modifies risk at all levels of risk as estimated from the SCORE cholesterol charts [50]. Furthermore, this effect is seen in both sexes and in all age groups, including older women [49]. This is particularly important at levels of risk just below the threshold for intensive risk modification of 5 %. Many of these subjects will qualify for intensive advice if their HDL cholesterol is low [50]. The electronic, interactive version of SCORE—HeartScore (available through www.heartscore.org) is currently being adapted to allow adjustment for the impact of HDL cholesterol on total risk.

The role of raised plasma triglycerides as a predictor of CVD has been debated for many years. Fasting triglycerides relate to risk in univariate analyses, but the effect is attenuated by adjustment for other factors, especially HDL cholesterol. After adjustment for HDL cholesterol, there is no significant association between triglycerides and CVD [52]. More recently, attention has focused on non-fasting triglycerides, which may be more strongly related to risk independently of the effects of HDL cholesterol [53–55].

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Heart rate has been shown to be an independent risk factor for CVD in the general population [56, 57]. Sudden cardiac death was particularly associated with elevated resting heart rate [57]. Measurement of resting heart rate should be done in the sitting position after 5 min rest and should form part of the routine physical examination when assessing cardiovascular risk.

Two large observational studies have demonstrated increased risk of cardiac events in individuals whose resting heart rate increased over time [58, 59]. However, the reverse has only been demonstrated in one of these studies; that individuals whose heart rate decreased over time had a lower risk of CVD [58]. No trial of heart rate lowering for CVD prevention in a healthy population has been conducted to date; therefore, pharmacological lowering of heart rate in primary prevention cannot be recommended.

Elevated heart rate has been shown to be associated with increased risk of further cardiac events in those with established CVD [60, 61]. In those post-myocardial infarction and in heart failure patients, use of beta-blockade in carefully titrated doses is associated with improved outcomes [62, 63]. More recently, in patients with resting heart rates ≥70 b.p.m. and reduced left ventricular function (either coronary artery disease or heart failure), trials of pure heart rate reduction have shown benefit [64, 65]. There is not enough evidence, at present, to recommend a target heart rate.

Dealing with the impact of additional risk factors such as HDL cholesterol, body weight, family history, and newer risk markers is difficult within the constraint of a paper chart. The electronic version of SCORE—HeartScore—is less constrained. It presently replicates SCORE in an electronic format but will be used to accommodate the results of new SCORE analyses, such as those relating to HDL cholesterol, as these are checked and validated. It should be stressed, however, that although many risk factors other than the few included in the available risk functions have been identified [such as C-reactive protein (CRP) and homocysteine levels], their contribution to absolute cardiovascular risk estimations of individual patients (in addition to traditional risk factors) is generally modest [66].

The impact of self-reported diabetes has been re-examined. While there is heterogeneity between cohorts, overall, the impact of diabetes on risk appears greater than in risk estimation systems based on the Framingham cohort, with relative risks of ~5 in women and 3 in men.

Some of the advantages of using the risk charts may be summarized:

Advantages of using the risk chart

- Intuitive, easy-to-use tool.
- Takes account of the multifactorial nature of cardiovascular disease.
- Allows flexibility in management if an ideal risk factor level cannot be achieved; total risk can still be reduced by reducing other risk factors.

- Allows a more objective assessment of risk over time.
- Establishes a common language of risk for clinicians.
- Shows how risk increases with age.
- The new 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.

The SCORE risk charts are shown in Figs. 3, 4 and 5, including a chart of relative risks. Instructions on their use and qualifiers follow.

Please note that the chart in Fig. 5 shows relative and not absolute risk. Thus a person in the top right-hand box has a risk that is 12 times higher than a person in the bottom left. This may be helpful when advising a young person with a low absolute but high relative risk of the need for lifestyle change.

Cardiovascular risk age

The risk age of a person with several cardiovascular risk factors is the age of a person with the same level of risk but with ideal levels of risk factors. Thus a high-risk 40 year old may have a risk age of ≥60 years. 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 cardiovascular disease will be exposed to if preventive measures are not adopted.

Risk age can be estimated visually by looking at the SCORE chart (as illustrated in Fig. 6). In this table, the risk age is calculated compared with someone with ideal risk factor levels, which have been taken as non-smoking, total cholesterol of 4 mmol/L (155 mg/dL), and blood pressure 120 mmHg [67]. Risk age is also automatically calculated as part of the latest revision of HeartScore (www.HeartScore.org).

Risk age has been shown to be independent of the cardiovascular endpoint used [67], which bypasses the dilemma of whether to use a risk estimation system based on CVD mortality or on the more attractive but less reliable endpoint of total CVD 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 re-calibration [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. It is not currently recommended to base treatment decisions on risk age.

What is a low-risk country? (countries in Fig. 4)

The fact that CVD mortality has declined in many European countries means that more countries 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 are based on 2008 CVD plus diabetes mortality in those aged 45–74 years (220/100 000 in men and 160/100 000 in women) [69]. This defines 21 countries and marks a point

Fig. 3 SCORE chart: 10-year risk of fatal cardiovascular disease (CVD) in countries at high CVD risk based on the following risk factors: age, sex, smoking, systolic blood pressure, and total cholesterol
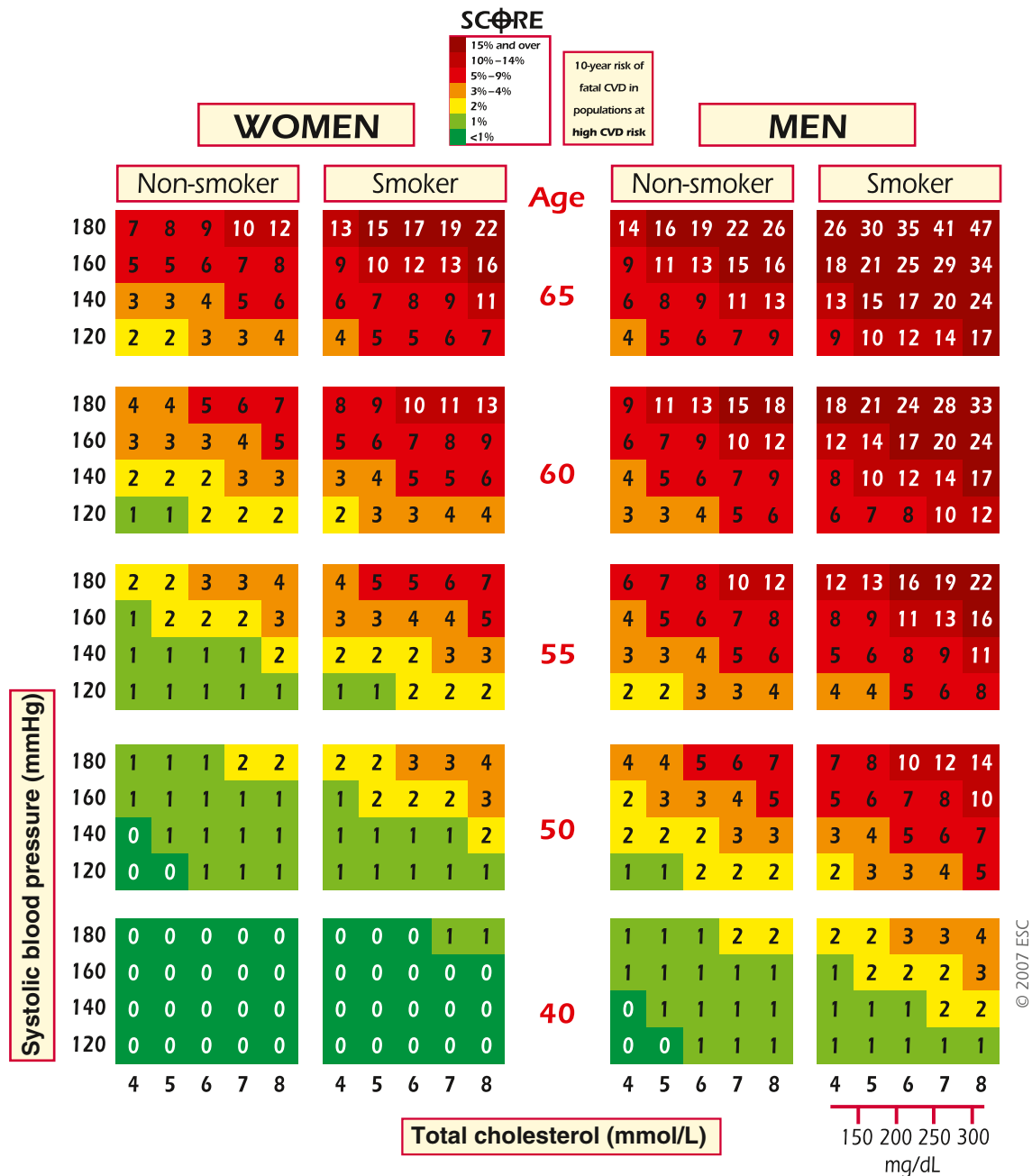
High CVD risk countries are all those not listed under the low risk chart (Figure 4). Of these, some are at very high risk, and the high-risk chart may underestimate risk in these. These countries are Armenia, Azerbaijan, Belarus, Bulgaria, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Macedonia FYR, Moldova, Russia, Ukraine, and Uzbekistan.

at which there is an appreciable gap before the 22nd country (Czech Republic).

This list is based on European countries that are ESC members. However, several European countries are not ESC members because they do not have a national cardiac society or because of size. In addition, the JTF felt it sensible to look also at Mediterranean countries that are ESC members while not strictly 'European' in WHO terminology.

Very-high-risk countries

Some European countries have levels of risk that are more than double the CVD mortality of 220/100 000 in men used to define low-risk countries. The male:female ratio is smaller than in low-risk countries, suggesting a major problem for women. Even the high-risk charts may underestimate risk in these countries. Countries with a CVD mortality risk of >500/100 000 for men and >250/100 000 for women are at very high risk and listed in Fig. 3. All remaining countries are high-risk countries.
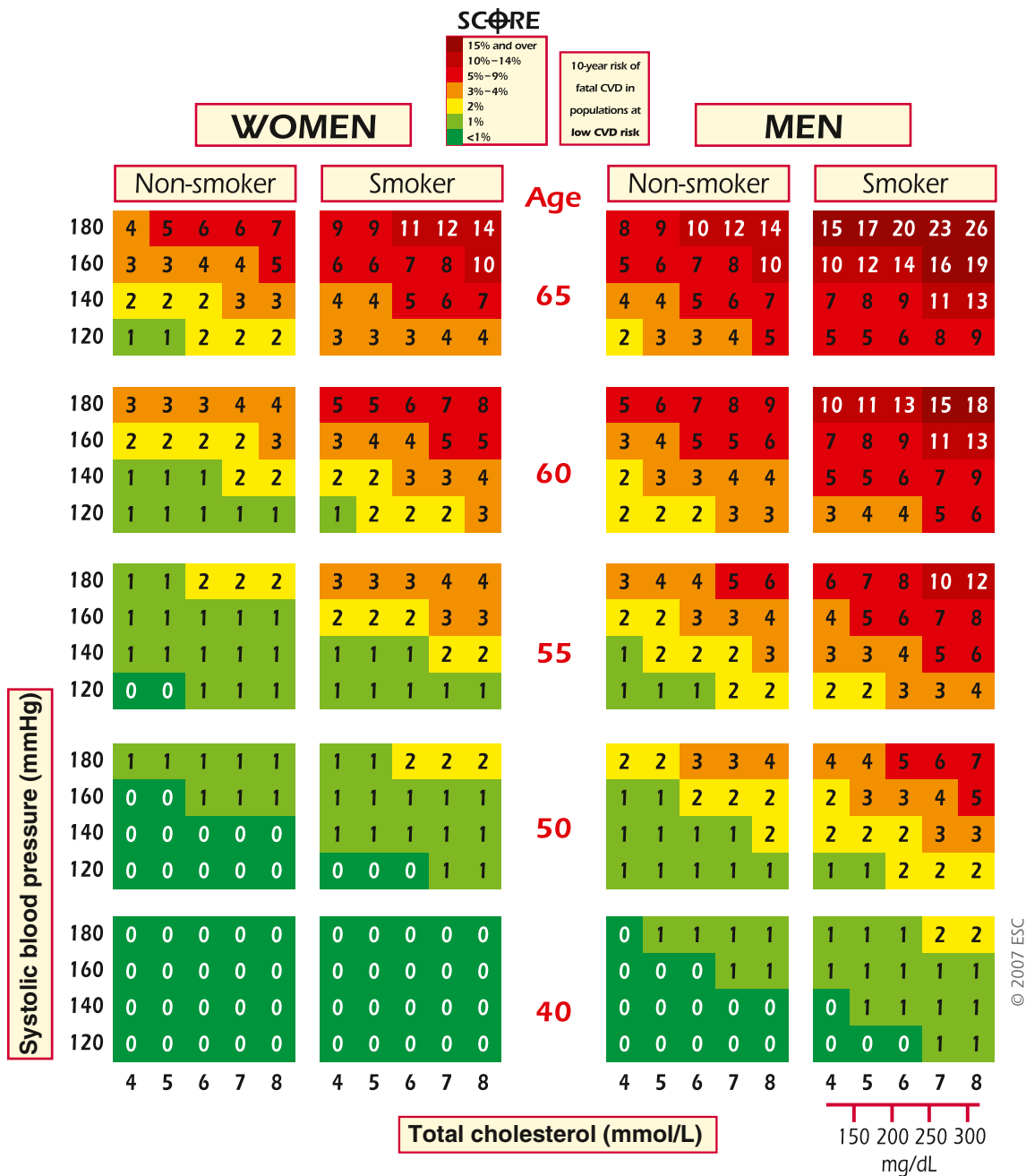
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Fig. 4 SCORE chart: 10-year risk of fatal cardiovascular disease (CVD) in countries at low CVD risk based on the following risk factors: age, sex, smoking, systolic blood pressure, and total cholesterol. Note that the risk of total (fatal + non-fatal) CVD events will be approximately three times higher than the figures given

How to use the risk estimation charts

- Use of the low-risk chart is recommended for the countries listed in Fig. 4. Use of the high-risk chart is recommended for all other European and Mediterranean countries. Note that several countries have undertaken national re-calibrations to allow for time trends in mortality and risk factor distributions. Such charts are likely to better represent current risk levels.

- To estimate a person's 10-year risk of CVD death, find the correct table for their gender, smoking status, and age. Within the table find the cell nearest to the person's BP and total cholesterol or cholesterol:HDL cholesterol ratio. Risk estimates will need to be adjusted upwards as the person approaches the next age category.
- Low-risk persons should be offered advice to maintain their low-risk status. While no threshold is universally
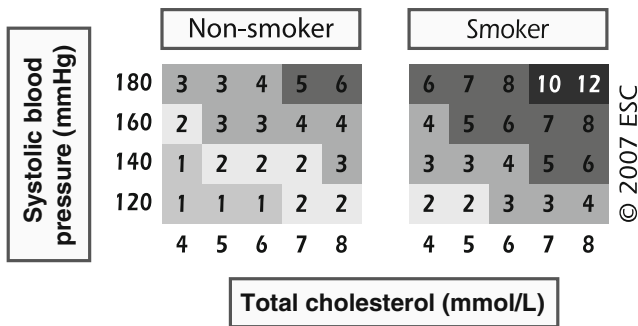
Fig. 5 Relative risk chart for 10-year mortality. Conversion of cholesterol mmol/L_mg/dL: 8 = 310, 7 = 270, 6 = 230, 5 = 190, 4 = 155

applicable, the intensity of advice should increase with increasing risk. In general, those with a risk of CVD death of ≥5 % qualify for intensive advice, and may benefit from drug treatment. At risk levels >10 %, drug treatment is more frequently required. In persons older than 60, these thresholds should be interpreted more leniently, because their age-specific risk is normally around these levels, even when other cardiovascular risk factor levels are 'normal'.

- The relative risk chart may be helpful in identifying and counselling in young persons, even if absolute risk levels are low
- 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 the results of RCTs in general give better estimates of benefits. Those who stop smoking in general halve their risk.

Qualifiers

- The charts can assist in risk assessment and management but must be interpreted in the light of the clinician's
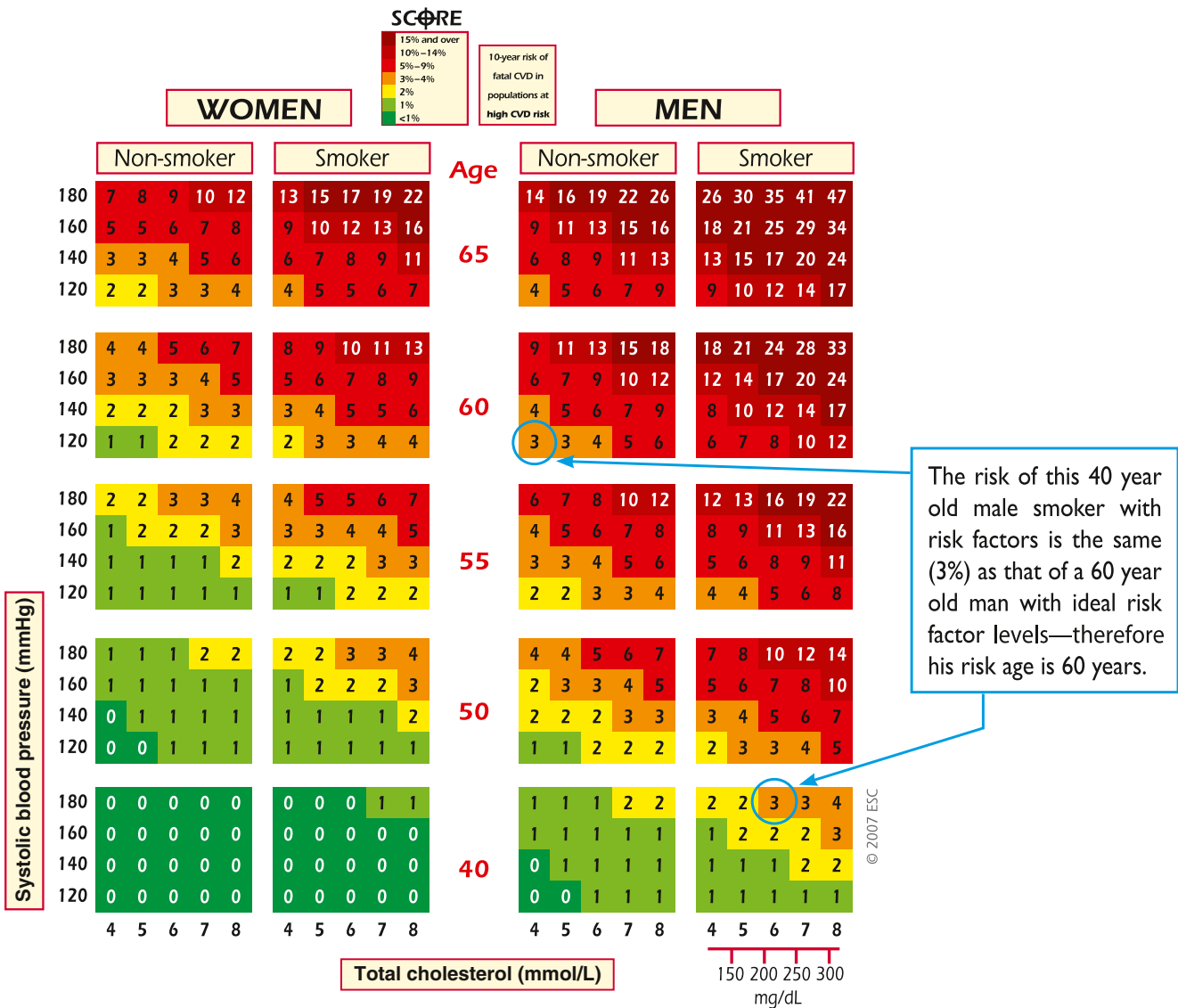
Fig. 6 Illustration of the risk–age concept

knowledge and experience, especially with regard to local conditions.

- Risk will be overestimated in countries with a falling CVD mortality, and underestimated in countries in which mortality is increasing.
- At any given age, risk estimates are lower for women than for men. Inspection of the charts indicates that risk is merely deferred in women, with a 60-year-old woman resembling a 50-year-old man in terms of risk.

Risk may also be higher than indicated in the charts in:

- Sedentary subjects and those with central obesity; these characteristics determine many of the other aspects of risk listed below. The increased risk associated with overweight is greater in younger subjects than in older subjects.
- Socially deprived individuals and those from ethnic minorities.
- Individuals with diabetes: SCORE charts should be used only in those with type 1 diabetes without target organ damage. Risk rises with increasing blood sugar concentration before overt diabetes occurs.
- Individuals with low HDL cholesterol, increased triglycerides, fibrinogen, apolipoprotein B (apoB), and lipoprotein(a) [Lp(a)] levels, especially in combination with familial hypercholesterolaemia, and perhaps increased high-sensitivity CRP (hsCRP). In particular, a low HDL level will indicate a higher level of risk in both sexes, all age groups, and at all levels of risk [49].
- Asymptomatic individuals with preclinical evidence of atherosclerosis, for example plaque on carotid ultrasonography.
- Those with moderate to severe chronic kidney disease [glomerular filtration rate (GFR) <60 mL/min/1.73 m^2].
- Positive family history of premature CVD.

Priorities
The higher the risk the greater the benefit from preventive efforts, which guides the following priorities:

1. Very high risk
   Subjects with any of the following:

   - Documented CVD by invasive or non-invasive testing (such as coronary angiography, nuclear imaging, stress echocardiography, carotid plaque on ultrasound), previous myocardial infarction, ACS, coronary revascularization (PCI, CABG), and other arterial revascularization procedures, ischaemic stroke, peripheral artery disease (PAD).
   - Diabetes mellitus (type 1 or type 2) with one or more CV risk factors and/or target organ damage (such as microalbuminuria: 30–300 mg/24 h).

   - Severe chronic kidney disease (CKD) (GFR <30 mL/min/1.73 m^2).
   - A calculated SCORE ≥10 %.

2. High risk
   Subjects with any of the following:

   - Markedly elevated single risk factors such as familial dyslipidaemias and severe hypertension.
   - Diabetes mellitus (type 1 or type 2) but without CV risk factors or target organ damage.
   - Moderate chronic kidney disease (GFR 30–59 mL/min/1.73 m^2).
   - A calculated SCORE of ≥5 % and <10 % for 10-year risk of fatal CVD.

3. Moderate risk
   Subjects are considered to be at moderate risk when their SCORE is ≥1 and <5 % at 10 years. Many middle-aged subjects belong to this category. This risk is further modulated by factors mentioned above.

4. Low risk
   The low-risk category applies to individuals with a SCORE <1 % and free of qualifiers that would put them at moderate risk.

These risk categories are compatible with the joint European Atherosclerosis Society/ESC lipid guidelines [70]. The joint guidelines offer further advice on lipid intervention based on these risk categories.

Conclusions
Estimation of total risk remains a crucial part of the present guidelines. The SCORE system has been updated with an estimate of total CVD risk as well as risk of CVD death. New information on diabetes is included. Information on relative as well as absolute risk is added to facilitate the counselling of younger persons whose low absolute risk may conceal a substantial and modifiable age-related risk.

The priorities defined in this section are for clinical use and reflect the fact that those at highest risk of a CVD event benefit 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, but they must be interpreted in the light of both the physician's detailed knowledge of their patient and local guidance and conditions.

Remaining gaps in the evidence

- Current systems of grading evidence give most weight to RCTs. While this is appropriate, many lifestyle measures are less amenable to such assessment than are drug

treatments, which will therefore tend to receive a higher grade. While the GRADE system attempts to address this issue, more debate is needed.

- There are no recent RCTs of a total risk approach to: (i) risk assessment; or (ii) 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.

3.2 Genetics

Key message

- The importance of the familial prevalence of early-onset CVD is not yet sufficiently understood in clinical practice.

Recommendations for genetic testing

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
DNA-based tests for common genetic polymorphisms do not presently add significantly to diagnosis, risk prediction, or patient management and cannot be recommended.	III	B	Strong	[71]
The added value of genotyping, as an alternative or in addition to phenotyping, for a better management of risk and early prevention in relatives, cannot be recommended.	III	B	Strong	[72]

[a]Class of recommendation
[b]Level of evidence
[c]References

Familial prevalence of atherosclerotic disease or of major risk factors (high BP, diabetes mellitus, hyperlipidaemia) should be systematically sought in the first-degree relatives of any patient affected before 55 years in men and 65 years in women [73]. This recommendation is not sufficiently applied. In SCORE, accounting for family history is probably very crude and is most certainly an underestimate. Family history is a variable combination of genetics and shared environment. There is evidence of strong heritability of many cardiovascular risk factors.

A number of genetic polymorphisms (sequence variants that occur at a frequency >1 %) appear to be associated with statistically significant effects on risk at the population level. Because of the polygenic and polyfactorial determinants of the most common CVDs, the impact of any single polymorphism remains rather modest. Genetic testing can identify variants associated with increased risk to individual CVD risk factors, CHD, or stroke. Commercial testing was recently made available to predict an individual's genetic risk, including direct-to-consumer testing. The clinical benefits of commercial testing have not yet been demonstrated [74].

In some conditions the process of genetic counselling can be optimized and extended with cascade screening, which identifies patients at risk and enables timely treatment of affected relatives, as is the case for familial hypercholesterolaemia [72, 75].

3.3 Age and Gender

Key messages

- CVD is by far the biggest cause of death in women.
- The risk of CVD in women, as in men, can be reduced by not smoking, by being active, avoiding overweight, and by having a blood pressure and blood cholesterol check (and intervention, if elevated).

Recommendation regarding age and gender

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
Women and older people should be included in CVD risk assessments in the same way as other groups to determine need for specific treatments.	I	B	Strong	[76, 77]

CVD = cardiovascular disease
[a]Class of recommendation
[b]Level of evidence
[c]References

Increasing age and male sex increase CVD risk and are 'fixed' characteristics used to stratify risk assessments [45]. Using age 55+ years as the only risk factor in determining need for pharmacological intervention with a combined low-dose antihypertensive, statin, and aspirin pill has been advocated [78]. However, exposure to common risk factors also increases with age, and between one-third and one-half of the age differences (between 25–49 vs. 50–59 and 60–64 years) in CHD risk in Finnish people is explained by smoking, HDL:total cholesterol ratio, SBP, body mass index (BMI), and diabetes [76]. Other risk factors such as physical inactivity and low socio-economic status are also likely to contribute to age differences in risk.

Age is a good marker of duration of exposure to known and unknown CHD risk factors. Relatively young people are at low absolute risk of a CVD event in the ensuing 10 years despite having a full complement of risk factors. For example, a man of 45 who smokes, has a SBP of 180 mmHg, and a blood cholesterol of 8 mmol/L has a risk of fatal CVD of only 4 % over 10 years (SCORE charts), suggesting no need for drug treatment. However, the relative risk chart (Fig. 5) indicates that his risk is already 12-fold higher than that of a man

with no risk factors. Five years later, when he reaches 50 years, his risk increases into the danger zone of 14 % over 10 years and he requires treatment. Similar considerations apply in women who are at lower absolute risk at younger ages and may have high levels of specific risk factors. In these circumstances, clinical judgement is required—risk scores guide and do not dictate treatment decisions. Investment in additional measurements such as imaging with computed tomography to obtain coronary calcium scores may be helpful [79], but adds considerably to the cost and time involved in risk factor scoring, and its benefit remains unproven [80].

CVD is the major cause of death in women in all European countries; below 75 years, 42 % of women die from CVD compared with 38 % of men [14]. The lower rates of CHD in women—but not of stroke—may be interpreted as a protective effect of endogenous oestrogens. However, exploration of trends over time and between countries shows that the relationship varies, making this an implausible explanation [81]. Sex differences in dietary fat intake (rather than excess smoking in men) may be responsible [81]. CVD mortality does not accelerate in women following the menopause, indicating that women are postponing their risk rather than avoiding it altogether. The American Heart Association (AHA) published an update of its guidelines for the prevention of CVD in women [82], which emphasizes that recommendations are the same for both men and women, with few exceptions. Use of the Framingham score is recommended but now includes a category of 'ideal cardiovascular health' comprising absence of raised risk factors, BMI <25 kg/m^2, regular moderate-to-vigorous physical activity, and a healthy diet. In the US Women's Health Initiative, only 4 % of women fell into this ideal state and a further 13 % had no risk factors but failed to follow a healthy lifestyle [83]. There was a 18 % difference in major CVD events in favour of the ideal lifestyle vs. the no-risk factor groups: 2.2 % and 2.6 % per 10 years, respectively.

Most important new information

- Asymptomatic women and older people benefit from risk scoring to determine management.

Remaining gaps in the evidence

- Clinical investigation to aid treatment decisions in younger people with high levels of risk factors requires further evaluation.

3.4 Psychosocial Risk Factors

Key messages

- Low socio-economic status, lack of social support, stress at work and in family life, depression, anxiety, hostility, and the type D personality contribute both to the risk of

developing CVD and the worsening of clinical course and prognosis of CVD.
- These factors act as barriers to treatment adherence and efforts to improve lifestyle, as well as to promoting health and wellbeing in patients and populations. In addition, distinct psychobiological mechanisms have been identified, which are directly involved in the pathogenesis of CVD.

Recommendation regarding psychosocial factors

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
Psychosocial risk factors should be assessed by clinical interview or standardized questionnaires. Tailored clinical management should be considered in order to enhance quality of life and CHD prognosis.	IIa	B	Strong	[84–86]

CHD = coronary heart disease
[a]Class of recommendation
[b]Level of evidence
[c]References

3.4.1 Risk Factors

Low socio-economic status
Multiple prospective studies have shown that men and women with low socio-economic status, defined as low educational level, low income, holding a low-status job, or living in a poor residential area, have an increased all-cause as well as CVD mortality risk [relative risk (RR) ~1.3–2.0] [87–91].

Social isolation and low social support
Recent systematic reviews confirm that people who are isolated or disconnected from others are at increased risk of dying prematurely from CVD. Similarly lack of social support leads to decreased survival and poorer prognosis among people with clinical manifestations of CVD (RR ~1.5–3.0) [92, 93].

Stress at work and in family life
According to a recent review, there is moderate evidence that work-related stress (e.g. high psychological demands, lack of social support, and job strain) are risk factors for incident CVD in men [odds ratio (OR) 1.5] [94, 95]. Studies involving women were too few to draw firm conclusions [94]. Conflicts, crises, and long-term stressful conditions in family life have also been shown to increase CHD risk [hazard ratio (HR) ~2.7–4.0], especially in women (RR ~2.9–4.0) [96, 97].

Depression
Several systematic reviews and meta-analyses have shown that clinical depression and depressive symptoms predict incident CHD (RR 1.6 and 1.9) [98–100], and worsen its prognosis (OR 1.6 and 2.4) [100–102]. Perceived social support seems to

counteract the adverse effect of depression [103], whereas lack of support was found to reinforce its adverse effects [104].

Anxiety

Large epidemiological studies indicate that panic attacks increase the risk of incident cardiovascular events (HR 1.7 and 4.2, respectively) [105, 106], and generalized, phobic anxiety, and panic attacks may worsen the course of established CVD (OR 1.01 and 2.0, respectively) [107–109]. In contrast to these findings, a recent post-hoc analysis of a large prospective cohort study found a lower all-cause mortality in anxious CVD patients (HR 0.7). A higher mortality could only be observed in post-myocardial infarction patients with reduced systolic left ventricular function (HR 1.3), suggesting antipodal effects of anxiety in different subgroups of CVD patients [110]. However, two recent meta-analyses confirmed that anxiety is an independent risk factor for incident CHD (HR 1.3) [111] and for adverse events following myocardial infarction (OR 1.5 and 1.7, respectively) [112].

Hostility and anger

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 recent meta-analysis has confirmed that anger and hostility are associated with an increased risk for cardiovascular events in both healthy and CVD populations (HR 1.2) [113]. Failure to express anger might be of particular importance, as patients with CVD who suppress their anger have an increased risk of adverse cardiac events (OR 2.9) [114].

Type D personality

In contrast to isolated depressive and anxious symptoms, which often occur in episodes, the type D ('distressed') personality involves an enduring tendency to experience a broader 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 CVD (OR 3.7), even after adjustment for depressive symptoms, stress, and anger [115].

3.4.2 Clustering of Psychosocial Risk Factors and Bio-Behavioural Mechanisms

In most situations, psychosocial risk factors cluster in the same individuals and groups. For example, both women and men of lower socioeconomic status and/or with chronic stress are more likely to be depressed, hostile, and socially isolated [116, 117].

Mechanisms that link psychosocial factors to increased CVD risk include unhealthy lifestyle (more frequent smoking, unhealthy food choice, and less physical exercise), increased healthcare utilization, and low adherence to behaviour-change recommendations or cardiac medications [88, 90, 116–119]. Financial barriers to healthcare have also been shown to predict negative outcomes after myocardial infarction [91].

In addition, persons and patients with depression and/or chronic stress show alterations in autonomic function (including reduced heart rate variability) in the hypothalamic–pituitary axis and in other endocrine markers, which affect haemostatic and inflammatory processes, endothelial function, and myocardial perfusion [117, 118, 120]. Enhanced risk in patients with depression may also be due in part to adverse effects of tricyclic antidepressants [121, 122].

3.4.3 Assessment of Psychosocial Risk Factors

The assessment of psychosocial factors in patients and persons with CVD risk factors is crucial as a means to stratify future preventive efforts according to the individual risk profile of the patient. Standardized measurements for depression, anxiety, hostility, socio-economic status, social support, psychosocial stress, and type D personality are available in many languages and countries [115, 123]. Alternatively, a preliminary assessment of psychosocial factors can be made within the physicians' clinical interview, as detailed in Table 6.

Table 6 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?
Depression	Do you feel down, depressed, and hopeless?
	Have you lost interest and pleasure in life?
Anxiety	Do you frequently feel nervous, anxious, or on edge?
	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?

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No more than mandatory education and/or a 'yes' for one or more items indicates a higher risk than that assessed with the SCORE tools or priority categories. Relevance of psychosocial factors with respect to quality of life and medical outcome should be discussed with the patient, and further tailored clinical management should be considered ("Management of Psychosocial Factors"). Routine screening for depression does not contribute to better cardiac prognosis in the absence of changes in current models of cardiovascular care [124].

Most important new information

- Recent meta-analyses have shown that symptoms of anxiety and the type D personality increase risk for CVD and contribute to worse clinical outcome.

Remaining gaps in the evidence

- There is limited evidence that routine screening for psychosocial risk factors contributes to fewer future cardiac events, as screening has not yet translated into improved healthcare models.

3.5 Other Biomarkers of Risk

Key messages

- Novel biomarkers have only limited additional value when added to CVD risk assessment with the SCORE algorithm.
- High-sensitive CRP and homocysteine may be used in persons at moderate CVD risk.

Recommendations for inflammatory biomarkers

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
High-sensitivity CRP may be measured as part of refined risk assessment in patients with an unusual or moderate CVD risk profile.	IIb	B	Weak	[125]
High-sensitivity CRP should not be measured in asymptomatic low-risk individuals and high-risk patients to assess 10-year risk of CVD.	III	B	Strong	[126]
Fibrinogen may be measured as part of refined risk assessment in patients with an unusual or moderate CVD risk profile.	IIb	B	Weak	[127]
Fibrinogen should not be measured in asymptomatic low-risk individuals and high-risk patients to assess 10-year risk of CVD.	III	B	Strong	[127]

CRP = C-reactive protein; CVD, cardiovascular disease
[a]Class of recommendation
[b]Level of evidence
[c]References

Recommendations for thrombotic biomarkers

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
Homocysteine may be measured as part of a refined risk assessment in patients with an unusual or moderate CVD risk profile.	IIb	B	Weak	[128]
Homocysteine should not be measured to monitor CVD risk prevention.	III	B	Strong	[128]
LpPLA2 may be measured as part of a refined risk assessment in patients at high risk of a recurrent acute atherothrombotic event.	IIb	B	Weak	[129]

CVD, cardiovascular disease; LpPLA2 = lipoprotein-associated phospholipase
[a]Class of recommendation
[b]Level of evidence
[c]References

Although the number of potential novel risk markers is ever expanding yearly, this number scales down to a level close to unity once the possible candidates have passed through the grading of clinical evidence. Emerging biomarkers were selected from published data, if tested as alternatives or on top of classical risk factors, for their ability to predict or modify 10-year cardiovascular morbidity or mortality. Only circulating biomarkers assessed by standardized and validated methods (and identified as risk factors worth translating into clinical practice) were considered in these guidelines, in a context of cost-effectiveness for assessment of individual risk in the general population.

After removing novel biomarkers relevant to glucose metabolism, lipid metabolism, or organ-specific biomarkers, which are included in the specific sections (see "How can cardiovascular disease prevention be used?"), two groups of systemic biomarkers relevant to CVD risk assessment were identified:

- Inflammatory: hsCRP, fibrinogen.
- Thrombotic: homocysteine, lipoprotein-associated phospholipase (LpPLA2).

3.5.1 Inflammatory: High-Sensitivity C-Reactive Protein, Fibrinogen

High-sensitivity CRP has shown consistency across large prospective studies as a risk factor integrating multiple metabolic and low-grade inflammatory factors underlying the development of unstable atherosclerotic plaques, with a magnitude of effect matching that of classical major risk factors. This marker was used in individuals showing a moderate level of risk from clinical assessment of major CVD risk factors [125, 126]. However, several weak points

exist when including this novel biomarker for risk assessment:

- Multiplicity of confounders: dependence on other classical major risk factors.
- Lack of precision: narrow diagnostic window for hsCRP level and risk of CVD.
- Lack of specificity: similar level of risk for other non-cardiovascular causes of morbidity and mortality (e.g. other low-grade inflammatory diseases).
- Lack of dose–effect or causality relationship between changes in hsCRP level and risk of CVD.
- Lack of specific therapeutic strategies or agents targeting circulating CRP and showing reduction in CVD incidence.
- Higher cost of test compared with classical biological risk factors (e.g. blood glucose and lipids).
- Similar statements are made for fibrinogen [127].

3.5.2 Thrombotic

Homocysteine

Homocysteine has shown precision as an independent risk factor for CVD. The magnitude of effect on risk is modest, and consistency is often lacking, mainly due to nutritional, metabolic (e.g. renal disease), and lifestyle confounders [128]. In addition, intervention studies using B vitamins to reduce plasma homocysteine have proven inefficient in reducing risk of CVD [128]. Together with the cost of the test, homo-cysteine remains a 'second-line' marker for CVD risk estimation.

Lipoprotein-associated phospholipase 2

LpPLA2 has recently emerged as a marker with high consistency and precision as an independent risk factor for plaque rupture and atherothrombotic events. The magnitude of effect on risk remains modest at the level of the general population; study limitations or bias are present. Together with the cost of the test, LpPLA2 remains a 'second-line' marker for CVD risk estimation [129].

Most important new information

- Overall, emerging validated biomarkers may add value in a context of specialized practice, to assess CVD risk more precisely in specific subgroups of patients at moderate, unusual, or undefined levels of risk (e.g. asymptomatic patients without multiple major classical risk factors, but affected with a rare metabolic, inflammatory, endocrine, or social condition associated with atherosclerosis or displaying signs of atherosclerosis progression).

Remaining gaps in the evidence

- For both biomarkers that are already well-established and novel biomarkers that arise in the future there is a need to redefine specific subgroups (intermediate, undefined, or unusual CVD risk) that would benefit most from the use of these biomarkers, particularly in early primary prevention.

3.6 Imaging Methods in Cardiovascular Disease Prevention

Key message

- Imaging methods can be relevant in CVD risk assessment in individuals at moderate risk.

Recommendations regarding imaging methods

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
Measurement of carotid intima-media thickness and/or screening for atherosclerotic plaques by carotid artery scanning should be considered for cardiovascular risk assessment in asymptomatic adults at moderate risk.	IIa	B	Strong	[130–132]
Measurement of ankle–brachial index should be considered for cardiovascular risk assessment in asymptomatic adults at moderate risk.	IIa	B	Strong	[133–135]
Computed tomography for coronary calcium should be considered for cardiovascular risk assessment in asymptomatic adults at moderate risk.	IIa	B	Weak	[136–138]
Exercise electrocardiography may be considered for cardiovascular risk assessment in moderaterisk asymptomatic adults (including sedentary adults considering starting a vigorous exercise programme), particularly when attention is paid to non-electrocardiogram markers such as exercise capacity.	IIb	B	Strong	[46, 139, 140]

[a]Class of recommendation
[b]Level of evidence
[c]References

The consequences of coronary atherosclerosis can be objectively assessed non-invasively using a variety of techniques such as bicycle or treadmill exercise electrocardiogram (ECG) testing, stress echocardiography, or radionuclide scintigraphy. Unfortunately, sudden cardiac death is for many individuals the first manifestation of CVD. Detection of asymptomatic but diseased patients is crucial for an adequate prevention programme.

At every level of risk factor exposure, there is substantial variation in the amount of atherosclerosis. This variation in disease is probably due to genetic susceptibility, combinations

of different risk factors, and interactions between genetic and environmental factors. Thus measurements of subclinical disease may be useful for improving CVD risk prediction. Non-invasive tests such as carotid artery scanning, electron-beam computed tomography, multislice computed tomography, ankle–brachial BP ratios, and magnetic resonance imaging (MRI) techniques offer the potential for directly or indirectly measuring and monitoring atherosclerosis in asymptomatic persons, but cost-effectiveness needs to be documented.

3.6.1 Early Detection by Magnetic Resonance Imaging of Cardiovascular Disease in Asymptomatic Subjects

Magnetic resonance imaging has been evaluated as a means of assessing coronary artery stenosis. The value of this technique is still in question [141, 142]. Currently, the sensitivity, specificity, and robustness of this technique are not sufficiently high to perform screening for coronary stenoses in asymptomatic people.

Recently, coronary wall MRI detected positive remodelling in asymptomatic patients with subclinical atherosclerosis, opening up a new research field in the prevention of CVD [143]. In vitro, MRI can differentiate the plaque components of carotid, aortic, and coronary artery specimens obtained at autopsy [144]. The current fast technical improvement has led to three-dimensional black blood vessel wall imaging, which permits in vivo distinction of 'normal' and diseased vessel walls [145]. At present, MRI is a promising research tool, but its routine use remains limited and it is not yet appropriate for identifying patients at high risk for CVD [146].

3.6.2 Coronary Calcium Score

Coronary calcifications indicate atherosclerosis of coronary arteries [147]. On the other hand, atherosclerotic diseased coronary arteries do not necessarily always show calcifications. The extent of the calcification correlates with the extent of the total coronary plaque burden [147]. Coronary calcification is an indicator neither of stability nor of instability of an atherosclerotic plaque [148]. In patients with an ACS, the extent of coronary calcification is more pronounced than in control groups without known CHD [149]. Moreover, the inflammatory component has been emphasized for patients with an ACS [150], underlining the concept of evaluation of the total coronary plaque burden by quantification of coronary calcium burden [151].

Most scientific data on the evaluation of the presence and extent of coronary calcified atherosclerosis are related to the use of the 'Agatston score' [152].

Recently it has been suggested that the score is to be replaced with volumetric variables, such as total calcium volume (mm^3), calcium mass (mg), or calcium density (mg/mm^3). For clinical purposes, however, it is not yet known if these new variables are superior to the Agatston score [153]. The value of the score can be further increased if the age and gender distribution within percentiles are also taken into account [153].

The presence of coronary calcium is not in the least identical to the presence of relevant coronary stenosis because its specificity regarding the presence of ≥50 % stenosis is only 50 %. Misunderstandings in recent years regarding coronary calcium and extrapolation to CHD are due to a mix-up of definitions: while the presence of coronary calcium proves a 'coronary disease' (coronary atherosclerosis)—it does not necessarily reflect 'CHD' defined as ≥50 % narrowing.

In contrast, coronary calcium scanning shows a very high negative predictive value: the Agatston score of 0 has a negative predictive value of nearly 100 % for ruling out a significant coronary narrowing [154]. However, recent studies have questioned the negative predictive value of the calcium score: the presence of significant stenosis in the absence of coronary calcium is possible. It is more likely in the setting of unstable angina or non-ST elevation myocardial infarction (NSTEMI) than in stable chest pain, and occurs more frequently in younger patients [155]. Many prospective studies have shown the prognostic relevance of the amount of coronary calcium [156].

The Agatston score is an independent risk marker regarding the extent of CHD [157] and prognostic impact [158]. The Rotterdam calcification study showed that the upper percentile range reflects a 12-fold increased risk of myocardial infarction—independent of the classical risk factors—even in elderly people [159].

Although calcium scanning is widely applied today, it is especially suited for patients at moderate risk [137]. The radiation exposure with the properly selected techniques is ~1 mSv. Recent studies have also shown that multislice computed tomography coronary angiography with decreased radiation levels is highly effective in re-stratifying patients into either a low or high post-test risk group [160].

3.6.3 Carotid Ultrasound

Population-based studies have shown a correlation between the severity of atherosclerosis in one arterial territory and the involvement of other arteries [130]. Therefore, early detection of arterial disease in apparently healthy individuals has focused on the peripheral arterial territory and on the carotid arteries. Risk assessment using carotid ultrasound focuses on the measurement of the intima-media thickness (IMT) and the presence of plaques and their characteristics.

The IMT is a measurement not only of early atherosclerosis but also of smooth muscle hypertrophy/hyperplasia, which may be related even to genetic factors, hypertension, and age-related sclerosis [132]. Although there is a graded increase in cardiovascular risk with rising IMT, a value >0.9 mm is considered abnormal. Persons without known CVD with

increased IMT are at increased risk for cardiac events and stroke. Although the relative risk for events is slightly lower after statistical correction for the presence of traditional risk factors, the risk remains elevated at higher IMT [130].

When IMT is used to predict the incidence of subsequent stroke, the risk is graded but non-linear, with hazards increasing more rapidly at lower IMTs than at higher IMTs [130]. The risk of cardiac events over 4–7 years of follow-up in patients free of clinical CVD at baseline is also non-linearly related to IMT [131].

Plaque is defined as a focal structure of the inner vessel wall at least ≥0.5 mm (or >50 %) of the surrounding IMT, or any IMT measurement ≥1.5 mm. Plaques may be characterized by their number, size, irregularity, and echodensity (echolucent vs. calcified). Plaques are related to both coronary obstructive disease and the risk of cerebrovascular events. Echolucent plaques imply an increased risk of cerebrovascular events as compared with calcified plaques.

Plaque characteristics as assessed by carotid ultrasound were found to be predictive of subsequent cerebral ischaemic events [131]. Patients with echolucent stenotic plaques had a much higher risk of cerebrovascular events than subjects with other plaque types. Ultrasound imaging of the carotids is a non-invasive means of assessing subclinical atherosclerosis. The extent of carotid IMT is an independent predictor of cerebral and coronary events, but seems to be more predictive in women than in men. Consequently, carotid ultrasound can add information beyond assessment of traditional risk factors that may help to make decisions about the necessity to institute medical treatment for primary prevention.

Arterial stiffness has been shown to provide added value in stratification of patients. An increase in arterial stiffness is usually related to damage in the arterial wall, as has been suggested in hypertensive patients [161, 162].

3.6.4 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, an ABI <0.90 is considered to be a reliable marker of PAD [133]. An ABI value indicating significant PAD adds additional value to medical history, because 50–89 % of patients with an ABI <0.9 do not have typical claudication [134]. In asymptomatic individuals over 55 years of age, an ABI <0.9 may be found in 12–27 %. Even in an elderly population (71–93 years), a low ABI further identifies a higher risk CHD subgroup.

The ABI also predicts further development of angina, myocardial infarction, congestive heart failure, CABG surgery, stroke, or carotid surgery [135]. ABI is inversely related to CVD risk [163].

3.6.5 Ophthalmoscopy

It has been shown that the extent of retinal artery atherosclerosis correlates with the extent of coronary artery atherosclerosis and with serum levels of cholesterol, triglycerides, and apoB [164]. However, its place in vascular disease risk assessment remains uncertain.

Most important new information

- Vascular ultrasound screening is reasonable for risk assessment in asymptomatic individuals at moderate risk.
- Measurement of coronary artery calcifications may be reasonable for cardiovascular risk assessment in asymptomatic adults at moderate risk.

Remaining gaps in the evidence

- The role of computed tomography scanning for screening in asymptomatic patients needs further investigation.
- Prospective studies proving the value of coronary scanning (level A evidence) do not as yet exist.
- Magnetic resonance imaging for detection of vascular plaque may be of interest for cardiovascular risk assessment in asymptomatic adults, but studies are still not convincing.

3.7 Other Diseases with Increased Risk for Cardiovascular Disease

Atherosclerosis is an inflammatory disease in which immune mechanisms interact with metabolic risk factors to initiate, propagate, and activate lesions in the arterial tree [165]. Several diseases in which infection or non-infectious inflammatory processes determine the clinical picture are associated with an increased cardiovascular event rate. The optimal concept of prevention in these diseases is not established, and randomized studies evaluating prognosis are not available. Management of all risk factors appears advisable even in the absence of randomized studies.

Recommendations regarding other diseases with increased risk for cardiovascular disease

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
In patients with chronic kidney disease, risk factors have to be attended to in the same way as for very highrisk persons.	I	C	Strong	[166, 167]
All persons with obstructive sleep apnoea should undergo medical assessment, including risk stratification and risk management.	IIa	A	Strong	[168, 169]

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Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
All men with erectile dysfunction should undergo medical assessment, including risk stratification and risk management.	IIa	B	Strong	[170]

[a]Class of recommendation
[b]Level of evidence
[c]References

3.7.1 Influenza

Influenza epidemics are associated with an increased rate of cardiovascular events. Influenza vaccination as a population-wide prevention measure was associated with a very cost-effective reduction in clinical events [171]. Annual influenza vaccinations are recommended for patients with established CVD [172].

3.7.2 Chronic Kidney Disease

Hypertension, dyslipidaemia, and diabetes mellitus are common among patients with CKD. They are major risk factors for the development and progression of endothelial dysfunction and atherosclerosis, and contribute to the progression of renal failure—yet these patients tend to be less intensely treated than patients with normal renal function [166]. Inflammatory mediators and promoters of calcification are increased and inhibitors of calcification are reduced in CKD, which favours vascular calcification and vascular injury [136]. Microalbuminuria increases cardiovascular risk two-to-four-fold. A decreasing GFR is an indicator of increased risk for CVD and all-cause mortality. In a large cohort study, anaemia, decreased GFR, and microalbuminuria were independently associated with CVD and, when all were present, CVD was common and survival was reduced [173].

There is a quantitative association between decreased GFR and cardiovascular risk: patients with moderately decreased renal function (stage 3, GFR 30–59 mL/min/1.73 m^2) have a two-to four-fold increased risk in comparison with persons free of CKD. The risk increases to four-to 10-fold in stage 4 (GFR 15–29 mL/min/1.73 m^2) and to 10-to 50-fold in stage 5 renal failure (end-stage) (GFR <15 mL/min/1.73 m^2 or dialysis) [136].

Lipid lowering appears useful in a wide range of patients with advanced CKD but with no known history of myocardial infarction or coronary revascularization: a reduction of low-density lipoprotein (LDL) cholesterol by 0.85 mmol/L (33 mg/dL) with daily 20 mg simvastatin plus 10 mg ezetimibe reduced the incidence of major events: non-fatal myocardial infarction, coronary death, non-haemorrhagic stroke, or any arterial revascularization procedure [174].

3.7.3 Obstructive Sleep Apnoea

Obstructive sleep apnoea (OSA) 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 [175].

Repetitive bursts of sympathetic activity, surges of blood pressure, 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 [176]. OSA has been associated with a 70 % relative increased risk of cardiovascular morbidity and mortality [177]. The risk correlates in men between 40 and 70 years with the apnoea–hypopnea index [168]. Screening for and treating OSA in patients with chronic coronary artery disease [178] and hypertension may result in decreased cardiac events and cardiac death [169].

3.7.4 Erectile Dysfunction

Erectile dysfunction (ED), defined as the consistent inability to reach and maintain an erection satisfactory for sexual activity, afflicts to some degree 52 % of male adults between the ages of 40 and 70 years. It may result from psychological, neurological, hormonal, arterial, or caver nosal impairment or from a combination of these factors [179–181]. ED has a high prevalence in individuals with multiple cardiovascular risk factors and in individuals with CVD. ED is a marker for CVD and a predictor of future events in middle-aged and older men but not beyond that offered by the Framingham risk score [182–184]. Lifestyle modification and pharmacotherapy for risk factors are effective in improving sexual function in men with ED [170].

3.7.5 Autoimmune Diseases

Psoriasis Psoriasis appears to be an independent risk factor for myocardial infarction. The pathophysiology of psoriasis is characterized by an increase in antigen presentation, T-cell activation, and T-helper cell type 1 cytokines, resulting in thick scaly red plaques and, in some patients, arthritis. Psoriasis is also associated with markers of systemic inflammation, such as increased CRP levels. The risk of myocardial infarction associated with psoriasis is greatest in young patients with severe psoriasis, is attenuated with age, and remains increased even after controlling for traditional cardiovascular risk factors. Patients in whom the psoriasis was classified as severe had a higher risk of myocardial infarction than patients with mild psoriasis, consistent with the hypothesis that greater immune activity in psoriasis is related to a higher risk of myocardial infarction and cardiovascular death [185, 186].

Rheumatoid Arthritis Patients with rheumatoid arthritis are twice as likely as the general population to suffer a

myocardial infarction. They also have a higher mortality rate after myocardial infarction, which may only partially explain their reduced life expectancy (5–10 years shorter than patients without the condition). CVD risk is increased at an early stage of the disease, and this risk excess beyond traditional risk parameters is possibly related to systemic inflammation and a prothrombotic state.

Modification of traditional risk factors through lifestyle changes, including dietary modification, smoking cessation, and increased daily exercise, and appropriate drug prescription may be of particular importance in reducing risk in individuals with psoriasis or rheumatoid arthritis.

Non-randomized observational studies report reductions in rates of vascular events and cardiovascular death among both rheumatoid arthritis and psoriasis patients being treated with weekly methotrexate in doses ranging from 10 to 20 mg [187, 188].

Lupus Erythematosus Systemic lupus erythematosus is associated with endothelial dysfunction and an increased risk of CHD that is not fully explained by classic CHD risk factors.

Chronic systemic inflammation in patients with systemic lupus erythematosus results in coronary microvascular dysfunction, with abnormalities in absolute myocardial blood flow and coronary flow reserve. Coronary microvascular dysfunction is an early marker of accelerated coronary atherosclerosis and may contribute to the increased cardiovascular morbidity and mortality in these patients [189].

3.7.6 Periodontitis

Periodontitis is associated with endothelial dysfunction, atherosclerosis, and an increased risk of myocardial infarction and stroke. Confounding factors, however, such as low socio-economic status and cigarette smoking probably play a significant role. Periodontitis can be considered a risk indicator for a generally decreased cardiovascular health status and its treatment is indicated as well as management of the underlying cardiovascular risk factors [190].

3.7.7 Vascular Disease after Radiation Exposure

The incidence of ischaemic heart disease and stroke is increased many years after radiation exposure for treatment of lymphomas and for breast cancer, as well as for head and neck cancer [191, 192].

From descriptive studies, the lesions exhibit typical features of atherosclerosis, including lipid accumulation, inflammation, and thrombosis [193]. Patients after radiation exposure should make great efforts to optimize their risk factor profile. The use of statins may be reasonable.

3.7.8 Vascular Disease after Transplantation

Cardiac allograft vasculopathy is the leading cause of late morbidity and mortality in heart transplant patients. Although it is a complex multi-factorial process arising from immune and non-immune pathogenic mechanisms, the approach to cardiac allograft vasculopathy has been modification of underlying traditional risk factors and optimization of immune suppression. Important non-immune risk factors include hyperlipidaemia, hypertension, diabetes mellitus, and hyperhomocysteinaemia. Administration of statins improves endothelial dysfunction, slows the development of cardiac allograft vasculopathy, and benefits survival [194].

Most important new information

- Treatment of periodontitis improves endothelial dysfunction, one of the earliest signs of atherosclerosis.

Remaining gaps in the evidence

- Randomized studies are lacking except in patients with vascular disease after transplantation.

4 How can Cardiovascular Disease Prevention be Used?

4.1 Principles of Behaviour Change

Key message

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

Recommendations for behavioural change

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
Established cognitive-behavioural strategies (e.g. motivational interviewing) to facilitate lifestyle change are recommended.	I	A	Strong	[195, 196]
Specialized healthcare professionals (e.g. nurses, dieticians, psychologists, etc.) should be involved whenever necessary and feasible.	IIa	A	Strong	[185, 197, 198]
In individuals at very high CVD risk, multimodal interventions, integrating education on healthy lifestyle and medical resources, exercise training, stress management, and counselling on psychosocial risk factors, are recommended.	I	A	Strong	[195, 197, 199, 200]

CVD = cardiovascular disease
[a]Class of recommendation
[b]Level of evidence
[c]References

4.1.1 Introduction: Why Do Individuals Find it Hard to Change Their Lifestyle?

'Lifestyle' is usually based on long-standing behavioural patterns. These patterns are framed during childhood and adolescence by an interaction of environmental and genetic factors, and are maintained or even promoted by the individual's social environment as an adult. Consequently, marked differences in health behaviour between individuals but also between social groups can be observed. In addition, these factors impede the ability to adopt a healthy lifestyle, as does complex or confusing advice from medical caregivers. Increased awareness of these factors facilitates empathy and counselling (simple and explicit advice), thus facilitating behavioural change.

4.1.2 Effective Communication and Cognitive-Behavioural Strategies as a Means towards Lifestyle Change

A friendly and positive interaction is a powerful tool to enhance an individual's ability to cope with illness and adhere to recommended lifestyle changes and medication use. Social support provided by caregivers may be of importance in helping individuals maintain healthy habits and follow medical advice. It is of special importance to explore each individual patient's experiences, thoughts and worries, previous knowledge, and circumstances of everyday life. Individualized counselling is the basis for evoking and gaining the patient's motivation and commitment. Decision-making should be shared between caregiver and patient (also including the individual's spouse and family) to the greatest extent possible, thus ensuring the active involvement of both the individual and family in lifestyle change and medication adherence. Use of the following principles of communication will facilitate treatment and prevention of CVD (Table 7).

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 in which attempts to change are made, and subsequently to maintain the lifestyle change. Behavioural interventions such as 'motivational interviewing' [201] increase motivation and self-efficacy [196]. Previous negative, unsuccessful attempts to change behaviour often result in a lower self-efficacy for future change and often lead to another failure. A crucial step in changing negative into positive experiences is to help the individual to set realistic goals; goal setting combined with self-monitoring of the chosen behaviour are the main tools needed to achieve a positive outcome [202]. This will in turn increase self-efficacy for the chosen behaviour; thereafter, new goals can be set. Moving forward in small, consecutive steps is one of the key points in changing long-term behaviour [202]. The way of offering relevant information must be sensitive to the particular patient's

Table 7 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 they require to follow it.
- Acknowledge that changing life-long habits can be difficult and that gradual change that is sustained 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.

thoughts and feelings. As this is a specific clinical skill, communication training is important for health professionals.

The following 'Ten strategic steps' have been shown to enhance counselling on behavioural change effectively (Table 8) [203].

4.1.3 Multimodal, Behavioural Interventions

Combining the knowledge and skills of clinicians (such as physicians, nurses, psychologists, and experts in nutrition,

Table 8 'Ten strategic steps' to enhance counselling on behavioural change [203]

1. Develop a therapeutic alliance.
2. Counsel all individuals at risk of or with manifest cardiovascular disease.
3. Assist the 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.

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cardiac rehabilitation, and sports medicine) into multimodal, behavioural interventions can help to optimize the preventive efforts [35, 202, 204, 205].

Multimodal, behavioural interventions are especially recommended for individuals at very high risk and for individuals with clinically manifest CVD. These interventions include promoting a healthy lifestyle through behaviour change including nutrition, exercise training, relaxation training, weight management, and smoking cessation programmes for resistant smokers [204]. They enhance coping with illness, and improve adherence with prescribed medication, efforts to change behaviour, and cardiac outcome [195, 197, 198]. 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 [195, 204].

There is evidence that more extensive/longer interventions may lead to better long-term results with respect to behaviour change and somatic outcome [195, 202]. Individuals of low socio-economic status, of older age, or female gender may need tailored programmes in order to meet their specific needs regarding information and emotional support [202, 206].

Most important new information

- Evidence has confirmed cognitive-behavioural strategies to be essential components of interventions targeting lifestyle change.

Remaining gaps in the evidence

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

4.2 Smoking

Key messages

- Changing smoking behaviour is a cornerstone of improved CVD health.
- Public health measures including smoking bans are crucial for the public's perception of smoking as an important health hazard.

Recommendations regarding smoking

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
All smoking is a strong and independent risk factor for CVD and has to be avoided.	I	B	Strong	[207, 208]
Exposure to passive smoking increases risk of CVD and has to be avoided.	I	B	Strong	[209, 210]
Young people have to be encouraged not to take up smoking.	I	C	Strong	[211]

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
All smokers should be given advice to quit and be offered assistance.	I	A	Strong	[212, 213]

CVD = cardiovascular disease
[a]Class of recommendation
[b]Level of evidence
[c]References

4.2.1 Introduction

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. Smoking is associated with increased risk of all types of CVD—CHD, ischaemic stroke, PAD, and abdominal aortic aneurysm. According to estimations from SCORE, 10-year fatal cardiovascular risk is approximately doubled in smokers. However, while the relative risk of myocardial infarction in smokers >60 years of age is doubled, the relative risk in smokers <50 years is five-fold higher than in non-smokers [214, 215].

Although the rate of smoking is declining in Europe, it is still very common among individuals who have received little education; and widening education-related inequalities in smoking-cessation rates have been observed in many European countries in recent years [214, 216, 217]. In the EUROASPIRE III survey 30 % of the participants were smokers up to the time of their coronary event and this had dropped by one-half after a median of 1.5 years. The survey also found that evidence-based treatment for smoking cessation was underused [33].

Historically, smoking was taken up mainly by men, but in recent years women have caught up or even surpassed the level of smoking among men in many regions. Risk associated with smoking is proportionately higher in women than in men [215, 218]. This could be related to differences in nicotine metabolism as women metabolize nicotine faster than men, especially women taking oral contraceptives [219], with possible effects on compensatory smoking.

4.2.2 Dosage and Type

The risk associated with smoking is primarily related to the amount of tobacco smoked daily and shows a clear dose–response relationship with no lower limit for deleterious effects [220]. 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 [211]. Smoking is deleterious regardless of how it is smoked, including by waterpipe [221, 222]. 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 [211, 220]. Also smokeless tobacco is associated with a small but statistically significant increased risk of myocardial infarction and stroke [223].

4.2.3 Passive Smoking

Accumulated evidence shows that passive smoking increases the risk of CHD, with a higher relative risk than might be expected [209, 224, 225]. A non-smoker living with a smoking spouse has an estimated 30 % higher risk of CVD [224], and exposure in the work place is associated with a similar risk increment [226]. Owing to the high incidence of CHD and the widespread exposure to environmental tobacco smoke, a large health benefit is expected to result from reducing environmental tobacco smoke. Indeed, recently imposed public smoking bans in different geographical locations have led to a significant decrease in the incidence of myocardial infarction [210]. Thus exposure to environmental tobacco smoke should be minimized in both asymptomatic individuals and individuals with CHD.

4.2.4 Mechanism by Which Tobacco Smoking Increases Risk

Although the exact mechanisms by which smoking increases the risk of atherosclerotic disease are not fully understood, it is clear that smoking enhances both the development of atherosclerosis and the occurrence of superimposed thrombotic phenomena. Mechanisms have been elucidated through observational cohort studies, experimental observations, and laboratory studies in humans and animals [225, 227–229], and point towards the effect of smoking on endothelial function [230, 231], oxidative processes [232], platelet function [233], fibrin olysis, inflammation [234–238], and modification of lipids and vasomotor function. Reactive oxygen species—free radicals—present in inhaled smoke cause oxidation of plasma LDL; oxidized LDL triggers the inflammatory process in the intimae of the arteries through stimulation of monocyte adhesion to the vessel wall, resulting in increased atherosclerosis [232, 239–242]. In experimental studies, several of these effects are fully or partly reversible within a very short time [243, 244]. A biphasic response to smoking cessation of CVD risk is thus compatible with the dual effects of smoking— acute and reversible effects on haemostasis and plaque stability and a more prolonged effect on plaque formation. 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. Most current evidence suggests that nicotine exposure from smoking has only minor effects on the atherosclerotic process [227, 245], and nicotine replacement has shown no adverse effect on outcomes in patients with cardiac disease [246, 247].

4.2.5 Smoking Cessation

The benefits of smoking cessation have been extensively reported [1, 37, 248]. Some of the advantages are almost immediate; others take more time. Studies of subjects without established CVD find risk in former smokers to be moderate between that of current and neversmokers [248]. Stopping smoking after a myocardial infarction is potentially the most effective of all preventive measures: a systematic review and meta-analysis of 20 cohort studies of smoking cessation after myocardial infarction showed a mortality benefit of 0.64 [95 % confidence interval (CI) 0.58–0.71] compared with continued smokers [249]. The mortality benefit was consistent over gender, duration of followup, study site, and time period. The risk is rapidly reduced after cessation, with significant morbidity reductions reported within the first 6 months [250]. Also, evidence from randomized trials supports the beneficial effect of smoking cessation [251, 252]. Further evidence points towards risk of CVD approaching the risk of never-smokers within 10–15 years, without ever quite reaching the same level [248].

Smoking reduction cannot generally be recommended as an alternative to quitting smoking due to compensatory smoking to avoid nicotine abstinence symptoms, which causes harm reduction to be disproportionately smaller than assumed. 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 [11, 253].

Quitting must be encouraged in all smokers (Table 9). There is no age limit to the benefits of smoking cessation. Non-smokers at high risk and patients with established CVD should be advised about the effects of passive smoking and recommended to avoid exposure. Public health measures such as smoking bans, tobacco taxation, and media campaigns are efficient aids in preventing smoking uptake and supporting smoking cessation.

Table 9 The 'Five As' for a smoking cessation strategy for routine practice

A–SK:	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.

Smoking Cessation Therapies

Quitting smoking is a complex and difficult process because the habit is strongly addictive both pharmacologically and psychologically. The most important predictor of successful quitting is motivation, which can be increased by professional assistance. The physician's firm and explicit advice that the person should stop smoking completely is important in starting the smoking-cessation process and increases the odds of success (OR 1.66, 95 % CI 1.42–1.94) [225, 254]. The momentum for smoking cessation is particularly strong at the time of diagnosing CVD and in connection with an invasive treatment such as CABG, percutaneous transluminal coronary angioplasty, or vascular surgery. Assessing whether the person is willing to try to quit, brief reiteration of the cardiovascular and other health hazards, and agreeing on a specific plan with a follow-up arrangement are the decisive first steps of the brief initial advice in clinical practice (Figure 7).

Smoking cessation initiated during hospital admission should continue for a prolonged period after discharge to increase success [255]. A smoking history including daily tobacco consumption and degree of addiction (most commonly assessed by the Fagerström test [256]) should 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.

4.2.6 Pharmacological Aids

Most quitters quit unassisted. However, pharmacological aid consistently improves quit rates. Consequently, in addition to advice and encouragement, nicotine replacement therapy (NRT) and, in some cases, varenicline or bupropion should be offered to assist cessation. NRT, varenicline, or bupropion should normally be prescribed as part of an abstinent-contingent treatment, in which the smoker makes a commitment to stop smoking on a particular date [253]. NRT in the form of chewing gum, transdermal nicotine patches, nasal spray, inhaler, and sublingual tablets has been widely used in helping quitters manage the difficult initial weeks or months of smoking cessation [225]. All available forms of NRT are effective: in a systematic review, the OR for abstinence with NRT vs. control was 1.58 (95 % CI 1.50–1.66) [213]. The use
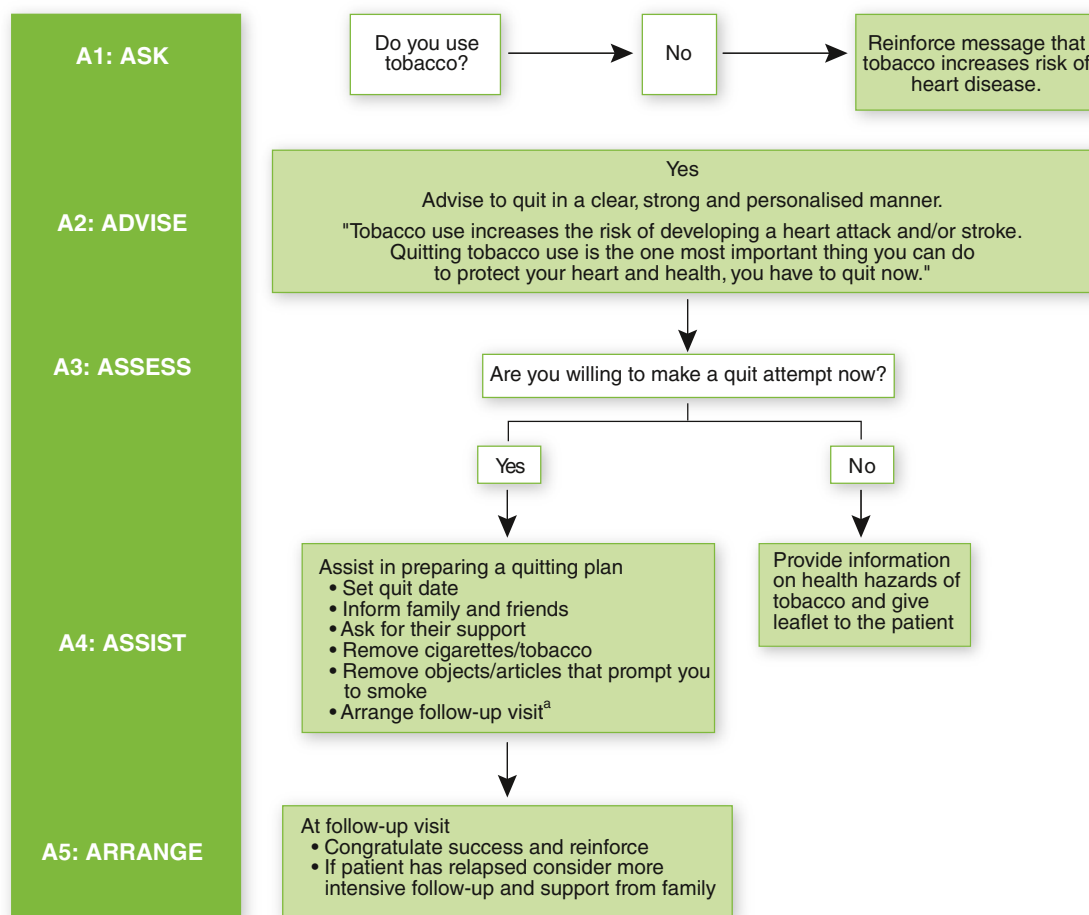

Fig. 7 Modified World Health Organization (WHO) smoking cessation algorithm

of nicotine patches has been successfully tested, without adverse effects, in patients who have CHD [257]. The antidepressant bupropion aids long-term smoking cessation with a similar efficacy to NRT. A meta-analysis of 36 trials comparing long-term cessation rates using bupropion vs. control yielded a relative success rate of 1.69 (95 % CI 1.53–1.85), whereas evidence of any additional effect of adding bupropion to NRT was insufficient [258].

The partial nicotine receptor agonist varenicline has been shown to increase the chances of successful long-term smoking cessation between two-and three-fold compared with pharmacologically unassisted quit attempts, including in patients with CVD [259, 260]. Trials suggested a modest benefit of varenicline over NRT and bupropion [258, 261]. Side effects are rare, but, due to links with serious adverse events, including depressed mood, agitation, and suicidal thoughts, a psychiatric history and suicide risk assessment should be taken before prescription. Current morbidity or distress may suggest use of cessation counselling and postponement of drugs other than NRT. A meta-analysis based on 14 RCTs including 8216 patients has indicated a small but significantly increased risk of cardiovascular events associated with the use of varenicline [262]. Following that, the European Medicines Agency has announced that the slightly increased risk of cardiovascular events associated with varenicline does not outweigh the benefits of the drug in helping people to stop smoking [263]. Cytisine, a low cost partial nicotine receptor agonist available in some European countries, also seems to increase the chances of quitting, but the evidence at present is not conclusive [264].

The antidepressant nortriptyline and the antihypertensive drug clonidine aid smoking cessation [258, 265], but, owing to side effects, are second-line choices. All pharmacological smoking-cessation therapies should be used short term since long-term safety and efficacy data are lacking.

4.2.7 Other Smoking-Cessation Interventions

Both individual and group behavioural interventions are effective in helping smokers quit [225, 266–268]. Support from the partner and family is very important. Getting other family members who smoke to quit together with the patient is of great help. Physicians and caregivers must set an example by not smoking. There is no consistent evidence that acupuncture, acupressure, laser therapy, hypnotherapy, or electrostimulation are effective for smoking cessation [269].

Most important new information

- New evidence on the health effects of passive smoking strengthens the recommendation on passive smoking.

Remaining gaps in the evidence

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

4.3 Nutrition

Key messages

- A healthy diet has the following 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 process food, and <1 % of total energy intake from natural origin.
- <5 g of salt per day.
- 30–45 g of fibre per day, from wholegrain products, fruits, and vegetables.
- 200 g of fruit per day (2–3 servings.)
- 200 g of vegetables per day (2–3 servings).
- Fish at least twice a week, one of which to be oily fish.
- Consumption of alcoholic beverages should be limited to two glasses per day (20 g/day of alcohol) for men and one glass per day (10 g/day of alcohol) for women.

- Energy intake should be limited to the amount of energy needed to maintain (or obtain) a healthy weight, i.e. a BMI <25 kg/m^2.
- In general, when following the rules for a healthy diet, no dietary supplements are needed.

Recommendation regarding nutrition

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
A healthy diet is recommended as being the cornerstone of CVD prevention.	I	B	Strong	[270–276]

CVD = cardiovascular disease
[a]Class of recommendation
[b]Level of evidence
[c]References

4.3.1 Introduction

Dietary habits are known to influence cardiovascular risk, either through an effect on risk factors such as serum cholesterol, BP, body weight, and diabetes, or through an effect independent of these risk factors. A healthy diet also reduces the risk of other chronic diseases such as cancer. Most evidence on the relationship between nutrition and cardiovascular diseases is based on observational studies. The impact of diet can be studied on different levels. The most detailed way is looking at specific nutrients. Looking at foods or food groups is another way of evaluating diet, which is more easily translated into dietary recommendations. Finally, there is growing interest in dietary patterns, of which the Mediterranean diet is the most studied. The dietary pattern approach can be seen as the equivalent of the shift from evaluating single risk factors to evaluating total risk profiles. A recent publication of the EHN provides an extensive overview of diet and CVDs [277].

4.3.2 Nutrients

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

Fatty Acids In the prevention of CVD through dietary changes, the fat content and fatty acid composition of the diet have been the focus of attention since the 1950s. In prevention, the fatty acid composition of the diet is more important than the total fat content. Our knowledge on the effects of subclasses of fatty acids (saturated, monounsaturated, and polyunsaturated) as well as on specific fatty acids within these subclasses (e.g. n-3 and trans fatty acids) on different lipoprotein fractions in the blood has improved considerably.

Saturated fatty acids
In 1965, Keys et al [278]. described how replacing saturated fat in the diet by unsaturated fatty acids lowered serum total cholesterol levels. Given the effect on serum cholesterol levels, an impact on CVD occurrence is plausible. However, after >40 years of research, the impact of saturated fatty acid intake on the occurrence of CVD is still debated. Recently, a meta-analysis of cohort studies did not show an increase in the relative risk for CHD or CVD with higher intake of saturated fat [279], although there may be several methodological issues explaining this null finding [280]. A number of studies adjusted the effect of saturated fatty acids on CVD for serum cholesterol levels—an example of overadjustment. Another important aspect is by which nutrient saturated fatty acids are replaced. The evidence from epidemiological, clinical, and mechanistic studies is consistent in finding that the risk of CHD is reduced by 2–3 % when 1 % of energy intake from saturated fatty acids is replaced with polyunsaturated fatty acids [270]. The same has not been clearly shown for the replacement with carbohydrates and monounsaturated fatty acids. Therefore, lowering saturated fatty acid intake to a maximum of 10 % of energy by replacing it with polyunsaturated fatty acids remains important in dietary prevention of CVD.

Unsaturated fatty acids Monounsaturated fatty acids have a favourable effect on HDL cholesterol levels when they replace saturated fatty acids or carbohydrates in the diet [281]. Polyunsaturated fatty acids lower LDL cholesterol levels, and to a lesser extent HDL cholesterol levels, when they replace saturated fatty acids. The polyunsaturated fatty acids can be largely divided into two subgroups: n-6 fatty acids, mainly from plant foods, and n-3 fatty acids, mainly from fish oils and fats. The fatty acids eicosapentaenoic acid and docosahexaenoic acid, representatives of the n-3 group, are important. They do not have an impact on serum cholesterol levels, but have been shown to reduce CHD mortality and to a lesser extent stroke mortality [271, 282]. In various studies, low doses of eicosapentaenoic acid and docosahexaenoic acid are associated with a lower risk of fatal CHD

but not of non-fatal CHD. A hypothesis for this differential effect is that they could prevent fatal cardiac arrhythmia [271].

The subclass of unsaturated fatty acids with a so-called 'trans configuration', the trans fatty acids, have been shown to increase total cholesterol and decrease HDL cholesterol levels. These fatty acids are found in margarine and bakery products. The food industry has eliminated part of the trans fatty acids from their products, but there is still more to be gained from further elimination. A small amount of trans fat in the diet will remain, coming from ruminant fat in dairy and meat products. Replacing 1 % energy of trans fatty acids with saturated, monounsaturated, or polyunsaturated fatty acids decreases the total cholesterol/HDL cholesterol ratio by 0.31, 0.54, and 0.67, respectively [283]. A meta-analysis of prospective cohort studies has shown that, on average, a higher trans fatty acid intake of 2 % of energy increases the risk of CHD by 23 % [272]. It is recommended to derive <1 % of total energy intake from trans fatty acids, the less the better.

Dietary cholesterol
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) on a healthy diet do not therefore give specific guidance on intake of dietary cholesterol; others recommend a limited intake of <300 mg/day.

Minerals
Sodium The effect of sodium intake on BP is well established. 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 [284]. The DASH trial showed a dose–response relationship between sodium reduction and BP reduction [285]. In most western countries salt intake is high (~9–10 g/day), whereas the recommended maximum intake is 5 g/day [1]. Optimal intake levels might be as low as ~3 g/day. Processed foods are an important source of sodium intake. A recent simulation study estimated that for the USA, a reduction in salt intake of 3 g/day would result in a reduction of 5.9–9.6 % in the incidence of CHD (low and high estimate based on different assumptions), a reduction of 5.0–7.8 % in the incidence of stroke, and a reduction of 2.6–4.1 % in death from any cause [286].

Potassium
Potassium is another mineral that affects BP. The main sources of potassium are fruits and vegetables. A higher potassium intake has been shown to reduce BP. Risk of stroke varies greatly with potassium intake: the relative risk of stroke in the highest quintile of potassium intake (average of 110 mmol/day) is almost 40 % lower than that in the lowest quintile of intake (average intake of 61 mmol/day) [287].

Vitamins

Vitamins A and E Many case–control and prospective observational studies have observed inverse associations between levels of vitamin A and E and risk of CVDs. This protective effect was attributed to their antioxidant properties. However, intervention trials designed to confirm the causality of these relationships have failed to confirm the results from observational studies [288].

B-vitamins (B6, folic acid, and B12) and homocysteine The B-vitamins B6, B12, and folic acid have been studied for their potential to lower homocysteine levels, which has been postulated as a risk factor for CVDs [289]. However, the question remained whether homocysteine was merely a marker of risk or a causally related factor. The Cochrane Collaboration concluded in a recent meta-analysis of eight RCTs that homocysteine-lowering interventions did not reduce the risk of fatal/non-fatal myocardial infarction (RR 1.03, 95 % CI 0.94–1.13), stroke (RR 0.89, 95 % CI 0.73–1.08), or death by any cause (RR 1.00, 95 % CI 0.92–1.09) [290]. Thereafter three large secondary prevention trials have been completed and published [291–293]. All trials [Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH), VITAmins TO Prevent Stroke (VITATOPS), and Supplementation with Folate, vitamin B6 and B12 and/or OMega-3 fatty acids (SU.FOL.OM3)] concluded that supplementation with folic acid and vitamin B6 and/or B12 offers no protection against the development of CVD. Thus, B-vitamin supplementation to lower homocysteine levels does not lower risk.

Vitamin D

Some epidemiological studies have shown associations between vitamin D deficiency and cardiovascular disease. Conclusive evidence showing that vitamin D supplementation improves cardiovascular prognosis is however lacking, but trials are underway [294].

Fibre Consumption of dietary fibre reduces the risk of CVD. Although the mechanism is not elucidated completely, it is known that a high fibre intake reduces post-prandial glucose responses after carbohydrate-rich meals, and lowers total and LDL cholesterol levels [295]. Important sources of fibre are wholegrain products, legumes, fruits, and vegetables. The American Institute of Medicine recommends an intake of 3.4 g/MJ, equivalent to an intake of 30–45 g/day for adults [296]. This intake is assumed to be the optimal preventive level.

4.3.3 Foods and Food Groups

Fruits and vegetables

Observational studies have shown a protective effect of consumption of fruits and vegetables on CVD prevention. Most of the evidence comes from prospective cohort studies, while RCTs are scarce. Individual studies have shown weak or non-significant effects of fruit and vegetable intake on CVD risk. Because measurement of diet is complex, measurement error is likely to attenuate the observed relationships. Furthermore, since it is known that individuals who consume a lot of fruits and vegetables differ in many respects from those who eat few fruits and vegetables (e.g. with respect to other dietary habits, smoking status, levels of physical activity), residual confounding, also after adjustment, may remain. Nevertheless, results in different cohort studies have been quite homogeneous, and several meta-analyses have reported statistically significant effect estimates. Dauchet et al. reported a decrease in CHD risk of 4 % (RR 0.96, 95 % CI 0.93–0.99) for each additional serving of fruits and vegetables per day [273]. In a meta-analysis of seven large prospective cohort studies, a 5 % reduction in risk of stroke for each additional serving of fruits and vegetables was reported [273]. He et al. updated this estimate by adding two additional cohorts, and reported a pooled RR of stroke of 0.89 (95 % CI 0.83–0.97) for those eating 3–5 servings of fruits and vegetables daily compared with those eating <3 servings, and a pooled RR of 0.74 (95 % CI 0.69–0.79) for those eating >5 servings [274]. One serving is equivalent to ~80 g.

The protective effect of fruits and vegetables seems to be slightly stronger for the prevention of stroke compared with the prevention of CHD. One of the reasons for this can be the effect of fruits and vegetables on BP, based on the fact that they are a major source of potassium. The DASH trial has shown that increasing fruit and vegetable intake contributed to the observed decrease in BP in the intervention arm [297]. Other constituents of fruits and vegetables that can contribute to the effect are fibre and antioxidants.

The recommendation is to eat at least 200 g of fruit (2–3 servings) and 200 g of vegetables (2–3 servings) per day.

Fish

The protective effect of fish on CVD is attributed to the n-3 fatty acid content. Pooled risk estimates show that eating fish at least once a week results in a 15 % reduction in risk of CHD (RR 0.85, 95 % CI 0.76–0.96) [271]. Another meta-analysis showed that eating fish 2–4 times a week reduced the risk of stroke by 18 % (RR 0.82, 95 % CI 0.72–0.94) compared with eating fish less than once a month [282]. The relationship between fish intake and cardiovascular risk is not linear. In particular, in the range of no or very low intake to moderate intake there is a strong increase in cardiovascular risk. The public health impact of a small increase in fish consumption in the general population is therefore potentially large. A modest increase in fish consumption of 1–2 servings a week would reduce CHD mortality by 36 % and all-cause mortality by 17 % [298]. The recommendation, therefore, is to eat fish at least twice a week, of which once oily fish.

Alcoholic beverages

Results from epidemiological studies show a protective effect of moderate alcohol consumption on the occurrence of CVD. The relationship is J-shaped, which is not explained by special characteristics of abstainers. There seems to be a favourable effect of red wine in particular, which may be due to the effect of polyphenols (especially resveratrol) [299]. Based on a meta-analysis [275], the optimal level of intake with respect to all-cause mortality is ~20 g/day for men and 10 g/day (equivalent to approximately one drink) for women. With respect to the prevention of CVDs, the optimal level of intake is somewhat higher. The recommendation is that drinkers should limit their alcohol intake to a maximum of one glass/day for women (10 g of alcohol) or two glasses/day for men (20 g of alcohol) to obtain the lowest level of chronic disease risk.

Soft drinks

Sugar-sweetened soft drinks are the largest single food source of calories in the US diet and are also important in Europe. In children and adolescents, beverages may now even account for 10–15 % of the calories consumed. A meta-analysis has suggested that for energy consumed in the form of a liquid, compensation of caloric intake at subsequent meals could be less complete than for energy from solid food [1]. The regular consumption of soft drinks has been associated with overweight and type 2 diabetes [300]. Similarly, regular consumption of sugar-sweetened beverages (i.e. two servings per day compared with one serving per month) was associated with a 35 % higher risk of CHD in women, even after other unhealthy lifestyle and dietary factors were accounted for, whereas artificially sweetened beverages were not associated with CHD [301].

4.3.4 Functional Foods

Functional foods containing phytosterols (plant sterols and stanols) are effective in lowering LDL cholesterol 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 [302]. Some recent research

indicates that, especially for stanols, further cholesterol reduction can be obtained with higher doses [303]. No studies with clinical endpoints have been performed as yet.

4.3.5 Dietary Patterns

In accordance with the shift from evaluating and treating single risk factors to evaluating a person's total risk profile, more research is focusing on dietary patterns instead of on single nutrients. 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 Seven Countries Study showed a large difference in cardiovascular mortality rates between northern and southern Europe. Even at similar cholesterol levels, and after adjusting for BP and smoking, the difference in cardiovascular risk remained (Figure 8) [304]. The diet consumed in the Mediterranean cohorts of the Seven Countries Study is probably an important factor underlying the large difference in CVD rates between southern and northern Europe.

The concept of the Mediterranean diet comprises many of the nutrients and foods that have been discussed previously: a high intake of fruits, vegetables, legumes, wholegrain products, fish, and unsaturated fatty acids (especially olive oil), a moderate consumption of alcohol (mostly wine, preferably consumed with meals), and a low consumption of (red) meat, dairy products, and saturated fatty acids.

A number of studies have demonstrated the protective effect of this diet, and recently a meta-analysis has been performed [276]. Adherence to the Mediterranean diet was operationalized by a scoring system (Mediterranean diet score), in which one point is obtained for each component of the diet, where the intake is above the median intake level for the study population (fruits, vegetables, legumes, cereals, fish, moderate consumption of red wine) or below the median (red and processed meats, dairy products). Depending on the number of food items for which information was obtained, the score could range from 0 to 7–9. The meta-analysis showed that greater adherence to the Mediterranean diet, by a 2-point higher score, was associated with a 10 % reduction in

Fig. 8 Cumulative 25-year coronary heart disease (CHD) mortality rates in different cohorts of the Seven Countries Study, according to baseline quartiles of total cholesterol level, adjusted for age, smoking, and blood pressure [304]
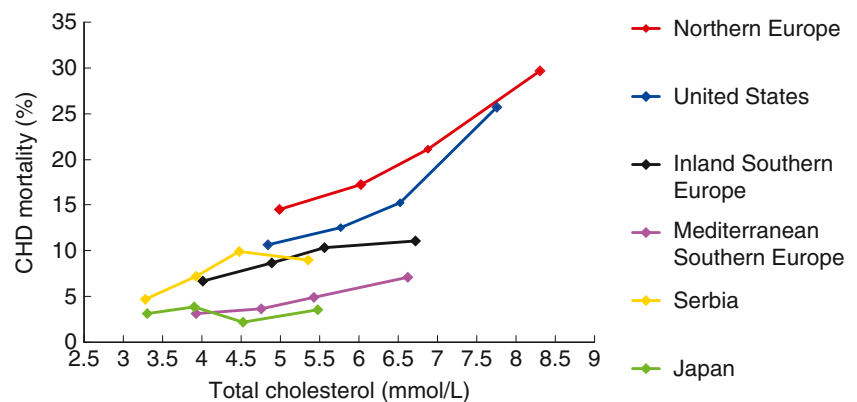
cardiovascular incidence or mortality (pooled RR 0.90, 95 % CI 0.87–0.93) and also with an 8 % reduction in all-cause mortality (pooled RR 0.92, 95 % CI 0.90–0.94).

Conclusion

It is clear that dietary modifications should form the basis for CVD prevention. Some changes in the diet will be reflected in favourable changes in measurable risk factors, such as BP and cholesterol levels. However, it should be kept in mind that dietary habits that do not show their effect on levels of BP or blood lipids can also make an important contribution to the prevention of CVD. The requirements for a healthy diet are summarized in the key messages at the beginning of this section.

The challenge for coming years is to translate nutritional guidelines into diets that are attractive to people and to find ways in which to make people change their (long-standing) dietary habits. Since it is not yet clear which specific substances cause the protective effect, it is recommended to eat a varied diet, based on the above-mentioned principles. In general, when eating a healthy diet, no supplements are needed, but when they are used they should not replace the consumption of 'real foods'. For some aspects of diet, legislation can help to change product formulation by the industry (trans fatty acids and salt reduction). The industry can make an important contribution in reducing the salt content of processed foods.

Most important new information

- Accumulated new evidence supports the view that homocysteine is not a causal risk factor for CVD.
- More evidence on the impact of total diet/dietary patterns has become available; the Mediterranean type of diet in particular has gained interest in recent years.

Remaining gaps in the 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.

4.4 Physical Activity

Key message

- Participation in regular physical activity and/or aerobic exercise training is associated with a decrease in cardiovascular mortality.

4.4.1 Introduction

Regular physical activity and aerobic exercise training are related to a reduced risk of fatal and non-fatal coronary events

in healthy individuals [305–308], subjects with coronary risk factors [309], and cardiac patients [310, 311] over a wide age range. A sedentary lifestyle is one of the major risk factors for CVD [312]. Physical activity and aerobic exercise training are therefore suggested by guidelines as a very important non-pharmacological tool for primary and secondary cardiovascular prevention [37, 204, 313]. In the EU, <50 % of the citizens are involved in regular aerobic leisure-time, and/or occupational physical activity [314, 315], and the observed increasing prevalence of obesity is associated with a sedentary lifestyle; [316, 317] moreover, probably fewer than one-third of patients eligible for cardiac rehabilitation are offered this service [33]. Thus a large gap exists in Europe between required and actual primary and secondary cardiovascular prevention exercise-based interventions [318], especially when considering that some of the Eastern European countries that recently joined the EU show age-related mortality rates for CVD among the highest in the world [319].

Recommendations regarding physical activity

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
Healthy adults of all ages should spend 2.5–5 h a week on physical activity or aerobic exercise training of at least moderate intensity, or 1–2.5 h a week on vigorous intense exercise. Sedentary subjects should be strongly encouraged to start light-intensity exercise programmes.	I	A	Strong	[305–307, 320]
Physical activity/aerobic exercise training should be performed in multiple bouts each lasting ≥10 min and evenly spread throughout the week, i.e. on 4–5 days a week.	IIa	A	Strong	[305–307, 320]
Patients with previous acute myocardial infarction, CABG, PCI, stable angina pectoris, or stable chronic heart failure should undergo moderate-to-vigorous intensity aerobic exercise training ≥3 times a week and 30 min per session. Sedentary patients should be strongly encouraged to start light-intensity exercise programmes after adequate exercise-related risk stratification.	I	A	Strong	[310, 311]

CABG = coronary artery bypass; PCI = percutaenous coronary intervention
[a]Class of recommendation
[b]Level of evidence
[c]References

4.4.2 Biological Rationale

Regular aerobic physical activity results in improved exercise performance, which depends on an increased ability to use oxygen to derive energy for work. These effects are attained for regular aerobic physical activity intensities ranging between 40 % and 85 % of VO2 [maximum volume (V) of oxygen (O2) in mL] or heart rate reserve, with higher intensity levels being necessary the higher the initial level of fitness, and vice versa [321]. Aerobic exercise also results in decreased myocardial oxygen demands for the same level of external work performed, as demonstrated by a decrease in the product of heart rate × SBP, so reducing the likelihood of myocardial ischaemia [322].

Moreover, myocardial perfusion can be improved by aerobic exercise, with an increase in the interior diameter of major coronary arteries, an augmentation of microcirculation, and an improvement of endothelial function [323, 324]. Additional reported effects of aerobic exercise are antithrombotic effects that can reduce the risk of coronary occlusion after disruption of a vulnerable plaque, such as increased plasma volume, reduced blood viscosity, decreased platelet aggregation, and enhanced thrombolytic ability [325], and a reduction of arrhythmic risk by a favourable modulation of autonomic balance [326].

Physical activity also has a positive effect on many of the established risk factors for CVDs, preventing or delaying the development of hypertension in normotensive subjects and reducing BP in hypertensive patients, increasing HDL cholesterol levels, helping to control body weight, and lowering the risk of developing non-insulin-dependent diabetes mellitus [37, 308]. Moreover, exercise training has been shown to induce ischaemic pre-conditioning of the myocardium, a process by which transient myocardial ischaemia during exercise enhances tolerance of the myocardium to subsequent more prolonged ischaemic stress, thereby reducing myocardial damage and the risk of potentially lethal ventricular tachyarrhythmias. Such cardioprotective mechanisms include anatomical alterations in the coronary arteries, induction of myocardial heat shock proteins, increase of myocardial cyclooxygenase-2 activity, elevation of endoplasmic reticulum stress proteins and nitric oxide production, improved function of sarcolemmal and/or mitochondrial adenosine triphosphate (ATP)-sensitive potassium channels and myocardial antioxidant capacity, up-regulation of key antioxidant enzymes, and induction of changes in mitochondrial phenotype that are protective against apoptotic stimuli [327].

4.4.3 Healthy Subjects

In healthy subjects, growing levels of both physical activity and cardiorespiratory fitness are associated with a significant reduction (~20–30 %) in risk of all-cause and cardiovascular mortality, in a dose–response fashion [305–308, 320, 328, 329]. The evidence suggests that the risk of dying during a given period continues to decline with increasing levels of physical activity and cardiorespiratory fitness; this seems to be true for both men and women and across a broad range of ages from childhood to the very elderly. As these conclusions are based on the results of observational studies, selection bias may be linked on the one hand to the existence of subclinical, undiagnosed diseases that may have made some individuals decrease their physical activity level before the start of the study, and on the other hand to the tendency to associate healthier habits (e.g. avoiding smoking and eating a healthier diet) with physically active individuals. However, studies controlling for these potential confounders still observed an inverse association between physical activity or cardiorespiratory fitness and all-cause and cardiovascular mortality.

Most of such a mortality-reduction effect seems to rely on a decrease in cardiovascular and CHD mortality, and the level of decreased coronary risk attributable to regular aerobic physical activity is similar to that of other lifestyle factors such as avoiding cigarette smoking. The risk of CVD (including CHD and stroke) or CHD alone is significantly reduced in more physically active or fit persons, with a relative risk reduction nearly twice as great for cardiorespiratory fitness than for physical activity increase at all percentiles >25th [320, 328, 329]. A possible explanation for the stronger dose–response gradient for fitness than for physical activity is that fitness is measured objectively, whereas physical activity is assessed by self-reports that may lead to misclassification and bias towards finding weaker physical activity or health benefit associations.

Physical activity intensity and volume

The volume of moderate-intensity physical activity or aerobic exercise training able to provide a reduction in all-cause and cardiovascular mortality ranges from 2.5 to 5 h/week; [306–309, 320] the longer the total duration of physical activity/aerobic exercise training performed over the week the greater the observed benefits. Of note, similar results are obtainable by performing 1–1.5 h/week of vigorous-intensity physical activity/aerobic exercise training or an equivalent combination of moderate-intensity and vigorous-intensity physical activity/aerobic exercise training. Moreover, the available evidence suggests that the total weekly volume of physical activity/aerobic exercise training can be obtained by summing multiple daily bouts of exercise, each lasting ≥10 min, and that physical activity/aerobic exercise training should be distributed over most days of the week.

Examples of physical activity/aerobic exercise training involve not only sport-related activities such as hiking, running or jogging, skating, cycling, rowing, swimming, cross-country skiing, and performing aerobic classes, but also

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lifestyle-common activities such as walking briskly, climbing stairs, doing more housework and gardening work, and engaging in active recreational pursuits. A moderate-intensity physical activity should be defined in relative terms as an activity performed at 40–59 % of VO2 or heart rate reserve, or at a rate of perceived exertion of 5–6 in the CR10 Borg scale, which would correspond to an absolute energy expenditure of ~4.8–7.1 metabolic equivalents (METs) in the young, 4.0–5.9 METs in the middle-aged, 3.2–4.7 METs in the old, and 2.0–2.9 METs in the very old [140]. Analogously, vigorous-intensity physical activity is performed at 60–85 % of VO2 or heart rate reserve, or at a rate of perceived exertion of 7–8 in the CR10 Borg scale, corresponding to an absolute energy expenditure of ~7.2–10.1 METs in the young, 6.0–8.4 METs in the middle-aged, 4.8–6.7 METs in the old, and 3.0–4.2 METs in the very old [140].

Risk assessment

The methodology according to which healthy subjects should be evaluated prior to engaging in regular physical activity/aerobic exercise training is controversial. Generally speaking, the exercise-related risk of major cardiovascular events in ostensibly healthy people is exceedingly low, ranging from 1 in 500 000 to 1 in 2 600 000 patient-hours of exercise [330, 331]. As recently proposed for leisure-time sport activities in middle-aged/senior subjects [332], the risk assessment accuracy should be tailored to the individual's cardiac risk profile, the current level of habitual physical activity, and the intended level of physical activity/aerobic exercise training, with a more aggressive screening (i.e. exercise testing) possibly reserved for people who are sedentary and/or with cardiovascular risk factors and/or willing to engage in vigorous-intensity activities. Individuals who exercise only occasionally seem to have an increased risk of acute coronary events and sudden cardiac death during or after exercise [330, 331]. Generally speaking, starting with a low-intensity activity is recommended in sedentary subjects and in those with cardiovascular risk factors.

4.4.4 Patients with Known Cardiovascular Disease

Aerobic physical activity in patients with known CVD is usually considered as an aerobic exercise training intervention included in a cardiac rehabilitation programme. Hence available data deal almost exclusively with cardiovascular fitness measurements and not with evaluation of habitual physical activity level. This is due to the need for a formal evaluation of both exercise capacity and exercise-associated risk in patients with established cardiac disease. In this context, the effects of physical activity alone on cardiovascular risk may not be easily discernible. However, a meta-analysis including mainly middle-aged men, most of whom had a previous acute

myocardial infarction and the rest with a previous CABG or percutaneous transluminal coronary angioplasty or affected by stable angina pectoris, showed a ~30 % reduction in total cardiovascular mortality for aerobic exercise training programmes of at least 3-months' duration; this percentage rose to ~35 % when only deaths from CHD were considered [333]. Insufficient data were available as to the effects of aerobic exercise training on revascularization rates; moreover, aerobic exercise training did not show any effect on the occurrence of non-fatal myocardial infarction. More extensive use of revascularization techniques and drug treatments during recent years has progressively resulted in a relatively low-risk general population of cardiac patients, in whom significant survival improvements are less likely to occur as a result of any added intervention. In any case, recent data confirm the existence of an inverse dose–response relationship between cardiovascular fitness (evaluated by treadmill stress testing and expressed in METs) and all-cause mortality in large populations of both male and female cardiovascular patients [a history of angiographically documented CHD, myocardial infarction, CABG, coronary angioplasty (PCI), chronic heart failure, peripheral vascular disease, or signs or symptoms suggestive of CHD during an exercise testing]. The results were the same irrespective of use of beta-blocking agents [334, 335]. Finally, aerobic exercise training in low-risk patients has been shown to be at least as effective in improving clinical status and myocardial perfusion, and associated with fewer cardiovascular events as compared with an invasive strategy such as a PCI [336].

The effects of aerobic exercise training on the cardiac mortality rate in patients with chronic heart failure have been evaluated in a meta-analysis [311]. Overall, moderate to vigorous intensity aerobic exercise training resulted in improved survival in patients with chronic heart failure due to left ventricular systolic dysfunction, and time to readmission to hospital was also significantly extended. Prognosis improvement was higher in patients with ischaemic aetiology, lower left ventricular ejection fraction and peak VO2, and higher New York Heart Association class. Adherence to prescribed aerobic exercise training intensity emerged as a crucial issue in determining such prognostic gains, as demonstrated by the results of the recent Heart Failure and A Controlled Trial Investigating Outcomes of Exercise TraiNing (HF-ACTION) trial [337].

Physical activity intensity and volume

In patients with CVD, available data do not allow definition of an aerobic exercise training weekly volume as precise as that indicated for healthy subjects [310, 311], and exercise prescription must be tailored to the clinical profile of the individual. Patients at low clinical risk with a previous acute myocardial infarction, CABG, PCI, or affected by stable angina pectoris or chronic heart failure can be assigned an

aerobic exercise training of moderate to vigorous intensity of 3–5 sessions per week, 30 min per session, with frequency, duration, and supervision of aerobic exercise training sessions to be in any case adapted to their clinical characteristics. Patients at moderate to high clinical risk should follow an even more strictly individualized exercise prescription, depending on the metabolic load known to evoke abnormal signs or symptoms. However, even in the more limited patients, small amounts of properly supervised physical activity are beneficial in order to enable maintenance of independent living and counteract disease-related depression. Information is available for evidence-based aerobic exercise training prescription in specific subpopulations of cardiac patients [205].

Clinical risk assessment

In patients with CVD, exercise prescription is strongly determined by exercise-related risk. Available risk stratification algorithms help to identify patients who are at increased risk for exercise-related cardiovascular events and who may require more intensive cardiac monitoring [338, 339], and the safety of medically supervised exercise programmes that follow such indications for exercise-related risk stratification is well established. The occurrence of major cardiovascular events during supervised aerobic exercise training in cardiac rehabilitation programmes is rare: from 1 in 50 000 to 1 in 120 000 patient-hours of exercise, with fatality incidence ranging between 1 in 340 000 and 1 in 750 000 patient-hours of exercise [340, 341]. The same is also true for patients with chronic heart failure and reduced left ventricular function, New York Heart Association class II–IV symptoms, and treated with optimal, guideline-based background heart failure therapy [342].

Most important new information

- No major pieces of new information have emerged in this field in recent years.

Remaining gaps in the evidence

It remains to be established whether:

- Prognostic gains can be achieved with less (duration/intensity) physical activity, in groups that are not able to meet the recommendations (elderly, deconditioned, patients with advanced chronic heart failure).
- The dose–response relationship between cardiorespiratory fitness and reduction in cardiovascular risk observed in primary prevention also holds in the secondary prevention setting.
- Regular physical activity yields a long-term prognostic gain in patients with chronic heart failure.
- High-intensity interval training is superior to moderate-intensity continuous training in improving functional

capacity and inducing favour-able left ventricular remodelling in chronic heart failure patients

4.5 Management of Psychosocial Factors

Key message

- Psychological interventions can counteract psychosocial stress and promote healthy behaviours and lifestyle.

Recommendations on the management of psychosocial factors

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
Multimodal behavioural interventions, integrating health education, physical exercise, and psychological therapy for psychosocial risk factors and coping with illness, should be prescribed.	I	A	Strong	[195, 197–200]
In the case of clinically significant symptoms of depression, anxiety, and hostility, psychotherapy, medication, or collaborative care should be considered. This approach can reduce mood symptoms and enhance health-related quality of life, although evidence for a definite beneficial effect on cardiac endpoints is inconclusive.	IIa	A	Strong	[85, 86, 199, 200, 343–347]

[a]Class of recommendation
[b]Level of evidence
[c]Reference

4.5.1 Introduction

Psychological interventions aim to counteract psychosocial stress and promote health behaviours and lifestyle. The interventions include individual or group counselling on psychosocial risk factors and coping with illness, cognitive-behavioural therapy, stress management programmes, meditation, autogenic training, biofeedback, breathing, yoga, and/or muscular relaxation [199, 200]. Psychological interventions are likely to have additional beneficial effects on physiological risk factors and distress, even when added to standard rehabilitation [199]. Two recent meta-analyses and two recent RCTs [86, 199, 343, 348] have also shown their additional impact on the prevention of clinical CHD, especially in patients who achieved their behavioural goals [349]. There is evidence that intervention programmes should be individualized based on individual risk constellations and include gender-specific aspects [199, 350].

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4.5.2 Specific Interventions to Reduce Depression, Anxiety, and Distress

Several RCTs and one meta-analysis have specifically targeted depression in CVD patients. Coronary patients with clinically significant depression can be safely and effectively treated with psychotherapy [84, 85, 351–353] or selective serotonin re-uptake inhibitors [354–356], although evidence for a beneficial effect on cardiac endpoints is inconclusive. Whereas most studies could show no significant beneficial effect [84, 351], a recent RCT revealed fewer depressive symptoms as well as fewer major adverse cardiac events [85]. A secondary analysis of another RCT found beneficial cardiovascular effects in white men only [344], and in patients who responded to antidepressant treatment [346]. Results from non-randomized studies indicate that selective serotonin re-uptake inhibitors may also have the potential to improve CVD prognosis in depressed patients with [345] and without [347] previously documented CVD.

In contrast to depression, until now very few studies specifically targeted anxiety in CVD patients. One RCT involving a nurse-led, home-based intervention in post-CABG patients revealed beneficial effects on anxiety, but the sample was too small and the follow-up period too short to demonstrate an impact on cardiac events [357].

While waiting for conclusive results to show that treating depression or anxiety will alter CVD prognosis, a prudent approach at present is to offer patients with clinically significant depression or anxiety treatment with psychotherapy and antidepressant/anxiolytic medication. Those not accepting treatment should be followed closely, and treatment offered again if symptoms persist for >4–6 weeks.

In addition to the treatment of mood symptoms, there are several other approaches to psychosocial intervention that have proved useful. Stress-management programmes have repeatedly been shown to improve not only subjective well-being but also risk factor levels and CVD outcomes [199, 200, 358]. In hostile CHD 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, and cardiovascular reactivity to mental stress, as well as to increased social support and satisfaction with life [359, 360]. For women, specific behavioural group treatments may be useful for reducing distress [348, 350, 361]. Recently, a group-based stress-reduction programme for women was shown to prolong lives independent of other prognostic factors [348, 358].

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 [362].

Most important new information

- Evidence is accumulating to suggest that psychological interventions counteract psychosocial stress, promote healthy behaviours, and contribute to the prevention of CVD.

Remaining gaps in the evidence

- Evidence that treatment of clinically significant depression and anxiety will improve cardiac endpoints is inconclusive.

4.6 Body Weight

Key messages

- Both overweight and obesity are associated with a risk of death in CVD [363–365].
- There is a positive linear association of BMI with all-cause mortality [363].
- All-cause mortality is lowest with a BMI of 20–25 kg/m^2 [363–365]..
- Further weight reduction cannot be considered protective against CVD [366–369].

Recommendation regarding body weight

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
Weight reduction in overweight and obese people is recommended as this is associated with favourable effects on blood pressure and dyslipidaemia, which may lead to less CVD.	I	A	Strong	[363–365]

CVD = cardiovascular disease
[a]Class of recommendation
[b]Level of evidence
[c]References

4.6.1 Introduction

In many countries, a reduction in major risk factors such as high blood cholesterol and BP and more recently smoking habit has translated into reduced cardiovascular mortality. The exceptions to these trends are body weight and diabetes, which have tended to increase as other risk factors have declined. Obesity is becoming a worldwide epidemic in both children and adults [370]. The scenario has changed to such a degree that in the USA, if obesity trends from 2005 to 2020 continue unchecked, obesity will increasingly offset the positive effects of declining smoking rates [371]. In Europe, a recent study of nearly 360 000 participants from nine European

countries showed that general obesity and abdominal adiposity are both associated with increased risk of death [372].

4.6.2 Body Weight and Risk

It is now clear that one of the components of abdominal fat, visceral adipose tissue, is a metabolically active endocrine organ capable of synthesizing and releasing into the bloodstream an important variety of peptides and non-peptide compounds that may play a role in cardiovascular homeostasis [373]. This process impacts on CVD risk factors and hence on risk, and the mechanical effects of overweight impact on noncardiovascular causes of morbidity and mortality. The health effects of increasing body weight are summarized in Table 10. Interestingly, the effects of multivariable adjustment on the association between lipid levels and risk and between body weight and risk are different. Raised blood cholesterol and reduced HDL cholesterol levels remain independently associated with risk after adjustment for other major risk factors, whereas the association between weight and risk tends to lose significance. This should not be interpreted as indicating that body weight is not important; rather, it may be critically important because it exerts its effect on risk by its adverse effects on many risk factors.

4.6.3 Which Index of Obesity is the Best Predictor of Cardiovascular Risk?

Body mass index [weight (kg)/length (m)^2] has been used extensively to define categories of body weight. In adults, overweight is defined by a BMI ranging from 25 to 29.9 kg/m^2, and obesity by a BMI $\geq$30 kg/m^2. Increasing BMI is highly associated with risk of CVD. However, regional distribution of adipose tissue was hypothesized to be more important in

Table 10 Potential adverse cardiovascular effects of increasing body weight

• Increases in insulin resistance (glucose intolerance, type 2 diabetes mellitus).
• Increased blood pressure.
• Increased systemic inflammation and prothrombotic state.
• Albuminuria.
• Dyslipidaemia (elevated total cholesterol, LDL cholesterol, non-HDL cholesterol, triglycerides, apolipoprotein B, small dense LDL particles, decreased HDL cholesterol, apolipoprotein A1).
• Cardiovascular and cerebrovascular abnormalities (endothelial dysfunction, heart failure, coronary heart disease, atrial fibrillation, stroke, abnormal left ventricular geometry, systolic and diastolic dysfunction, increased sym athetic activity).

HDL = high-density lipoprotein; LDL = low-density lipoprotein

determining cardiovascular risk than total body weight. This has led to increased interest in anthropometric measures of risk and in a more precise distribution between fat and lean mass (Table 11). 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 [374] thresholds for waist circumference are the most widely accepted in Europe; two action levels are recommended:

- Action level 1—waist circumference $\geq$94 cm in men and $\geq$80 cm in women represents the threshold at which no further weight should be gained.
- Action level 2—waist circumference $\geq$102 cm in men and $\geq$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-off points for anthropometric measurements are required in different races and ethnicities.

Some prospective studies have found evidence of stronger associations of abdominal adiposity measures with CHD than with BMI and CHD in women [375, 376] but not in men; these studies have generally been small. A large, case–control prevalence study found that the waist:hip ratio was to a greater extent associated with myocardial infarction than BMI in both men and women [377].

It is possible that waist circumference might be more strongly associated than BMI with diabetes in women but not in men. A recent meta-analysis of 32 studies found no overall difference between BMI, waist circumference, and waist:hip ratio in their association with incident diabetes [378], and showed no important differences between the sexes. However, the authors could only investigate heterogeneity in findings related to sex in a limited way because of the small number of studies in each group. Recent findings from the Prospective Studies Collaboration [363], involving >900 000 participants, found positive linear associations of BMI from 22.5 to 25.0 with all-cause mortality.

In a revised pooled analysis of 19 prospective studies (1.46 million white adults) [364], all-cause mortality was lowest with a BMI of 20.0–24.9. In an Asian population (1.1 million persons recruited in 19 cohorts) [365], the lowest risk of death was seen with a BMI in the range of 22.6–27.5. The risk was elevated with BMI levels either higher or lower than these ranges, with a U-shaped association. The finding that the same optimal weight range is associated with the lowest risk of death both in this study and in previous studies of European origin argues against the use of race-or ethnicity-specific BMI cut-off points to define overweight and obesity [363].

In the multicentre European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study, BMI, waist

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circumference, and waist:hip ratio were all independently associated with all-cause mortality; the authors recommended the use of waist circumference or waist:hip ratio in addition to BMI for assessing risk of death; however, no direct comparisons of the magnitudes of associations between the different measures were made [372]. The data are consistent with the results of four cohorts of adults from the British Women's Heart and Health Study, the Caerphilly Prospective Study, the Boyd Orr Study, and the Maidstone–Dewsbury Study [379]. The data from these studies explain the slightly stronger associations of central adiposity with all-cause mortality by reverse causality, which is likely to affect BMI (because of general total body muscle wasting and fat loss) more so than adiposity [380].

On the basis of evidence regarding the poorer accuracy and reliability of measuring waist circumference and hip circumference [381–383], it is not possible to establish these measures of visceral adiposity as alternatives to BMI in routine practice; it is also notable that BMI was not a stronger predictor of any outcomes than were the other measures, whereas measures of central obesity had somewhat stronger associations with all-cause mortality and type 2 diabetes. An additional related question is whether measurements of regional adiposity would add value to the predictive ability of BMI in identifying those at risk of future CVD. On the other hand, calls for more direct measurements of fat mass, such as by bioelectrical impedance analysis or the use of skinfold thickness, may be problematic in routine clinical and public health practice because of difficulties with accurate and reliable measurements [383–386]. Several measurements have been described for assessing the anatomical distribution of fat, such as computed tomography, ultrasound (particularly at the epicardial level), dual-energy X-ray absorptiometry, and MRI. All of these techniques can be used to monitor changes in intra-abdominal fat. They are, however, expensive and time consuming, and are to be regarded as specialist research tools rather than everyday risk assessment tools in common practice.

Currently, there does not appear to be strong evidence that measurements of waist or direct measurement of fat mass should replace BMI in routine public health surveillance or clinical practice.

4.6.4 The Obesity Paradox in Established Coronary Artery Disease

If, at the population level, obesity is associated with an increased risk of CVD incidence and mortality, among those with established coronary artery disease, the evidence is contradictory. Systematic reviews of patients with coronary artery disease or undergoing PCI have suggested an 'obesity paradox' whereby obesity appears protective against an adverse prognosis [366–369].

4.6.5 Treatment

Although diet, exercise, and behaviour modifications are the mainstay therapies for overweight and obesity (Table 12), they are often unsuccessful for long-term treatment. Medical therapy with orlistat [388] and/or bariatric surgery [389] for patients with a BMI ≥40 kg/m² or a BMI ≥35 kg/m² in the presence of high-risk comorbid conditions are the only options. These patients should have attempted prior conventional methods of diet and exercise, should be free of uncontrolled psychiatric disorders, and should be sufficiently healthy that the benefits of surgery outweigh the risks. The major issues in the field of bariatric surgery are the lack of consensus in terms of the diverse procedures available and of the refinement of techniques that will evolve to decrease the associated risks.

Most important new information

- It cannot be ruled out that being underweight is associated with increased cardiovascular morbidity and mortality.

Remaining gaps in evidence

- Whether measurements of regional adiposity add value to the predictive ability of BMI in identifying those at risk of future CVD.
- To identify the relative roles of diet, exercise, and behaviour modification in the management of overweight and obese people.

Table 12 Classification of body weight according to body mass index in adults [387]

Adults (>18 years of age)	Body mass index (kg/m²)
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
Class 4	≥50
Class 5	≥60

The National Institute of Health and WHO classification schemes do not include class 4 and 5 obesity

4.7 Blood Pressure

Key message

- Elevated BP is a major risk factor for CHD, heart failure, cerebrovascular disease, PAD, renal failure, and atrial fibrillation.

Recommendations on blood pressure

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
Lifestyle measures such as weight control, increased physical activity, alcohol moderation, sodium restriction, and increased consumption of fruits, vegetables, and low-fat dairy products are recommended in all patients with hypertension and in individuals with high normal BP.	I	B	Strong	[274, 285, 390–393]
All major antihypertensive drug classes (i.e. diuretics, ACE inhibitors, calcium antagonists, angiotensin receptor antagonists, and beta-blockers) do not differ significantly in their BP-lowering efficacy and thus should be recommended for the initiation and maintenance of antihypertensive treatment.	I	A	Strong	[394]
Beta-blockers and thiazide diuretics are not recommended in hypertensive patients with multiple metabolic risk factors increasing the risk of new-onset diabetes.	III	A	Strong	[395, 396]
In patients with diabetes, an ACE inhibitor or a renin–angiotensin receptor blocker is recommended.	I	A	Strong	[397–399]
Risk stratification using the SCORE risk chart is recommended as a minimal requirement in each hypertensive patient.	I	B	Strong	[45, 400]
However, as there is evidence that subclinical organ damage predicts cardiovascular death independently of SCORE, a search for subclinical organ damage should be encouraged, particularly in individuals at low or moderate risk (SCORE 1–4 %).	IIa	B	Weak	[45, 400]
	I	C	Strong	[401]

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
Drug treatment is recommended to be initiated promptly in patients with grade 3 hypertension, as well as in patients with grade 1 or 2 hypertension who are at high or very high total cardiovascular risk.				
In patients with grade 1 or 2 hypertension and at moderate total cardiovascular risk, drug treatment may be delayed for several weeks, and in grade 1 hypertensive patients without any other risk factor, for several months while trying lifestyle measures.	IIb	C	Weak	[401]
Systolic BP should be lowered to <140 mmHg (and diastolic BP <90 mmHg) in all hypertensive patients.	IIa	A	Strong	[402–404]
All hypertensive patients with established cardiovascular disease, or with type 2 diabetes, or with an estimated 10-year risk of cardiovascular death ≥5 % (based on the SCORE chart) should be considered for statin therapy.	**IIa**	B	**Strong**	[405]
Antiplatelet therapy, in particular low-dose aspirin, is recommended for hypertensive patients with cardiovascular events.	**I**	A	**Strong**	[398]
Antiplatelet therapy may be considered in hypertensive patients without a history of cardiovascular disease, but with reduced renal function or at high cardiovascular risk.	**IIb**	A	**Weak**	[406–408]

ACE inhibitor = angiotensin-converting enzyme inhibitor; BP = blood pressure
[a]Class of recommendation
[b]Level of evidence
[c]References

4.7.1 Introduction

In a number of epidemiological studies, elevated BP has been identified as a risk factor for CHD, heart failure, cerebrovascular disease, PAD renal failure, and, more recently, atrial fibrillation (AF) [409, 410]. Observational evidence is also available that BP levels correlate negatively with cognitive function and that hypertension is associated with an increased incidence of dementia [411]. Observational data involving >1 million

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individuals have indicated that death from both CHD and stroke increases progressively and linearly from BP levels as low as 115 mmHg systolic and 75 mmHg diastolic upwards [412].

A wide pulse pressure (SBP minus DBP) has been shown in some studies to be a better predictor of adverse cardiovascular outcomes than either SBP or DBP individually [413], and to identify patients with systolic hypertension who are at particularly high risk [414]. However, in the largest meta-analysis of observational data from 61 studies (70 % of which have been conducted in Europe) [412], pulse pressure was less predictive than both SBP and DBP. This meta-analysis also confirmed the increasing contribution of pulse pressure after age 55 years.

Individuals with an elevated BP more commonly have other risk factors for CVD (diabetes, insulin resistance, dyslipidaemia) and target organ damage. Because risk factors may interact, the overall risk of hypertensive patients is increased although the BP elevation is only mild or moderate.

4.7.2 Definition and Classification of Hypertension

The definition and classification of hypertension are shown in Table 13.

Isolated systolic hypertension should be graded (1,2, and 3) according to SBP values in the ranges indicated, provided that diastolic values are <90 mmHg. Grades 1, 2, and 3 correspond to classification into mild, moderate, and severe hypertension, respectively. These terms have now been omitted to avoid confusion with quantification of total cardiovascular risk.

4.7.3 Diagnostic Evaluation

The current European Society of Hypertension–ESC guidelines [401] suggest the following tests to be performed routinely in hypertensive patients: fasting plasma glucose and serum tests for total cholesterol, LDL cholesterol, and HDL cholesterol, fasting triglycerides, potassium, uric acid, creatinine, estimated creatinine clearance (using the Cockcroft–Gault formula) or estimated GFR [eGFR; using the Modification of Diet in Renal Disease (MDRD) formula; the CKD-EPI equation is more accurate than the MDRD study equation overall and across most subgroups but particularly for eGFR >60 mL/min/1.73 m^2], haemoglobin, and haematocrit, urine analysis (microalbuminuria dipstick test and sediment, quantitative proteinuria if dipstick test positive), and ECG; whereas echocardiography, carotid ultrasound, ABI, fundoscopy, and measurement of pulse wave velocity are listed as recommended tests. If fasting plasma glucose is >5.6 mmol/L (100 mg/dL) or glycated haemoglobin (HbA$_{1c}$) is 5.7–6.4 % [Diabetes Control and Complications Trial (DCCT) standardization], the glucose tolerance test is recommended (see "Treatment targets in patients with type 2 diabetes"). Blood pressure measurement at home or 24-h ambulatory BP monitoring is included among the recommended tests.

4.7.4 Blood Pressure Measurement

Blood pressure should be measured in each individual several times, on several separate occasions. 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 the BP is more markedly elevated or accompanied by target organ damage, other cardiovascular risk factors, or established cardiovascular or renal disease, repeated BP measurements are required within a shorter period in order to make treatment decisions. Repeated BP measurements on several occasions are necessary to identify the relatively large number of persons in whom BP elevation disappears following the first few visits. These individuals may need to undergo BP measurement more frequently than the general population, but drug treatment may not be necessary because their cardiovascular risk is probably low.

In post-myocardial infarction patients treated for hypertension before their infarction, BP may remain much lower, or even return to normotensive values without antihypertensive treatment. In such instances, BP has to be measured frequently to detect whether hypertensive values are regained, and treatment restarted without delay.

4.7.5 Office or Clinic Blood Pressure Measurement

As medical use of mercury has been banned in some European countries, non-mercury BP measuring devices are becoming increasingly important. These devices should be properly tested and validated according to standardized protocols [415]. Devices measuring BP in

Table 13 Definitions 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

the fingers or on the wrist should be avoided because of their possible inaccuracy. The auscultatory technique with a trained observer and a mercury sphygmomanometer continues to be the method of choice for measurement in the office or clinic.

4.7.6 Ambulatory and Home Blood Pressure Monitoring

Both ambulatory and home BP values are closely related to prognosis [416]. 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. They also allow two specific clinical conditions to be diagnosed, namely 'white coat' or isolated clinic hypertension characterized by higher office BP with normal ambulatory BP values, and 'masked' hypertension characterized by normal office BP with high ambulatory BP values [417]. BP thresholds for the definition of hypertension by 24-h ambulatory and home BP monitoring differ from those measured at office or clinic (Table 14).

Diagnosis of hypertension and assessment of treatment are still largely based on office or clinic blood pressure.

4.7.7 Risk Stratification in Hypertension

The decision to start pharmacological treatment depends not only on the BP level but also on total cardiovascular risk, which calls for a proper history, physical examination, and laboratory examination to identify the:

- presence of clinically established cardiovascular or renal disease
- presence of subclinical CVD
- co-existence of other cardiovascular risk factors.

Established cardiovascular or renal disease (Table 15) dramatically increases the risk of subsequent cardiovascular events regardless of BP level. This is also the case for the

Table 14 Blood pressure thresholds for definition of hypertension with different types of blood pressure 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

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

association of hypertension and other cardiovascular risk factors, not least diabetes.

The co-existence of other risk factors (smoking, increased plasma cholesterol, diabetes mellitus, family history of premature CVD) also greatly adds to the risk associated with mild BP elevation [45]. Risk stratification using the SCORE risk chart is a minimal requirement in each hypertensive patient.

Owing to the importance of target organ damage as an intermediate stage in the continuum of vascular disease and as a determinant of overall cardiovascular risk, signs of organ involvement should be sought carefully.

Electrocardiographic left ventricular hypertrophy (LVH), detected by the Sokolow–Lyons index, Cornell voltage QRS duration product, or the recently developed Novacode estimate [418], is an independent predictor of cardiovascular events. ECG LVH can be used as a tool documenting LVH regression, possibly associated with a reduced incidence of new-onset AF [419]. A recent prospective study focused on the R-wave voltage in the aVL lead as a prognostic sign in hypertensive patients without ECG LVH.

Echocardiography is more sensitive than electrocardiography in diagnosing LVH and in predicting cardiovascular risk, and may help in more precise stratification of the overall risk and in directing therapy. Cardiac abnormalities detected by echocardiography more precisely quantify left ventricular mass and geometric LVH patterns, and have an additional predictive power [420].

Carotid ultrasound with measurement of IMT or the presence of plaques predicts both stroke and myocardial infarction [421]. Ultrasound scans limited to the common carotid arteries (an infrequent site of atherosclerosis) are likely to detect vascular hypertrophy only, whereas assessment of atherosclerosis also requires scanning of bifurcations and/or internal carotids where plaques are more frequent. These alterations are common in untreated hypertensive individuals without target organ damage on routine examination; thus, carotid ultrasound may often detect vascular damage and make risk stratification more precise.

Evidence of arterial damage may also be suggested by an ABI <0.9. A low ABI indicates advanced atherosclerosis [422], whereas carotid IMT measurements are able to detect earlier changes [421].

Measurement of carotid–femoral pulse wave velocity provides a comprehensive non-invasive assessment of arterial stiffness [423] and has an independent predictive value for all-cause and cardiovascular morbidity, coronary events, and strokes in patients with uncomplicated essential hypertension as well as in the general population. Although the relationship between aortic stiffness and events is continuous, a threshold >12 m/s has been suggested as a conservative estimate of significant alterations of aortic function in middle-aged hypertensive patients.

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Table 15 Factors influencing prognosis in hypertension

Risk factor	Target organ damage	Diabetes mellitus	Established CVD or renal disease
SBP and DBP	Electrocardiographic LVH (Sokolow–Lyons >38 mm or Cornell >2440 mm/ms); or Novacode LVMI >130 g/m^2 (M), >115 g/m^2 (F).	Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) or post-load plasma glucose >11.0 mmol/L (198 mg/dL).	Cerebrovascular disease: ischaemic stroke, cerebral haemorrhage, transient ischaemic attack.
Pulse pressure (in the elderly)	Echocardiographic LVH[a] [LVMI ≥125 g/m^2 (M), ≥110 g/m^2 (F)]		Heart disease: myocardial infarction, angina, coronary revascularization, heart failure.
Age (M >55 years, F >65 years)	Carotid wall thickening (IMT >0.9 mm) or plaque		Renal disease: diabetic nephropathy, renal impairment [serum creatinine >133 μmol/L (1.5 mg/dL) (M), >124 μmol/L (1.4 mg/dL) (F)], proteinuria (>300 mg/24 h).
Smoking	Carotid–femoral PWV >12 m/s		PAD
Dyslipidaemia: TC >5.0 mmol/L (190 mg/dL); or LDL cholesterol >3.0 mmol/L (115 mg/dL); or HDL cholesterol <1.0 mmol/L (40 mg/dL) (M), <1.2 mmol/L (46 mg/dL) (F); or TG >1.7 mmol/L (150 mg/dL)	ABI <0.9		Advanced retinopathy: haemorrhages or exudates, papilloedema.
Fasting plasma glucose 5.5–6.9 mmol/L (100–125 mg/dL)	Slight increase in plasma creatinine: 115–133 μmol/L (1.3–1.5 mg/dL) (M), 107–124 μmol/L (1.2–1.4 mg/dL) (F)		
Abnormal glucose tolerance test	Low eGFR[b] (<60 mL/min/1.73 m^2) or creatinine clearance[c] (<60 mL/min)		
Abdominal obesity: waist circumference >102 cm (M), >88 cm (F)	Microalbuminuria 30–300 mg/24 h or albumin/creatinine ratio: ≥22 mg/g (≥2.5 mg/mmol) (M), ≥31 mg/g (≥3.5 mg/mmol) (F)		
Family history of premature CVD: age <55 years (M), <65 years (F).			

ABI = ankle–brachial index; CVD = cardiovascular disease; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; F, females; HDL = high-density lipoprotein; IMT = intima-media thickness; LDL = low-density lipoprotein; LVH, left ventricular hypertrophy; LVMI = left ventricular mass index; M = males; PAD = peripheral artery disease; PWV = pulse wave velocity; SBP = systolic blood pressure; TC = total cholesterol; TG = triglycerides

[a] Risk maximal for concentric LVH: increased LVMI with a wall thickness/radius ratio ≥0.42

[b] Modification of Diet in Renal Disease (MDRD) formula

[c] Cockcroft–Gault formula

The diagnosis of hypertension-induced renal damage is based on the finding of a reduced renal function and/or the detection of elevated urinary albumin excretion. Renal insufficiency is classified according to the eGFR calculated using the MDRD, Cockroft–Gault formula, or CKD-EPI. The three formulae help to detect mildly impaired renal function, particularly if serum creatinine values are still within the normal range and the body weight low and/or the age advanced.

In hypertensive patients with and without diabetes, microalbuminuria, even below the currently used threshold values, predicts cardiovascular events [424], and a continuous relationship between cardiovascular as well as non-cardiovascular mortality and urinary protein/creatinine ratios ≥3.9 mg/g in men and ≥7.5 mg/g in women has been reported in several studies. Microalbuminuria can be measured from spot urine samples (24-h or night-time urine samples are discouraged due to the inaccuracy of urinary sample collection) by indexing the urinary albumin concentration to the urinary creatinine concentration.

In conclusion, there is evidence that subclinical organ damage predicts cardiovascular death independently of SCORE, and the combination may improve risk prediction, especially in subjects at low or moderate risk (SCORE 1–4 %) [400].

4.7.8 Whom to Treat, and When to Initiate Antihypertensive Treatment

The decision to start antihypertensive treatment depends on BP (Table 13) and total cardiovascular risk (Table 15). All patients in whom repeated BP measurements show grade 2

or 3 hypertension are candidates for treatment; a large number of placebo-controlled trials have conclusively demonstrated that in patients with these BP values, BP reduction lowers cardiovascular morbidity and mortality independently of their level of total risk.

The evidence for the benefit of treating patients with grade 1 hypertension is admittedly scantier, because earlier trials in mild hypertension included patients mostly at high risk.

Promptness in the initiation of pharmacological therapy depends on the level of total cardiovascular risk. A delay in achieving BP control in high-risk hypertensive patients is associated with a worse outcome. Drug treatment should be initiated promptly in grade 3 hypertension, as well as in patients with grade 1 and 2 hypertension who are at high or very high total cardiovascular risk. In patients with grade 1 or 2 hypertension at moderate total cardiovascular risk, drug treatment may be delayed for several weeks, and in those with grade 1 hypertension without any other risk factor it may be delayed for several months. However, even in these patients, lack of BP control after a suitable period of non-pharmacological measures may lead to adding drug treatment.

In general, early BP-lowering treatment before organ damage develops or becomes irreversible appears a prudent recommendation. This is because, in high-risk hypertensive patients, even intense cardiovascular drug therapy—although beneficial—cannot lower total cardiovascular risk below the high-risk threshold.

Initiation of antihypertensive drug therapy in patients with diabetes with high normal BP is presently unsupported by prospective trial evidence. For the time being, it appears prudent to recommend treatment initiation in patients with diabetes and high normal BP if subclinical organ damage (particularly microalbuminuria or proteinuria) is present.

In subjects with high normal BP (SBP 130–139 or DBP 85–89 mmHg) uncomplicated by diabetes or previous cardiovascular events, no trial evidence is available of treatment benefits, except for a delayed onset of hypertension.

Lifestyle measures and close BP monitoring should be the recommendation for individuals with high normal BP who are at low or moderate added risk [401].

4.7.9 How to Treat

Lifestyle Lifestyle interventions alone may be sufficient for patients with mildly elevated BP, and should always be advised for patients receiving antihypertensive drugs as they may reduce the dosage of antihypertensives needed to achieve BP control.

Lifestyle interventions include: weight reduction in overweight individuals; reduction in the use of sodium chloride to <5 g/day; restriction of alcohol consumption to no more than 20 g/day ethanol in men and to no more than 10 g/day ethanol in women; and regular physical activity in sedentary individuals.

As the BP-lowering effect of increased potassium has been well documented in the DASH diet (rich in fruits, vegetables, and low-fat dairy 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 (4–6 servings per day, i.e. 400 g) and to reduce intake of saturated fat and cholesterol.

As tobacco smoking has a particularly adverse effect on cardiovascular risk, intensive efforts should be made to help hypertensive smokers stop smoking, with nicotine replacement, bupropione therapy, or varenicline considered. Because the acute pressure effect of smoking may raise daytime BP [425], this may also directly favour BP control, at least in heavy smokers. As long-term compliance with lifestyle changes may be poor, reinforcement in connection with BP measurements is needed.

Antihypertensive Drugs The large number of randomized trials of antihypertensive therapy, both those comparing active treatment vs. placebo, and those comparing treatment regimens based on different compounds, confirm that: (i) the main benefits of antihypertensive treatment are due to lowering of BP per se, and are largely independent of the drugs employed; and (ii) thiazide and thiazide-like diuretics (chlorthalidone and indapamide), beta-blockers, calcium antagonists, ACE inhibitors, and angiotensin receptor antagonists can adequately lower BP, and significantly reduce risk of cardiovascular morbidity and mortality. These drugs are thus all recommended for initiation and maintenance of antihypertensive treatment, either as monotherapy or in combination.

The position of beta-blockers as first-choice antihypertensive drugs has been questioned in the past decade. The latest meta-analysis of 147 randomized trials [394] reports only a slight inferiority of beta-blockers in preventing stroke (17 % reduction rather than 29 % reduction with other agents) but a similar effect to other agents in preventing coronary events and heart failure, and higher efficacy than other drugs in patients with a recent coronary event. These findings are consistent with the longitudinal United Kingdom Prospective Diabetes Study (UKPDS) follow-up [426]. They also concur with a large observational study of patients treated with different antihypertensive treatment regimens for longer periods than in randomized trials, and in which the incidence of cardiovascular outcomes was not higher on atenolol-based treatment vs. other antihypertensive agents [405].

However, as beta-blockers induce weight gain, have adverse effects on lipid metabolism [395], and increase (compared with other drugs) the incidence of new-onset diabetes, they should not be preferred in hypertensive patients with multiple metabolic risk factors (i.e. abdominal obesity, impaired fasting glucose, and impaired glucose tolerance), conditions that increase the risk of new-onset diabetes. This also applies to thiazide diuretics, which have dyslipidaemic and diabetogenic effects, particularly when used at high doses.

Thiazides have often been administered together with beta-blockers in trials showing a relative excess of new-onset diabetes, thus making a distinction between the contributions of the two agents difficult to dissociate. 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 diabetes compared with conventional beta-blockers. Furthermore, it is still unclear whether drug-induced diabetes carries the same negative prognosis as naturally occurring diabetes.

Trials assessing moderate endpoints suggest other differences between various antihypertensive agents or compounds: ACE inhibitors and angiotensin receptor antagonists are particularly effective in reducing LVH, including the fibrotic component; they are also quite effective in reducing microalbuminuria and proteinuria and in preserving renal function and delaying end-stage renal disease; calcium antagonists, besides being effective in LVH, appear particularly beneficial in slowing down progression of carotid hypertrophy and atherosclerosis.

Evidence concerning the benefits of other classes of agents is much more limited. Alpha1-blockers, centrally acting agents [alpa2adrenoreceptor agonists and imidazoline (I1) receptor agonists], and antialdosterone drugs effectively lower BP. However, there are no data documenting the ability of these drugs to reduce cardiovascular morbidity and mortality in hypertension. All of these agents, however, have frequently been used as added drugs in trials documenting cardiovascular protection and can thus be used for combination treatment.

Aliskiren, which inhibits the effect of renin and pro-renin on their specific receptors, effectively lowers BP in hypertension [427] and has an antiproteinuric effect. However, its effect on cardiovascular morbidity and mortality has not yet been proven, but a number of studies are under way.

Cost considerations should never predominate over the efficacy, tolerability, and safety for the individual patient. Drugs with 24-h efficacy should be 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 cardiovascular events.

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 recommendable 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 [428]. The combination of two drugs may also offer advantages for treatment initiation, particularly in patients at high risk in whom early BP control may be desirable. Fixed-dose combinations simplify treatment and may thus improve patient compliance. Trial evidence of outcome reduction has been obtained particularly for the combination of a diuretic with an ACE inhibitor or an angiotensin receptor antagonist or calcium antagonist [429, 430].

Despite the trial evidence of outcome reduction, the beta-blocker/diuretic combination favours the development of diabetes and should thus be avoided unless required for other reasons. The combination of an ACE inhibitor and an angiotensin receptor blocker is associated with a consistent increase in serious side effects [431]. Specific benefits in nephropathic patients with proteinuria (because of a superior antiproteinuric effect) await confirmation in event-based trials.

In 15–20 % of hypertensive patients, a combination of three drugs is needed to achieve BP control; the most rational combinations appear to be a blocker of the renin–angiotensin system, a calcium antagonist, and a diuretic at effective doses.

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

The recommendation of previous guidelines [401] to aim at a lower SBP goal (<130 mmHg) in patients with diabetes and those at very high cardiovascular risk (previous cardiovascular events) is not consistently supported by trial evidence. 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 or even harm in lowering systolic BP below 130 mmHg, except perhaps for stroke. A J-curve phenomenon for achieved SBP below 130 mmHg cannot be excluded [432].

Despite their obvious limitations and a lower strength of evidence, post-hoc analyses of trial data indicate a progressive reduction in incidence of cardiovascular events with progressive lowering of SBP down to ~120 mmHg and DBP down to ~75 mmHg [412], although the additional benefit at low BP values becomes rather small. A J-curve phenomenon is unlikely to occur down to these values except, perhaps, in patients with advanced atherosclerotic disease.

Based on current data, it may 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. More critical evidence from specific RCTs is desirable.

Hypertension in Special Conditions Diabetes mellitus (see "Treatment targets in patients with type 2 diabetes") In patients with diabetes, antihypertensive treatment should always be initiated when the BP is ≥140/90 mmHg. Initiation of treatment in the high-normal BP range is at present not sufficiently supported by outcome evidence from trials.

Meta-analyses of available trials show that, in diabetes, all major antihypertensive drug classes protect against cardiovascular complications, probably because of the protective effect of BP lowering per se. They can thus all be considered for treatment. Combination treatment is commonly needed to lower BP effectively in diabetes. A renin–angiotensin system blocker (ACE inhibitor/angiotensin receptor blocker) should always be included because of the evidence of its superior protective effect against initiation or progression of nephropathy.

Hypertension in the elderly Large meta-analyses confirm that treatment is highly beneficial in the elderly hypertensive patient. The proportional benefit in patients aged >65 years is no less than that of younger patients.

The claim that antihypertensive drug classes differ significantly in their ability to lower BP and to exert cardiovascular protection, both in younger and in elderly patients, has not been proven. Thus the choice of the drugs should not be guided by age. Thiazide diuretics, ACE inhibitors, calcium antagonists, angiotensin receptor antagonists, and beta-blockers can be considered for initiation and maintenance of treatment also in the elderly.

In the elderly, outcome trials have only addressed patients with an entry SBP ≥160 mmHg, and no trial achieved an average SBP <140 mmHg. Evidence from outcome trials addressing lower entry and achieving lower on-treatment values is thus needed.

Evidence is now available from an outcome trial that antihypertensive treatment also has benefits in patients aged ≥80 years. Treatment with BP-lowering drugs should be continued or initiated when patients turn 80, starting with monotherapy and adding a second drug if needed. Because patients in the Hypertension in the Very Elderly Trial (HYVET) were generally in a good condition [433], the extent to which HYVET data can be extrapolated to more fragile octogenarians is uncertain. 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.

Duration of Treatment Generally, antihypertensive therapy should be maintained indefinitely. Cessation of therapy in hypertensive patients is mostly followed by the return of BP to pre-treatment levels.

Lipid-Lowering Drugs All hypertensive patients with established cardiovascular disease or with type 2 diabetes or with an estimated 10-year risk of cardiovascular death ≥5 % (based on the SCORE chart) should be considered for statin therapy aiming at goals referred to in "Lipids".

Antiplatelet Therapy Antiplatelet therapy, in particular low-dose aspirin, should be prescribed to hypertensive patients with cardiovascular events. It can also be considered in hypertensive patients without a history of cardiovascular disease, with reduced renal function, or at high cardiovascular risk. In patients receiving aspirin, careful attention should always be paid to the increased possibility of bleeding, particularly gastrointestinal.

Important new information

- Subclinical organ damage in hypertension predicts cardiovascular death independently of SCORE, and a combination of both may improve risk prediction, particularly in individuals at low and moderate risk (SCORE 1–4 %).
- Antihypertensive treatment is beneficial in patients aged ≥80 years.

Remaining gaps in the evidence

- Should drugs be prescribed to all individuals with grade 1 hypertension, even when their total cardiovascular risk is low or moderate?
- Should drugs be prescribed to the elderly with grade 1 hypertension, and should their BP goal be set <140/90 mmHg?
- Should drug treatment be initiated in patients with diabetes or those with a previous cerebrovascular or cardiovascular event when the BP is still within the high-normal range, and should the BP goal be <130/80 mmHg in these patients?
- What are the lowest safe BP values to achieve by treatment in different clinical conditions?
- Are lifestyle measures known to reduce BP also capable of reducing morbidity and mortality in hypertension?

4.8 Treatment Targets in Patients with Type 2 Diabetes

Key messages

- Intensive management of hyperglycaemia in diabetes reduces the risk of microvascular complications and, to a lesser extent, that of cardiovascular disease.
- Intensive treatment of BP in diabetes reduces the risk of macrovascular and microvascular outcomes.

- Multiple antihypertensive drugs are usually required to reach the target.

Recommendations on diabetes mellitus

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
The target HbA$_{1c}$ for the prevention of CVD in diabetes of <7.0 % (<53 mmol/mol) is recommended.	I	A	Strong	[434, 435]
Statins are recommended to reduce cardiovascular risk in diabetes.	I	A	Strong	[167, 436]
Hypoglycaemia and excessive weight gain must be avoided and individual approaches (both targets and drug choices) may be necessary in patients with complex disease.	**I**	B	Strong	[435, 437, 438]
Metformin should be used as first-line therapy if tolerated and not contraindicated	IIa	B	Strong	[439]
Further reductions in HbA$_{1c}$ to a target of <6.5 % (<48 mmol/mol) (the lowest possible safely reached HbA$_{1c}$) may be useful at diagnosis. For patients with a long duration of diabetes this target may reduce risk of microvascular outcomes.	IIb	B	Weak	[435]
BP targets in diabetes are recommend to be <140/80 mmHg.	I	A	Strong	[440, 441]
Target LDL cholesterol is <2.5 mmol/L, for patients without atherosclerotic disease total cholesterol may be <4.5 mmol/L, with a lower LDL cholesterol target of <1.8 mmol/L (using higher doses of statins) for diabetic patients at very high CVD risk.	IIb	B	Weak	[442]
Antiplatelet therapy with aspirin is not recommended for people with diabetes who do not have clinical evidence of atherosclerotic disease.	III	A	Strong	[443]

ACS = acute coronary syndrome; BP = blood pressure; CKD = chronic kidney disease; CVD = cardiovascular disease; HbA$_{1c}$ = glycated haemoglobin; LDL = low-density lipoprotein

[a]Class of recommendation

[b]Level of evidence

[c]References

4.8.1 Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in people with diabetes mellitus. Aggressive control of hypertension and lowering cholesterol levels with statins reduce the risk of cardiovascular events, and there is conclusive evidence that improving glycaemic control significantly reduces the risk of developing diabetic microvascular complications (retinopathy, nephropathy, and neuropathy). While existing data indicate a relationship between increased levels of glycaemia and cardiovascular events, until recently there has been little evidence that specifically targeting glycaemic control can reduce the frequency of cardiovascular endpoints.

4.8.2 Evidence for Current Recommendations on Cardiovascular Disease Prevention in Diabetes

With the exception of glucose management, prevention of CVD follows the same general principles as for people without diabetes. A multi-factorial approach to treatment and achieving low BP levels and low LDL and total cholesterol concentrations is particularly important, and many of the treatment targets are tougher for patients with diabetes. The typical patient with type 2 diabetes has multiple cardiovascular risk factors, each of which should be treated in accordance with existing guidelines.

4.8.3 Glucose Control

The UKPDS evaluated the effect of improved metabolic control on the risk of developing CHD or other cardiovascular outcomes [434, 439]. The study demonstrated a 16 % risk reduction for myocardial infarction that was not statistically significantly (P=0.052) associated with the 0.9 % difference in HbA$_{1c}$ that was obtained between the intensive and conventional treatment groups. The average HbA$_{1c}$ in the intensive group was 7.0 % (53 mmol/mol). In overweight patients treated with metformin, a significant reduction in risk of myocardial infarctions was seen (P<0.01).

Most patients in the UKPDS were followed for a further 10 years of post-trial observational monitoring [444]. No attempt was made to maintain previously assigned therapies and the glycaemic control in the two groups rapidly converged. The intensive treatment group had a 17 % relative risk reduction in diabetes-related death (P=0.01), a 15 % reduction in risk of myocardial infarction (P=0.01), and a 13 % reduction in risk of death from any cause (P=0.007). This so-called 'legacy' effect also occurred in the metformin arm, in which patients treated with metformin maintained a reduction in cardiovascular events compared with those on conventional therapy. Similar legacy effects of early, intensive glycaemic control were seen in patients with type 1 diabetes in the DCCT/EDIC trial [445].

4.8.4 Glucose Targets

Three recent trails were conducted to see if cardiovascular events could be reduced further with lower target HbA_{1c} levels [435, 438, 446]. In the ACCORD study, >10 000 patients with type 2 diabetes and either a history of CVD or additional cardiovascular risk factors were randomized to intensive therapy, with a target HbA_{1c} <6.0 % (42 mmol/mol) or standard glycaemic control (target HbA_{1c} 7.0–7.9 %, 53–63 mmol/mol). HbA_{1c} dropped rapidly in the intensive group, with a median HbA_{1c} of 6.7 % (50 mmol/mol) within 4 months and 6.4 % (46 mmol/mol) at 1 year. The trial was stopped prematurely at 3.5 years due to a significantly increased total mortality in the intensive treatment group: 257 vs. 203 (P=0.04) for deaths due to any cause and 135 vs. 94 (P=0.02) for deaths due to cardiovascular causes. There were significantly more cases of hypoglycaemia requiring assistance in the intensive group, who also experienced significantly more weight gain. The reason for the poorer outcome in the intensive group is not clear, but may be associated with hypoglycaemia.

The Action in Diabetes and Vascular Disease Trial (ADVANCE) randomized >11 000 patients with type 2 diabetes to either standard or intensive glucose control [435]. The target HbA_{1c} was 6.5 % (48 mmol/mol) (0.5 % higher than in ACCORD). Final mean HbA_{1c} levels were similar to those in the ACCORD trial, but the reduction in HbA_{1c} in the intensive group was achieved more slowly in ADVANCE, with mean HbA_{1c} at 6 months of 7 % (53 mmol/mol) and not reaching the final value of 6.5 % (48 mmol/mol) until 36 months. Intensive control significantly reduced the total number of major macrovascular events (death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke) and major microvascular events (new or worsening nephropathy or retinopathy), but only the reduction in micro-vascular events was statistically significant. Weight gain and hypoglycaemia were less frequent than in the ACCORD study.

The smaller Veterans Affairs Diabetes Trial (VADT) achieved a median HbA_{1c} of 6.9 % (52 mmol/mol) in the intensive group compared with 8.4 % (68 mmol/mol) in the standard group [438]. There was no significant difference between groups for any of the individual composites of the primary outcome or for all-cause mortality.

4.8.5 Meta-Analysis and Systematic Reviews

A meta-analysis of intensive glucose control including data from UKPDS, Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive), ACCORD, ADVANCE, and VADT [447] showed a significant reduction in non-fatal myocardial infarction and CHD events, but no effect on stroke or total mortality. This analysis can be criticized as the PROactive trial was a study of pioglitazone

vs. placebo and not a trial of intensive glucose control [448]. A more recent meta-analysis examined trials of intensive vs. conventional glycaemic control, but did not include PROactive, and again identified the UKPDS, ACCORD, ADVANCE, and VADT trials [449]. Similar results were found with a significant reduction in CHD and CVD events, but no reduction in cardiovascular mortality or total mortality. A similar result was also found in another systematic review of the same data [450].

4.8.6 Blood Pressure

Hypertension is more common in patients with type 2 diabetes compared with the general population. The effect of BP reduction on the risk of developing CVD has been studied in trials including diabetic as well as non-diabetic patients, and much of the existing evidence is based on subgroup analysis from these combined trials. For example, in the Systolic Hypertension in the Elderly Program (SHEP) and Systolic Hypertension in Europe (Syst-Eur) studies, treatment effects were generally bigger in diabetic groups than in non-diabetic groups. The Hypertension Optimal Study (HOT), which compared different DBP goals, showed the benefit from more aggressive treatment of BP (DBP goal: 80 mmHg), resulting in a reduction in risk of cardiovascular events in diabetic vs. non-diabetic individuals [440].

In a substudy of the UKPDS, patients with hypertension were randomized to intensive (mean BP 144/82 mmHg) or less intensive antihypertensive therapy [441]. There was a marked and significant 44 % risk reduction for stroke and a non-significant 21 % risk reduction for myocardial infarction associated with a 10 mmHg reduction in SBP and a 5 mmHg reduction in DBP. Post-trial monitoring of the UKPDS substudy showed no legacy effect (i.e. intensive BP control has to be maintained for continued benefit) [426]. In the ADVANCE BP study, lowering BP to a mean of 135/75 mmHg further reduced the risk of cardiovascular events and total mortality [397].

In diabetic patients, antihypertensive treatment should be initiated when the BP is ≥140/80 mmHg. The SBP goal traditionally recommended in diabetes (i.e. <130 mmHg) is based on epidemiological evidence, and not on evidence from randomized trials. It has also been very difficult to achieve in most patients. The recent ACCORD BP study [451] tested the hypothesis that a target SBP of <120 mmHg would be of further benefit in reducing cardiovascular events in patients with type 2 diabetes. There was no improvement in the primary endpoint, with slight reductions in the secondary endpoint of strokes, and an increase in side effects with a lower target.

Meta-analyses of available trials show that, in diabetes, all major antihypertensive drug classes protect against

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cardiovascular complications, probably because of the protective effect of BP lowering per se. Thus all of these drugs can be considered in this population.

Combination treatment is commonly needed to lower BP effectively in diabetes. An ACE inhibitor or angiotensin receptor antagonist should always be included because of the evidence of superior protective effects against initiation or progression of nephropathy.

4.8.7 Dyslipidaemia

The Heart Protection Study (HPS) demonstrated that treatment with simvastatin 40 mg reduced the risk of CHD and stroke in diabetic and non-diabetic individuals without prior myocardial infarction or angina pectoris [436]. The reactive treatment effect was independent of baseline cholesterol, although the absolute risk and treatment effect increased with rising cholesterol concentration. The Collaborative AtoRvastatin Diabetes Study (CARDS), a specifically designed RCT in type 2 diabetic patients without clinically manifest CVD, also showed that cholesterol lowering with atorvastatin 10 mg reduced the risk of CHD and stroke events [167]. Meta-analysis has confirmed the benefits of lipid lowering with statins compared with placebo in people with diabetes [452].

A subgroup analysis of 1501 diabetic patients included in the Treating to New Targets (TNT) study, which compared intensive statin therapy (atorvastatin 80 mg) with standard statin therapy (atorvastatin 10 mg), showed a reduction in risk of primary events, cerebrovascular events, and all cardiovascular events in patients in the intensive statin therapy group [442].

Earlier and intensive prevention using lipid-lowering drugs irrespective of basal LDL cholesterol and aiming at lower lipid level goals, particularly in patients with type 2 diabetes, is needed. For patients with type 2 diabetes who have overt CVD or CKD and have one or more other CVD risk factors, the optimal level of LDL cholesterol should be <1.8 mmol/L (~70 mg/dL). However, it has to be stressed that in patients with type 2 diabetes, LDL cholesterol often remains within the normal range or is just moderately elevated, while one of the major CVD risk factors in these patients is diabetic dyslipidaemia characterized by hypertriglyceridaemia and low HDL cholesterol. Studies examining possible benefits of lipid lowering with fibrates in diabetes have given inconsistent results.

4.8.8 Antithrombotic Therapy

Patients with type 1 or type 2 diabetes have an increased tendency to develop thrombotic phenomena. The Antiplatelet Trialists' Collaboration meta-analysis demonstrated

benefits of antithrombotic therapy in diabetic patients with clinically established CHD, cerebrovascular disease, or other forms of atherothrombotic disease [453]. They analysed data from ~4500 diabetic patients in the trials and concluded that treatment with antiplatelet drugs (mainly aspirin) resulted in a 25 % significant reduction in risk of cardiovascular events.

The role of aspirin in primary prevention remains unproven. In the HOT study, 75 mg of aspirin further reduced the risk of major cardiovascular events in well-controlled hypertensive patients with diabetes, but non-fatal major bleeds were significantly more common among patients receiving aspirin [440]. A further analysis by the Antithrombotic Trialists' Collaboration demonstrated a nonsignificant 7 % reduction in risk of vascular events in patients who were at high risk because of the presence of diabetes [454]. A recent meta-analysis of six RCTs found no statistically significant reduction in the risk of major cardiovascular events or all-cause mortality when aspirin was compared with placebo or no aspirin in people with diabetes and no pre-existing CVD [443]. Aspirin significantly reduced the risk of myocardial infarction in men, but not in women. Evidence relating to harm was inconsistent.

4.8.9 Microalbuminuria and Multifactorial Intervention

Microalbuminuria (urinary albumin excretion from 30 to 300 mg/24 h) predicts the development of overt diabetic nephropathy in patients with type 1 or type 2 diabetes, while the presence of overt proteinuria (.300 mg/24 h) generally indicates established renal parenchymal damage. In both diabetic and non-diabetic hypertensive patients, microalbuminuria—even below the currently used threshold values—predicts cardiovascular events, and a continuous relationship between cardiovascular as well as non-cardiovascular mortality and urinary protein/creatinine ratios has been reported in several studies. Microalbuminuria can be measured from spot urine samples (24-h or nighttime urine samples are discouraged due to the inaccuracy of urinary sample collection) by indexing the urinary albumin concentration to the urinary creatinine concentration. Patients with microalbuminuria and proteinuria should be treated with an ACE inhibitor or angiotensin II receptor antagonist regardless of baseline BP.

The Steno-2 study included 160 high-risk patients with type 2 diabetes and microalbuminuria who were randomized to conventional treatment, as provided in general practice, or an intensified multifactorial intervention including glucose management, statins, ACE inhibitors, other antihypertensive agents, aspirin, and lifestyle interventions (smoking cessation, increased physical activity, and diet) [455]. The benefit of the intensive multifactorial intervention was demonstrated by a significant reduction in the incidence of microvascular complications after 4 years, and a significant 53 % risk reduction

in macrovascular complications after 8 years [455]. After a further 5 years of observational follow-up this was associated with a significant reduction in cardiovascular mortality [456]. Thus in high-risk patients polypharmacological multi-factorial intervention is needed to obtain the maximum risk reduction.

Most important new information

- The usual treatment target for HbA$_{1c}$ has been increased from <6.5 % to <7.0 %.
- Aspirin is no longer recommended for primary prevention in people with diabetes.

Remaining gaps in the evidence

- The most appropriate way of reaching the target HbA$_{1c}$ without excessive weight gain or hypoglycaemia has not been established.
- The possible cardiovascular benefits of new antidiabetic drugs with low risks of hypoglycaemia, such as dipeptidyl peptidase-4 inhibitors, which are weight neutral, or glucagon-like peptide 1 receptor agonists, which are associated with weight loss, are currently being studied in RCTs.

Recommendations on management of hyperlipidaemia

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
The recommended target levels are <5 mmol/L (less than ~190 mg/dL) for total plasma cholesterol and <3 mmol/L (less than ~115 mg/dL) for LDL cholesterol for subjects at low or moderate risk.	I	A	Strong	[457, 458]
In patients at high CVD risk, an LDL cholesterol goal <2.5 mmol/L (less than ~100 mg/dL) is recommended.	I	A	Strong	[459–461]
In patients at very high CVD risk, the recommended LDL cholesterol target is <1.8 mmol/L (less than ~70 mg/dL) or a ≥50 % LDL cholesterol reduction when the target level cannot be reached.	I	A	Strong	[459, 462, 463]
All patients with familial hypercholesterolaemia must be recognized as high-risk patients and be treated with lipid-lowering therapy.	I	A	Strong	[464, 465]
In patients with an ACS, statin treatment in high doses has to be initiated while the patients are in hospital.	I	A	Strong	[466–468]
Prevention of non-haemorrhagic stroke: treatment with statins must be started in all patients with established atherosclerotic	I	A	Strong	[469, 470]

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
disease and in patients at high risk for developing CVD. Treatment with statins must be started in patients with a history of non-cardioembolic ischaemic stroke.				
Occlusive arterial disease of the lower limbs and carotid artery disease are CHD risk-equivalent conditions and lipid-lowering therapy is recommended.	I	A	Strong	[471, 472]
Statins should be considered as the first-line drugs in transplant patients with dyslipidaemia.	IIa	B	Strong	[473]
Chronic kidney disease (stages 2–5, i.e. GFR <90 mL/min/ 1.73 m^2) is acknowledged as a CHD risk-equivalent and the LDL cholesterol target in these patients should be adapted to the degree of renal failure.	IIa	C	Strong	[474]

ACS = acute coronary syndrome; CHD = coronary heart disease; CVD, cardiovasular disease; GFR = glomerular filtration rate; LDL = low-density lipoprotein
[a]Class of recommendation
[b]Level of evidence
[c]References

4.9 Lipids

Key messages

- Increased plasma cholesterol and LDL cholesterol are among the main risk factors for CVD.
- Hypertriglyceridaemia and low HDL cholesterol are independent CVD risk factors.
- Statin therapy has a beneficial effect on atherosclerotic CVD outcomes.

4.9.1 Introduction

Genetic and pathological studies, as well as observational and interventional studies, have established the crucial role of dyslipidaemia, especially hypercholesterolaemia, in the development of CVD.

In blood plasma, lipids such as cholesterol and triglycerides are bound to various proteins (apoproteins) to form lipoproteins. HDLs do not cause atherosclerosis; on the contrary, they have antiatherogenic properties. In contrast, LDLs, particularly small, dense LDLs, are atherogenic. Chylomicrons and very low-density LDLs (VLDLs) are not atherogenic but high concentrations of these triglyceride-rich lipoproteins can cause pancreatitis.

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4.9.2 Low-Density Lipoprotein Cholesterol

Most of the cholesterol in blood plasma is normally carried in LDLs and, over a wide range of cholesterol concentrations, there is a strong and graded positive association between total as well as LDL cholesterol and risk of CVD [457]. This association applies to individuals (women as well as men) without CVD as well as to patients with established disease.

The evidence that reducing plasma LDL cholesterol reduces CVD risk is unequivocal; the results of epidemiological studies as well as trials with angiographic or clinical endpoints confirm that the reduction of LDL cholesterol must be of prime concern in the prevention of CVD [42].

Meta-analyses of many trials show a clear dose-dependent relative reduction in CVD with LDL cholesterol lowering. Every 1.0 mmol/L reduction in LDL cholesterol is associated with a corresponding 20–25 % reduction in CVD mortality and non-fatal myocardial infarction. More recently trials have confirmed that lowering LDL cholesterol to ≤1.8 mmol/L (~70 mg/dL) is associated with the lowest risk of recurrent CVD events in secondary prevention populations [459]. Therefore, for very high-risk subjects, the target LDL cholesterol level should be <1.8 mmol/L (~70 mg/dL) or a ≥50 % reduction from baseline LDL cholesterol.

4.9.3 Apolipoprotein B

Because apoB (the main apoprotein of atherogenic lipoproteins) levels have so frequently been measured in outcome studies in parallel with LDL cholesterol, apoB can be substituted for LDL cholesterol [475], but it does not add further to the risk assessment. Based on the available evidence, it appears that apoB is a similar risk marker to LDL cholesterol and a better index of the adequacy of LDL-lowering therapy [476]. Also, there appears to be less laboratory error in the determination of apoB than LDL cholesterol, particularly in patients with hypertriglyceridaemia, and laboratories could easily and inexpensively provide standardized measurements of apoB. However, apoB is not presently being measured in most laboratories but, if measured, it should be <80 and <100 mg/dL for subjects with very high or high CVD risk, respectively.

4.9.4 Triglycerides

Hypertriglyceridaemia is a significant independent CVD risk factor, but it seems that the association is not as strong as for hypercholesterolaemia [55]. 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.

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. There is evidence that non-fasting triglycerides may predict CHD risk even better, as individuals are in the postprandial state most of the time [477]. However, due to the lack of standardization, measuring non-fasting triglycerides is not recommended.

4.9.5 High-Density Lipoprotein Cholesterol

Low concentrations of HDL cholesterol are independently associated with higher CVD risk, therefore HDL cholesterol is also included in new SCORE charts [478]. The combination of moderately elevated triglycerides and low concentrations of HDL cholesterol is very common in high-risk patients with type 2 diabetes, abdominal obesity, insulin resistance, and who are physically inactive. It is part of a pattern of deranged plasma lipoproteins characterized by a triad of increased triglycerides, the presence of small, dense, and very atherogenic LDL particles, and low concentrations of HDL cholesterol. Low concentrations of HDL cholesterol may even rival hypercholesterolaemia (due to high concentrations of LDL cholesterol) as a risk factor for CHD [479]. However, there is still not sufficient scientific evidence for any HDL cholesterol value to be considered as a goal of therapy, although HDL cholesterol <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.

4.9.6 Lipoprotein(a)

Lipoprotein(a) is a low-density lipoprotein to which is attached an additional protein called apolipoprotein(a). High concentrations of Lp(a) are associated with increased risk of CHD and ischaemic stroke, although there is no randomized intervention showing that reducing Lp(a) decreases CVD risk [480]. There is no justification for screening the general population for Lp(a) at present, and no evidence that any value should be considered as a target.

4.9.7 Apolipoprotein B/Apolipoprotein A1 Ratio

Apolipoprotein A1 (apoA1) is the major apoprotein of HDL. It is beyond doubt that the apoB:apoA1 ratio is one of the strongest risk markers [475, 481]. However, it is still not established whether this variable should be used 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 does not add more information, its use is not as yet generally recommended.

4.9.8 Calculated Lipoprotein Variables

Low-density lipoprotein cholesterol

Low-density lipoprotein cholesterol can be measured directly, but is usually calculated using the Friedewald formula: [482]

$$
\begin{aligned}
\text{In mmol/L}: \text{LDL cholesterol} =\ & \text{total cholesterol} \\
& - \text{HDL cholesterol} \\
& - (0.45 \times \text{triglycerides})
\end{aligned}
$$

$$
\begin{aligned}
\text{In mg/dL}: \text{LDL cholesterol} =\ & \text{total cholesterol} \\
& - \text{HDL cholesterol} \\
& - (0.2 \times \text{triglycerides})
\end{aligned}
$$

The calculation is valid only when the concentration of triglycerides is <4.5 mmol/L (400 mg/dL) as the triglyceride/cholesterol ratio in triglyceride-carrying lipoproteins (VLDL and chylomicrons) progressively increases as hypertriglyceridaemia increases in severity.

Non-high-density lipoprotein cholesterol

Non-HDL cholesterol comprises the cholesterol in LDL, intermediate-density lipoprotein, and VLDL particles. Non-HDL cholesterol predicts CVD risk similarly to or even better than LDL cholesterol [483]. LDL limits may be transferred to non-HDL limits by adding 0.8 mmol (30 mg/L). Calculated by simply subtracting HDL cholesterol from total cholesterol, non-HDL cholesterol—unlike LDL cholesterol— does not require the triglyceride concentration to be <4.5 mmol/L (~400 mg/dL). Therefore, it is a better measure than calculated LDL cholesterol, particularly for patients with high non-fasting triglyceride concentrations. Like apoB, non-HDL cholesterol is a measure of the concentration of atherogenic lipoproteins in plasma but it is more readily available than measurements of apoB and apoA1.

4.9.9 Exclusion of Secondary Dyslipidaemia

The presence of dyslipidaemias secondary to other conditions must be excluded before beginning treatment, especially with drugs, as often the treatment of underlying disease improves hyperlipidaemia and no other antilipaemic therapy is necessary. This is particularly true for hypothyroidism.

Secondary dyslipidaemias can also be caused by alcohol abuse, diabetes, Cushing's syndrome, diseases of the liver and kidneys, and several drugs (e.g. corticosteroids, isotretinoin and etretinate, cyclosporin). Patients who could have genetic dyslipidaemias such as familial hypercholesterolaemia should, if possible, be referred for specialist evaluation, which might include a molecular genetic diagnosis.

4.9.10 Who Should be Treated and What are the Goals?

In general, total plasma cholesterol should be <5 mmol/L (~190 mg/dL), and LDL cholesterol should be <3 mmol/L (~115 mg/dL). In subjects with higher CVD risk, the treatment goals should be lower (see below).

The highest priority for treatment are patients with CVD irrespective of their lipid levels [484]. In these patients at very high CVD risk (see Section 3.4.1), the LDL cholesterol goal is <1.8 mmol/L (less than ~70 mg/dL) or a ≥50 % LDL cholesterol reduction when the target level cannot be reached.

In patients at high CVD risk (see Section 3.4.1), an LDL cholesterol goal <2.5 mmol/L (less than ~100 mg/dL) should be considered.

In subjects at moderate risk (a SCORE level ≥1to <5 %), an LDL cholesterol goal <3.0 mmol/L (less than ~115 mg/dL) should be considered.

In asymptomatic individuals, the first step is to assess total cardiovascular risk and to identify those components of risk that are to be modified [42]. Risk assessment should be repeated at 5-year intervals if the absolute CVD risk is low and/or there are no significant changes in the recommended values of the major risk factors.

The assessment of total risk does not pertain to patients with familial hypercholesterolaemia, since total cholesterol >8 mmol/L (~320 mg/dL) and LDL cholesterol >6 mmol/L (~240 mg/dL) by definition places such patients at high total risk of CVD. Familial hypercholesterolaemia is a dominantly inherited condition affecting ~1 in 500 people of European descent (heterozygous) most commonly caused by a mutation of the LDL receptor, and is characterized by very high levels of LDL cholesterol (usually 5–10 mmol/L or ~200–400 mg/dL) [42].

The benefit of cholesterol-lowering therapy depends on initial levels of risk: the higher the risk, the greater the benefit (Table 16). There are no differences in beneficial effects of cholesterol lowering between men and women and between younger and older age groups, even individuals >75 years of age, although the benefits in healthy women are not proven [485].

Although low HDL cholesterol is an independent risk factor for CVD, no specific treatment goals are as yet defined, but may be considered at concentrations <1.0 mmol/L

(~40 mg/dL) in men and <1.2 mmol/L (~45 mg/dL) in women. Similarly, fasting triglycerides should be >1.7 mmol/L (~150 mg/dL).

4.9.11 Patients with Peripheral Artery Disease

Occlusive arterial disease of the lower limbs and carotid artery disease are CHD risk-equivalent conditions, and lipid-lowering therapy is recommended in these patients irrespective of their plasma lipid levels [472, 486]. However, increased carotid IMT without evidence of atherosclerotic plaques is not an indication for lipid-lowering treatment in patients without proven CVD or other risk factors.

Although abdominal aortic aneurysm is also a CHD risk-equivalent condition, there is no conclusive evidence that treatment with statins reduces perioperative CVD morbidity and mortality in these patients [220, 487]. The benefit of lipid-lowering treatment in atherosclerosis in other types of arteries (e.g. retinal arteries) remains to be proven [488].

4.9.12 Stroke Prevention

In contrast to earlier observations, recent studies have now shown that high cholesterol levels are a risk factor for ischaemic but not haemorrhagic stroke [489]. Major statin trials reported significant reductions in stroke rates in patients with CHD or at high risk due to a reduction in the rates of ischaemic stroke [469]. Increased concentrations of triglycerides and low HDL cholesterol are also associated with nonhaemorrhagic stroke [490, 491]. Therefore, patients with ischaemic cerebrovascular disease merit the same degree of attention to treatment of plasma lipids as do patients with CHD.

In the prevention of stroke, treatment with statins should be started in all patients with established atherosclerotic disease and in patients at high risk for developing CVD. After a cerebrovascular event, statins should be started in patients with a history of non-cardioembolic ischaemic stroke or transient ischaemic attack for prevention of further cardiovascular events but should be avoided following haemorrhagic stroke unless there is evidence of atherosclerotic disease or high CVD risk.

4.9.13 Patients with Kidney Disease

Chronic kidney disease is characterized by mixed dyslipidaemia (high triglycerides, high LDL cholesterol, and low HDL cholesterol) [492]. Microalbuminuria is a risk factor for CVD, which rises progressively from a normal GFR to end-stage renal disease. CKD (stages 2–5, i.e. GFR <90 mL/min/1.73 m^2) is acknowledged as a CHD risk-equivalent, and the LDL cholesterol target in these patients has been adapted to the degree of renal failure (see page 19) [42].

Table 16 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 <2.5 mmol/L	100 to <155 mg/dL 2.5 to <4.0 mmol/L	155 to <190 mg/dL 4.0 to <4.9 mmol/L	>190 mg/dL >4.9 mmol/L
<1	No lipid intervention	No lipid intervention	Lifestyle intervention	Lifestyle intervention	Lifestyle intervention, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/A
≥1 to <5	Lifestyle intervention	Lifestyle intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, 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 intervention, consider drug	Lifestyle intervention, consider drug	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention
Class[a]/Level[b]	IIa/A	IIa/A	IIa/A	I/A	I/A
≥10 or very high risk	Lifestyle intervention, consider drug*	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention
Class[a]/Level[b]	IIa/A	IIa/A	I/A	I/A	I/A

Reference table [42]

CV = cardiovascular; LDL = low-density lipoprotein

[a] Class of recommendation

[b] Level of evidence

The statin dose should be modified according to GFR. Statin therapy has a beneficial effect on CVD outcomes in CKD stages 2 and 3 and slows the rate of kidney function loss [493].

4.9.14 Transplant Patients

Dyslipidaemia is common in patients who have undergone organ transplantation due to a combination of factors relating to the underlying disease, lifestyle, and treatments, including immunosuppressive therapy. CVD risk management is a priority in this patient population, and pharmacotherapy is commonly required. Statins are recommended as the first-line drugs.

Initiation should be at low doses with careful up-titration and with caution regarding potential drug–drug interactions, particularly for those on cyclosporin. In patients who are intolerant of statins or who have significant dyslipidaemia and a high residual risk despite a maximally tolerated dose of statin, an alternative or additional therapy may be considered: ezetimibe for those with high LDL cholesterol as the main finding, fibrates (with caution if in combination with a statin) or niacin for those with hypertriglyceridaemia and/or low HDL cholesterol [494].

4.9.15 Patients with an Acute Coronary Syndrome

In all patients with an ACS, statin treatment in high doses has to be initiated as early as possible while the patients are in the hospital, aiming to reach the LDL cholesterol level of <1.8 mmol/L (~70 mg/dL) [466, 467]. The early drug treatment should be combined with effective lifestyle changes and particularly dietary counselling after hospital discharge. Blood lipids should be checked 4–6 weeks after the ACS to determine whether the target level has been reached and the treatment has to be continued with the same dose or the dose should be adapted accordingly.

4.9.16 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), and selective cholesterol absorption inhibitors (e.g. ezetimibe).

Statins, by decreasing LDL cholesterol, reduce cardiovascular morbidity and mortality as well as the need for coronary artery interventions [167, 436]. Statins at doses that effectively reduce LDL cholesterol by 50 % also seem to halt progression or even contribute to regression of coronary atherosclerosis [495]. Therefore, they should be used as the drugs of first choice in patients with hypercholesterolaemia or combined hyperlipidaemia.

Higher activity of liver enzymes in plasma occurs occasionally, and in most cases is reversible: 5–10 % of patients receiving statins develop myopathy, but rhabdomyolysis is

extremely rare. The risk of myopathy can be minimized by identifying vulnerable patients and/or by avoiding statin interactions with specific drugs (Table 17). 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 [496].

In general, the safety profile of statins is acceptable, and earlier observations that lipid-lowering treatment may contribute an increase in non-cardiovascular mortality (e.g. cancers, suicides, depression) or mental disorders have not been confirmed. There are reports indicating increased blood sugar and HbA_{1c} levels, i.e. increased risk of type 2 diabetes, as a possible adverse effect of long-term statin therapy, but the benefits of statins far outweigh the risks for the vast majority of patients [497, 498].

Non-statin treatment: selective cholesterol absorption inhibitors are not used as monotherapy to decrease LDL cholesterol concentrations. Bile acid sequestants also decrease total and LDL cholesterol but tend to increase triglyceride concentrations. Fibrates and niacin are used primarily for triglyceride lowering and increasing HDL cholesterol, while fish oils (omega-3 fatty acids) in doses of 2–4 g/day are used for triglyceride lowering [479, 499].

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 diabetes with insulin, withdrawal of oestrogen therapy, etc. In the rare patients with severe primary hypertriglyceridaemia, it is necessary to restrict absolutely the intake of alcohol and severely restrict long-chain fat of both animal and vegetable origin. Fibrates are the drugs of choice for these patients, and prescription omega-3 fatty acids might be added if elevated triglycerides are not decreased adequately.

Table 17 Selected drugs that may increase risk of myopathy and rhabdomyolysis when used concomitantly with statin (CYP3A4 inhibitors/substrates or other mechanisms)

Cyclosporin, tacrolimus
Macrolides (azithromycin, clarithromycin, erythromycin)
Azole antifungals (itraconazole, ketoconazole, fluconazole)
Calcium antagonists (mibefradil, diltiazem, verapamil)
Nefazodone
HIV protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir)
Sildenafil
Others   Digoxin, niacin, fibrates (particularly gemfibrozil)

4.9.17 Drug Combinations

Patients with dyslipidaemia, particularly those with established CVD, diabetes, or asymptomatic high-risk individuals, may not always reach treatment targets. Therefore, combination treatment may be needed.

Combinations of a statin and a bile acid sequestrant or a combination of a statin and ezetimibe can be used for greater reduction of LDL cholesterol than can be achieved with either drug alone. Another advantage of combination therapy is that lower doses of statins can be used, thus diminishing the risk of adverse effects associated with high doses. However, statins should be used in the highest tolerable doses to reach the LDL cholesterol target level before combination therapy [500].

Combinations of niacin and a statin increase HDL cholesterol and decrease triglycerides better than either of these drugs alone, but flushing is the main adverse effect of niacin, which may affect compliance. Adding laropiprant to niacin might help in reducing the incidence of this adverse effect.

Fibrates, particularly fenofibrate, may be useful, not only for decreasing high triglyceride concentrations and increasing low HDL cholesterol, but can further lower LDL cholesterol when applied together with a statin. 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 these adverse effects are very rare. Avoiding the addition of gemfibrozil to a statin regimen is advised.

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 to which dyslipidaemia has been improved. In these patients, increased attention to other risk factors may help to reduce total risk.

4.9.18 Low-Density Lipoprotein Apheresis

Rare patients with severe hypercholesterolaemia, especially homozygous familial hypercholesterolaemia, require specialist evaluation of the need for LDL apheresis. By this demanding and expensive but effective technique, LDL is removed from plasma during extracorporeal circulation, weekly or every other week. LDL apheresis should be combined with treatment with lipid-lowering drugs.

Most important new information

- LDL cholesterol is recommended as the primary lipid analysis for screening and risk estimation as well as target for treatment.
- HDL cholesterol is also a strong risk factor and is recommended to be used for risk estimation, but is not recommended as a target for treatment.

Remaining gaps in the evidence

- There is still insufficient evidence for any triglyceride or HDL cholesterol value to be considered as the target for therapy that would reduce CVD events and mortality.
- There is insufficient evidence to prove whether Lp(a) lowering against background statin therapy can reduce the risk of CVD.
- Non-HDL cholesterol is a better measure than calculated LDL cholesterol, but there is as yet no information on the practical implication.
- Evidence is lacking that some functional foods with a lipid-lowering effect can reduce the risk of CVD.
- There are insufficient data to prove whether combination treatment with different lipid-lowering drugs can reduce the risk of CVD events and mortality.

4.10 Antithrombotics

4.10.1 Antiplatelet Therapy in Individuals Without Overt Cardiovascular Disease

Primary prevention in individuals without overt cardiovascular or cerebrovascular disease was investigated using long-term aspirin vs. 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 [501]. This 12 % proportional risk reduction was due mainly to a reduction in non-fatal myocardial infarction. There was a slight increase in haemorrhagic stroke and a reduction of ischaemic stroke. The net effect on stroke was not statistically significant. Major gastrointestinal and extracranial bleeds increased by 0.03 % per year. Risk of vascular mortality was not changed by treatment with aspirin. Aspirin cannot be recommended in primary prevention due to its increased risk of major bleeding. In individuals with multiple risk factors, clopidogrel was tested vs. aspirin in the Clopidogrel for High Athero-thrombotic Risk and Ischemic Stabilisation, Management, and Avoidance (CHARISMA) trial and was not of significant benefit [502].

4.10.2 Antiplatelet Therapy in Individuals with Overt Cardiovascular or Cerebrovascular Disease

In the acute state of cerebral ischaemia, aspirin reduced the risk of new vascular events within 2–4 weeks (RR 0.78, 95 % CI 0.76–0.80) by preventing four recurrent strokes and five vascular deaths per 1000 patients treated [503].

Following an episode of acute coronary ischaemia [unstable angina, NSTEMI, ST-elevation myocardial infarction

(STEMI)], dual antiplatelet therapy with clopidogrel and aspirin reduced the risk of myocardial infarction, stroke, and death over 14 days from 10.1 % to 9.2 % (P=0.002) in STEMI [Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT)] [504], and from 6.4 % to 4.5 % (P=0.03) over a period of 8 months in NSTEMI patients [Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE)] [505].

In patients with ACS for whom an early invasive strategy is planned, dual antiplatelet therapy with a P2Y12 inhibitor (ticagrelor or prasugrel) added to aspirin was superior to clopidogrel and aspirin. With ticagrelor given for 12 months the composite endpoint of death from vascular causes, myocardial infarction, or stroke occurred in 9.8 % as compared with 11.7 % of those receiving clopidogrel (HR 0.84, 95 % CI 0.77–0.92; P<0.001). No significant difference in rate of major bleeding was found [506–508].

With prasugrel, the primary efficacy endpoint occurred in 9.9 % of patients as compared with 12.1 % receiving clopidogrel (HR 0.81, 95 % CI 0.73–0.90; P<0.001). The risk of major bleeding was increased with prasugrel [506].

In long-term secondary prevention after myocardial infarction, stroke, or PAD, aspirin is the most studied drug. In a meta-analysis of 16 trials comprising 17 000 individuals, the Antithrombotic Trialists' Collaboration, 2009 [501] found that allocation to aspirin was associated with serious vascular events in 6.7 % of patients per year vs. 8.2 % of controls. The risk of total stroke was 2.08 % per year vs. 2.59 % (P=0.002) and coronary events 4.3 % per year vs. 5.3 % (P=0.0001). Aspirin was associated with a 10 % reduction in total mortality (RR 0.90, 95 % CI 0.82– 0.99), and was also associated with a significant excess of major bleeds; nevertheless, the benefits of aspirin exceeded the bleeding hazards.

Recommendations on antithrombotic therapy

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
In the acute phase of coronary artery syndromes and for the following 12 months, dual antiplatelet therapy with a P2Y12 inhibitor (ticagrelor or prasugrel) added to aspirin is recommended unless contraindicated due to such as excessive risk of bleeding.	I	B	Strong	[506–508]
Clopidogrel (600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel.	I	A	Strong	[504, 505]
In the chronic phase (>12 months) after myocardial infarction,	I	A	Strong	[454, 501]

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
aspirin is recommended for secondary prevention.				
In patients with non-cardioembolic transient ischaemic attack or ischaemic stroke, secondary prevention with either dipyridamole plus aspirin or clopidogrel alone is recommended	I	A	Strong	[509–512]
In the case of intolerance to dipyridamole (headache) or clopidogrel, aspirin alone is recommended.	I	A	Strong	[454, 501]
In patients with non-cardioembolic cerebral ischaemic events, anticoagulation is not superior to aspirin and is not recommended.	III	B	Weak	[513, 514]
Aspirin or clopidogrel cannot be recommended in individuals without cardiovascular or cerebrovascular disease due to the increased risk of major bleeding.	III	B	Weak	[501]

[a]Class of recommendation
[b]Level of evidence
[c]References

In patients with prior myocardial infarction, stroke, or peripheral vascular disease, clopidogrel was tested against aspirin in the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial [510], which showed a slight superiority of clopidogrel; the rate of serious vascular events was 5.32 % per year with clopidogrel vs. 5.83 % with aspirin (P=0.043). There were slightly more bleeds with aspirin.

Dual antiplatelet therapy with clopidogrel plus aspirin vs. clopidogrel in patients with transient ischaemic attack and ischaemic stroke was associated with an excess of serious bleeds in the Management of Atherothrombosis with Clopidogrel in High-risk Patients with Recent Transient Ischaemic Attack or Ischaemic Stroke (MATCH) trial [511], and is not recommended in cerebral ischaemia.

In patients with prior non-cardioembolic ischaemic stroke, dual antiplatelet therapy with dipyridamole plus aspirin showed superiority over aspirin [512]. In such patients oral vitamin K antagonists are not superior to aspirin but are associated with a higher bleeding risk [513, 514].

In patients with transient ischaemic attack or ischaemic stroke, a direct comparison of dipyridamole plus aspirin vs. clopidogrel alone [509] showed that the two regimens had similar rates of recurrent stroke, including haemorrhagic stroke (916 vs. 898; HR 1.01, 95 % CI 0.92–1.11). There was a higher frequency of major haemorrhagic events with

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dipyridamole plus aspirin (4.1 % vs. 3.6 %). Stroke, myocardial infarction, and vascular death occurred in 13.1 % in both groups. The two regimens may be considered equivalent.

Finally for the guidance on the use of cardioprotective drugs after acute coronary syndromes we refer to the existing guidelines for this condition; it will not be dealt with in the prevention guidance.

4.10.3 Antithrombotic Therapy in Atrial Fibrillation

Stroke is the most serious complication of AF. AF is often unrecognized and untreated in patients admitted with acute ischaemic stroke. Recommendations for antithrombotic therapy should be based on the presence (or absence) of risk factors for stroke and thromboembolism, and we refer further to the recent guidelines of the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology [515, 516].

Most important new information

- In patients with ACS, dual antiplatelet therapy with a P2Y12 inhibitor plus aspirin is superior to clopidogrel plus aspirin.

Remaining gaps in the evidence

- Long-term experience with new antiplatelet drugs is still limited.

4.11 Adherence

Key messages

- Adherence to medication in individuals at high risk and in patients with CVD is still low.
- Several types of interventions are effective in improving medication adherence.

Recommendations on patients adherence

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
Physicians must assess adherence to medication, and identify reasons for nonadherence in order to tailor further interventions to the individual needs of the patient or person at risk.	I	A	Strong	[517–519]
In clinical practice, reducing dosage demands to the lowest acceptable level is recommended. In addition, repetitive monitoring and feedback should be implemented. If feasible, multisession or combined behavioural interventions	IIa	A	Strong	[519]

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
should be offered in the case of persistent non-adherence.				

[a]Class of recommendation
[b]Level of evidence
[c]References

4.11.1 Why Do Patients not Adhere to Prescribed Medication?

Numerous studies have shown that adherence to medication in individuals at high risk and in patients with CVD is low, resulting in worse outcomes and higher healthcare costs. For example, 1 month after acute myocardial infarction, 25–30 % of patients stop at least one medication, with a progressive decline in adherence over time. After 1 year, <50 % of patients report persistent use of statins, beta-blockers, or antihypertensive therapy [517, 518].

The reasons for poor adherence are multifactorial. As outlined in Table 18, the WHO has categorized potential reasons for medication non-adherence into five broad groupings that include health system-related, condition, patient, therapy, and socio-economic factors [517].

Cost-related medication non-adherence is a relevant problem in many healthcare systems, especially in the elderly and people of low socio-economic status. For example, in American veterans, adherence to lipid-lowering medication decreased as co-payment increased [520]. Even the implementation of Medicare Part D in order to spend on basic needs could not reduce cost-related medication non-adherence among the sickest beneficiaries. Depression also doubles the risk for medication non-adherence, even after control for age, ethnicity, education, social support, and measures of cardiac disease severity [521].

Reasons for non-adherence tend to cluster; for example, complex medication regimens may be important in individuals with chronic, asymptomatic disease or multiple risk factors, who are lacking motivation and a clear understanding of the therapeutic regimen. This situation places high demands on the physician to provide explicit and clear advice and continuous care [518]. However, physicians might 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) [522]. Thus there is need to train physicians to identify risk factors for non-adherence and promote adherence to medication.

A recent systematic review has shown that several types of interventions are effective in improving adherence in chronic medical conditions; however, effect sizes on adherence varied and so did medical outcome [519]. Solely reducing dosage demands resulted in strong effects (effect size 0.89–1.20), but other interventions such as repetitive monitoring and feedback (effect size 0.27–1.2), multisession

Table 18 Reasons for medication non-adherence according to the World Health Organization [517]

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.
Socio-economic	Low literacy; high medication costs; poor social support.

Table 19 Recommendations for promoting medication adherence

- 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.
- Reduce dosage demands 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.
- In the case of lack of time, introduce physicians assistants and/or trained nurses whenever its necessary and feasible.
- In the case of persistent non-adherence, offer multisession or combined behavioural interventions.

information (effect size 0.35–1.13), and combined behavioural interventions (effect size 0.43–1.20) have shown effects ranging from low to strong [519].

In clinical practice, physicians should assess adherence to medication, identify reasons for possible non-adherence, and promote adherence according to established principles (Table 19).

In addition, as adherence with placebo also improves survival [523], physicians should be aware that adherence to medication may reflect generally better health behaviour. Therefore, measures should be taken to improve adherence and health behaviour in general (see "Principles of behaviour change").

Reducing dosage demands in persons at high CVD risk may result in the prescription of combination pharmacotherapy, the 'polypill' [524, 525]. Recently, a randomized phase II trial in middle-aged individuals without CVD demonstrated that the 'Polycap' formulation could conveniently reduce multiple risk factors [526].

Most important new information

- Evidence suggests that reducing dosage demands is the most effective single approach to enhancing medication adherence.

Gaps in the evidence

- There is limited evidence about which interventions are the most effective in whom (e.g. young–old, male–female, high–low socioeconomic status).
- The 'polypill' requires further evaluation before it can be judged suitable for use in routine care.

5 Where Should Programmes be Offered?

Key message

- Cardiovascular disease is the single most important cause of death for both men and women and can often be prevented!

Recommendation on programme provision

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
Actions to prevent cardiovascular disease should be incorporated into everyone's daily lives, starting in early childhood and continuing throughout adulthood and senescence.	IIa	B	Strong	[527]

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

Introduction

As mentioned in "Why is prevention of cardiovascular disease needed?", prevention of CVD is a lifetime approach, starting ideally before birth by educating young parents, and continuing in the pre-school age (kindergarten) and throughout the advancing grades of the school system. During this phase, the emphasis should be on conveying the pleasures of healthy nutrition and the joys and feelings of wellbeing associated with physical activity, rather than focusing on the prevention of disease. Beginning in the sixth grade (age 11–12 years—or even earlier, depending on the social environment), nonsmoking behaviour should be actively encouraged.

In the adult age group—depending on the healthcare system—different options are available to promote risk-

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adjusted prevention: nurse-based activities in the community, preventive efforts of general practitioners and practising cardiologists, hospital-based programmes, and society-based programmes.

In addition, legislative activities, such as restricting the use of trans fatty acids or protecting non-smokers from 'second-hand' smoke, banning tobacco commercials, and programmes to increase risk factor awareness produced by non-governmental organizations and medical societies, can ideally supplement each other in striving for a healthy population.

After a cardiovascular event, secondary preventive efforts within a structured rehabilitation programme have been shown to be particularly important and cost-effective.

All of these programmes are important components for preventing CVD, but to improve the health status of the citizens of our communities we cannot rely on our health system alone; as Brown and O'Connor formulated it: 'We need to create healthy communities and incorporate prevention into our daily lives as health care providers and citizens.' [528]

Most important new information

- Smoking bans in public places, by law, lead to a decrease in incidence of myocardial infarction.

5.1 Cardiovascular Disease Prevention in Primary Care: Role of Nurses

Key message

- Nurse-co-ordinated prevention programmes are effective across a variety of practice settings.

Recommendation on nurse-co-ordinated care

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
Nurse-co-ordinated prevention programmes should be well integrated into healthcare systems.	IIa	B	Strong	[35, 529, 530]

[a]Class of recommendation
[b]Level of evidence
[c]References

Nurse case management models tested in several randomized trials of secondary prevention have shown significant improvements in risk factors, exercise tolerance, glucose control, and appropriate medication use, along with decreases in cardiac events and mortality, regression of coronary

atherosclerosis, and improved patient perception of health compared with usual care [529, 530]. Other studies have demonstrated the effectiveness of nurse-led prevention clinics in primary care compared with usual care, with greater success in secondary as opposed to primary prevention [531–533].

5.1.1 Nurse-Co-Ordinated Prevention Programmes Effective in Various Healthcare Systems

A nurse-co-ordinated multidisciplinary prevention programme in both hospitals and primary care practices was evaluated in the EUROACTION trial studying patients with CHD and those at high risk of CVD in eight countries [35]. The approach was family centred and led to healthier lifestyle changes in terms of diet and physical activity, improvements in lifestyle (diet and physical activity), and more effective control of risk factors such as blood pressure in both patients and their partners in the intervention arm compared with usual care. A particular strength of the programme was the demonstration of the feasibility of this type of programme in hospitals and in general practice, outside of specialist centres, and in eight different healthcare systems across Europe.

Differences are found in the degree of effectiveness of various nurse-led programmes, which could reflect an inadequate dose of the intervention, inconsistencies in the components of the intervention, or lack of specific expertise, as well as the inherent difficulty in achieving meaningful change in multiple factors. Nurse case management models which were more intensive with more sustained contact have shown the most successful outcomes, including regression of atherosclerosis and decreased cardiac events [534]. The EUROACTION trial consisted of eight visits with a multidisciplinary team, and attendance at a group workshop and supervised exercise class over a 16-week period; other studies have evaluated interventions of shorter duration.

5.1.2 Sustained Contact is Necessary for Lifestyle Change

Strategies used to elicit behavioural change and healthy lifestyles in various trials included individualized assessment, risk communication, shared decision-making, inclusion of family, goal setting, individual and group education, and motivational interviewing. Because of differing intensity, duration, and intervention components in these trials, the optimal 'dose' of contact or most effective and cost-effective components needed for long-term results are not known, or how they may vary by patient characteristics. Type and duration of training for nurses to deliver the intervention also differed in these trials, as has the involvement of multidisciplinary teams. The success of the interventions despite these

differences support the basic concept that more sustained contact is necessary to achieve changes in lifestyle and improvement of compliance. Further research is needed to determine the optimal format of interventions necessary to achieve sustained risk reduction, and how these can be titrated and adapted for people with different risks and healthcare needs in a variety of healthcare and community settings. Although there is evidence that these models are likely to be cost-effective [535, 536], this needs further evaluation, as does the greater challenge of conveying risk and changing behaviours in primary prevention.

A recent consensus document led by the Preventive Cardiovascular Nurses Association, the Council on Cardiovascular Nursing and Allied Professions (CCNAP), and the Cardiovascular Nursing Council of the AHA has issued a call to action for nurses for greater activity in CVD prevention [530]. This document reviews the worldwide need for prevention, the evidence supporting nurse-led or co-ordinated programmes, life-course prevention, public health and multilevel policies, and preparation for nurses assuming active roles in CVD prevention.

The evidence shows that nurse case management and nurse-co-ordinated multidisciplinary prevention programmes are more effective than usual care in reducing cardiovascular risk, and can be adapted to a variety of healthcare settings. Nurses comprise a large portion of the healthcare workforce, and their educational preparation in many countries includes a focus on patient education and counselling, communication, and achievement of behavioural change, which are the skills required for prevention programmes. Nurses are also viewed by the public as credible sources of information and help, and nursing roles typically include co-ordination of care and collaboration with multiple providers. One challenge in Europe for this type of programme is the heterogeneity of different healthcare systems as well as the heterogeneity of nursing education and practice across countries, and acceptance of nurses moving beyond less autonomous traditional roles. However, the need for effective prevention programmes is undeniable, and the evidence shows that nurses can successfully lead or coordinate such schemes in a variety of settings.

Most important new information

- Nurse-led clinics or nurse-co-ordinated multidisciplinary prevention programmes are more effective than usual care in reducing cardiovascular risk, in a variety of healthcare settings.

Remaining gaps in the evidence

- The optimal (and most cost-effective) intensity and duration of individual components of the intervention need

to be established to achieve sustained risk reduction in patients at high risk or with vascular disease.
- Research is also needed to determine the knowledge and skills needed for effective prevention programmes, and the education required to ensure competence.

5.2 Cardiovascular Disease Prevention in General Practice

Key messages

- Risk factor screening including the lipid profile may be considered in adult men ≥40 years old and in women ≥50 years of age or post-menopausal [42].
- The physician in general practice is the key person to initiate, co-ordinate, and provide long-term follow-up for CVD prevention [537].

General practitioners are critical to the implementation and success of CVD prevention programmes in Europe. In most countries, they deliver >90 % of consultations and provide most public health medicine (preventive care, disease screening, chronic disease monitoring, and follow-up). In the case of CVD prevention they have a unique role in identifying individuals at risk of but without established CVD and assessing their eligibility for intervention based on their risk profile.

5.2.1 Identifying Individuals at Risk

Despite the enormous burden of CVD, many patients remain undiagnosed and untreated. Even among patients with established disease, there are substantial treatment gaps; among patients receiving lipid-modifying therapy, 43 % do not achieve total cholesterol targets (<4.5 mmol/L, 175 mg/dL) in Europe [5], whereas 64 % fail to reach LDL cholesterol targets in the USA [538]. There is also the issue of under-management and little improvement over time in other CVD risk factors such as smoking, high BP, and obesity [539].

The performance of primary prevention of CVD is even worse, at least partly because of additional difficulties in predicting those at greater risk who may benefit from treatment interventions. Calculation of global CVD risk involves replacing the 'classical' two-sided classification (yes or no; present or absent) with the concept of a continuum in risk in the development of CVD events, such as the SCORE risk charts (see "Risk estimation"). Most of the current CVD prevention risk calculators focus on short-term (5 or 10 year) risk,

and therefore inevitably are more likely to classify the elderly as at high risk and the young as at low risk. The development of lifetime risk calculators is intended to provide another method for determining cardiovascular risk that is less dependent on age. Presenting relative as opposed to absolute risk is another option for discussing CVD risk with younger adults.

5.2.2 Use of Rrisk Scoring in Clinical Practice

A number of studies have investigated the use of prediction rules and risk calculators by primary care physicians. An ESC survey conducted in six European countries indicates why physicians rely on their own expertise for the prevention and treatment of CHD: although most cardiologists and physicians (85 %) knew they should base CVD risk assessment on the combination of all CVD risk factors, 62 % of physicians used subjective methods to gauge risk rather than using risk calculators [540]. The most common barriers to guideline implementation were government or local health policy (40 %), patient compliance (36 %), and lack of time (23 %). Suggestions proposed to improve implementation included development of clear, easy to use, and simpler guidelines (46 % prompted; 23 % unprompted) and financial incentives (24 % unprompted).

Although preferred by many physicians, intuitive assessment based on personal experience appears to underestimate the real risk of CVD: physicians (110 general practitioners and 29 internists) estimated CVD risk as being less severe than detailed in recommendations provided in the WHO–International Society of Hypertension guidelines [541, 542]. Moreover, physicians were less willing to prescribe antihypertensive medications to patients identified as eligible in guidelines.

5.2.3 Barriers to Implementing Routine Risk Assessment

In addition to the limitations of risk scoring itself, several barriers to implementing the existing risk assessments in clinical practice have been identified by physicians. A survey among general practitioners and internists working in clinical practice in two Swiss regions revealed that 74 % rarely or never used CVD prediction rules [543], due to fears of oversimplification of risk assessment (58 %) or overuse of medical therapy (54 %). More than half of the physicians (57 %) believed that the numerical information resulting from prediction rules is frequently unhelpful for clinical decision-making [543]. A Dutch qualitative study of the use of risk tables as a key component of risk assessments for primary prevention reported that physicians' knowledge of the risk tables and ability to communicate that knowledge to the patient influenced their implementation [544].

Patients may have a limited understanding of risk tables and how risk relates to disease development [545]. Development of patient educational materials may increase patient understanding, and this may also facilitate physician–patient communication. The length of routine patient consultations, which provides little time for discussion, is widely recognized as a barrier to conducting risk assessments [544, 546].

Physicians are also concerned about overestimating risk in national populations, which may lead to overuse of medical therapy [544, 546]. Results of a Norwegian study suggest that using the European SCORE assessment would double the number of individuals who need drugs for primary prevention of CVD [547]. Affected individuals would include men and elderly individuals who would have a higher tendency to require lipid-lowering medications. Increasing numbers of patients receiving medications may result in higher healthcare costs. However, modelling strategies to use resources efficiently and to identify 70 % of the CVD burden in the UK have reported that prioritizing patients by estimated CVD risk may reduce healthcare costs by £45 000 compared with a diabetes and hypertension first strategy [546].

5.2.4 Methods for Improving Awareness and Implementation of Risk Scoring

Improved awareness of global risk scoring is needed in patients, healthcare providers (relevant clinicians), payers, and politicians, including via the lay press. Perceived individual benefit is a key driver for many patients. Improved implementation of risk scoring may be improved by using two main approaches: incentives and computerization. Incentives have been shown to be effective in the UK, where the Quality and Outcomes Framework (QOF) scheme links primary care income with achievement of specific evidence-based targets in healthcare delivery [548]. The QOF, a form of performance-related remuneration, introduced a payment for primary prevention risk scoring of patients on the hypertension registry in 2009.

Computerization may take one of three approaches and ideally involves all three. Patient self-assessments may be performed using online risk-assessment tools such as SCORE. Online risk-assessment calculators may be used regardless of whether cholesterol or BP measurements are available. The disadvantage of this approach is that it requires highly motivated and computer-literate patients.

Assessment of high-risk patients may be performed using pre-existing clinic population data, generating a list of individuals ranked in terms of their likelihood to score highly on a formal vascular risk assessment and enabling physicians to reduce costs by calling in the most appropriate patients first. This approach requires a robust electronic patient database and needs significant financial support; however, it is inclusive of all patients and provides a rational approach to identifying patients most likely to derive benefit from treatment in a priority sequence.

Finally, embedded CVD risk calculators automatically provide a CVD risk score based on data extracted from the patient's electronic record. For example, in New Zealand, system improvements in primary care practice software were highly successful, increasing the CVD risk assessment screening rate from 4.7 % to 53.5 % over 12 months (n=6570); [549] integration of a web-based decision-support system (PREDICT-CVD) with primary care electronic medical record software improved CVD risk documentation four-fold in a primary care practice of 3564 patients [550]. The weakness of this approach is the need to have an electronic record, the fact that data are often missing, and the lack of uniformity in the scoring method.

5.2.5 Better Risk Factor Management

Although general practice will, in most countries, have a unique role in screening or identifying patients eligible for CVD primary prevention, primary care also has an essential role in better monitoring and follow-up in those patients identified as at high risk and warranting interventions. The implementation strategies for better uptake of lifestyle advice and therapeutic interventions are common across primary and secondary care.

Most important new information

- Barriers to implementation of risk-adjusted prevention are multiple: risk scoring is considered to be time consuming, simplifying a complex situation, and may result in overmedication.
- Resource spent after risk assessment is more likely to reduce future healthcare costs.

Remaining gaps in the evidence

- Application of risk scoring in general practice vs. individual risk factor treatment has not been shown to reduce hard events.
- The use of risk scoring based on electronic patient records is promising, but needs to be tested in a general practice setting.

5.3 Cardiovascular Disease Prevention in Primary Care: Role of the Cardiologist

Key messages

- The practising cardiologist should be the advisor in cases where there is uncertainty over the use of preventive medication or when usual preventive options are difficult to apply [82, 437, 551].

- The practising cardiologist should regularly review the discharge recommendations of the hospital after a cardiac event or intervention [82, 437, 551].

5.3.1 The Cardiologist in General Practice: Consultant Role

Cardiologists working out-of-hospital have an essential role in CVD prevention, acting as consultants to general practitioners and general internists. The practising cardiologist has a pivotal role in the evaluation of patients with cardiovascular problems referred from the primary care physician. A thorough examination by a practising cardiologist will often include assessment of exercise capacity, measurement of ABI, evaluation of cardiac structure and function by echocardiography, and assessment of preclinical atherosclerosis by vascular ultrasound. This will in many patients with perceived low risk often change the risk score profoundly.

Although the identification and basal treatment of risk factors and advice for lifestyle modification is the task of the general practitioner or the general internist, the practising cardiologist is the advisor in cases where there is uncertainty about prevention drug therapy or when the usual preventive modalities are difficult to apply (e.g. nicotine addiction, resistant obesity, side effects, or insufficient efficacy of medication).

The advice of a cardiologist is requested when balancing hormone replacement therapy with symptoms and global cardiovascular risk. The cardiologist also advises on treatment with antiaggregatory drugs after PCI in patients with an additional need for oral anticoagulation (e.g. in chronic AF or in patients with mechanical heart valve prostheses).

5.3.2 Implementing Evidence-Based Medicine

The cardiologist is the physician who, based on the current guidelines, reviews together with the patient the hospital discharge recommendations after a cardiac event or an intervention, and he or she implements the further treatment strategy. The cardiologist also helps the patient comply with the recommendations, by providing them with written information and ensuring that, at given intervals, treatment goals are reached [82, 551]. This approach has a significant impact on mid-term prognosis [250, 437].

The higher the level of care based on the guidelines and performance measures, the better the impact on prevention and recurrent events [82, 437].

5.3.3 Improving Healthcare Using Electronic Records

The increased use of electronic medical records could have a positive impact on CVD prevention at the practising

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cardiologist level. The ability to identify systematically all patients with risk factors, address and document their barriers to care, and control the degree of implementation of risk reduction at pre-determined intervals should result in better outcomes. A link exists between accuracy in recordings and both quality of care and adherence to guidelines [437].

Specific training of practising cardiologists in using electronic medical records for implementing and maintaining long-term prevention strategies should be considered. Maintaining data confidentiality is important.

Most important new information

- The higher the level of care based on guidelines and performance measures, the greater the impact on prevention and recurrent events.

Remaining gaps in the evidence

- The positive impact of electronic records on CVD prevention through improved communication between different healthcare providers needs to be tested and balanced against the danger of losing control of data confidentiality.

Recommendation on self-help programmes

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
Patients with cardiac disease may participate in self-help programmes to increase or maintain awareness of the need for risk factor management, for maintaining physical fitness, or for diligent self-management of oral anticoagulation.	IIa	B	Strong	[552]

[a]Class of recommendation
[b]Level of evidence
[c]References

5.4 Primary Care-Based Self-Help Programmes

In many countries, heart foundations (which also form part of the EHN) support self-help programmes for cardiac patients who organize their own self-help groups. Most of these programmes are organized by patients with CHD, irrespective of a history of myocardial infarction, PCI, CABG, or congestive heart failure. Information on the importance of guideline-orientated treatment is essential for these patients in order to maintain optimal preventive treatment, which has a tendency to be abandoned within 6 months of hospital discharge after myocardial infarction, PCI, or CABG [250]. Regular exercise sessions at weekly or 2-week intervals under the guidance of a physiotherapist, with

or without the supervision of a physician, help to emphasize the importance of maintaining physical fitness. On the other hand, increasing angina at higher exercise levels than reached in daily life can provide an early signal that an examination by the cardiologist is necessary.

In self-help groups of patients with congestive heart failure, emphasis is on: weight management with proper diuretic use; a low level of exercise training, including interval training; and the goal to maintain muscle strength by individualized strength and resistance training of single muscle groups in order to avoid overexertion. All of these activities can also be offered in a structured cardiac rehabilitation programme [205].

Patients with AF or after valve replacement with mechanical valves who need lifelong oral anticoagulation can be taught about the basic principles of this treatment; they can also be taught to determine (at home) their international normalized ratio (INR) at weekly intervals, and to dose the vitamin K antagonist medication in order to keep the INR within the individually determined narrow target range required to avoid bleeding or thrombo-embolic events. Although there was no difference in hard endpoints, self-testing gives greater independence and results in a better quality of life [552]. In addition, after mechanical valve replacement, patients may face problems with intercurrent non-cardiac surgical procedures such as prostate surgery, hip or knee replacement surgery, tumour surgery, tooth extractions, or other surgical procedures where sophisticated perioperative anticoagulation management is needed as well as advice for a prophylaxis against bacterial endocarditis.

Regularly published patient-orientated journals, usually issued by heart foundations, can help to maintain patients' awareness of the need for optimal treatment by discussing the importance of improving lifestyle to control risk factors or improving health factors such as: maintaining a non-smoking status, increasing levels of regular physical activity, and eating a Mediterranean-style diet [553]. Also, new developments in patient care or side effects of commonly used medications such as statins, platelet inhibitors, and amiodarone are discussed. The idea of the self-help programmes is to increase the responsibility of the patient for the disease management and to make the patient a more educated partner for counselling. Self-help programmes form a part of the social network, which serves as a platform for mutual support, and for the exchange of ideas and communication between patients with the same disease. They can improve and facilitate medical management and improve the quality of life of patients who help each other manage their disease in daily life.

Most important new information

- Self-help groups increase independence and improve quality of life.

Remaining gaps in the evidence

- There are no randomized studies to evaluate the effect of self-help groups on hard cardiovascular endpoints.

Recommendation on hospital-based programmes

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
All patients with cardiovascular disease must be discharged from hospital with clear guidelineorientated treatment recommendations to minimize adverse events.	I	B	Strong	[250, 554]

[a]Class of recommendation
[b]Level of evidence
[c]References

5.5 Hospital-Based Programmes: Hospital Services

5.5.1 Evidence-Based Discharge Recommendations Necessary for Optimal Therapy

Guidelines for disease management after a cardiovascular event recommend treatment modalities to minimize the risk of further cardiovascular events. However, only about half of all patients were discharged with optimal medical therapy in an observational study of 5353 patients with acute myocardial infarction compared with the standards in these guidelines [554].

The percentage of patients discharged on optimal medical therapy may vary in patients with different diagnoses, in elderly vs. younger patients, in men vs. women, after different procedures, or in different institutions; [555] patients discharged on less than optimal medical therapy have a worse 1-year prognosis [554]. In the national programme of the AHA—'Get with the Guidelines'—discharge medications with a prognostic impact were part of the evaluation programme, which included ACE inhibitors, aspirin, beta-blockers, and lipid-lowering therapies, as well as smoking cessation advice and counselling. Defect-free (100 %) compliance was highest for PCI patients (71.5 %), followed by CABG patients (65.1 %), then no-intervention patients (62.1 %). Multivariable analysis adjusting for 14 clinical variables confirmed that compliance with all performance measures was statistically significantly higher for PCI patients than for CABG patients and was lowest for nonintervention patients [555]. The new ESC Guidelines provide a check list of measures necessary at discharge from hospital to ensure that intense risk factor modification and lifestyle change are implemented in all patients following the diagnosis of ACS including recommendation for enrolment in a cardiovascular prevention and rehabilitation programme [556].

5.5.2 Systematic Quality Improvement Programmes are Essential

The introduction of an intensive, educational, and process-orientated quality-improvement initiative, based on the 2001 American College of Cardiology/AHA secondary prevention guidelines [557], resulted in significantly improved compliance rates at discharge for aspirin, ACE inhibitors, lipid-lowering drugs, smoking cessation counselling, and dietary counselling [558].

A low-intensity quality-improvement programme in a randomized national study of 458 hospitals after bypass surgery included check lists, patient activation materials, and patient educational materials that stressed the importance of secondary prevention medications and lifestyle modification. A significant increase was observed in the rate of optimal secondary prevention, with better adherence to guidelines in all patient subgroups, particularly women and the elderly; previously existing treatment gaps were almost eliminated, and improvements were seen in the use of lipid-lowering therapy, ACE inhibitor treatment, and tobacco-cessation counselling. There appears to be a learning curve: over the course of 2 years there was a continuous increase in guideline adherence by the physicians at discharge of the patients [559].

Thus structured programmes to implement guideline-defined therapy at the time of hospital discharge should be offered in order to achieve the highest possible percentage of patients with guideline-advocated therapy—a prerequisite for good long-term compliance with a guideline-orientated treatment regimen.

Most important new information

- The introduction of quality-improvement programmes improves discharge recommendations.

Remaining gaps in the evidence

- Still missing is evidence that efforts for optimal treatment at hospital discharge result in better long-term maintenance of secondary prevention efforts and greater reduction in cardiac events.
- Appropriately timed booster interventions may also be necessary.

Recommendation for specialized prevention centres

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
All patients requiring hospitalization or invasive intervention after an acute ischaemic event should participate in a cardiac	IIa	B	Strong	[205, 250]

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Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
rehabilitation programme to improve prognosis by modifying lifestyle habits and increasing treatment adherence.				

[a] Class of recommendation
[b] Level of evidence
[c] References

5.6 Hospital-Based Programmes: Specialized Prevention Centres

Following a cardiovascular event, long-term adherence to prescribed medications is of similar importance to continued lifestyle improvement in order to reduce the risk of a recurrent ischaemic event. In randomized studies with a structured treatment regimen and frequent follow-up following an ACS, the compliance rate is high and the event rate low [560].

5.6.1 Cardiac Rehabilitation Centres Help Improve Lifestyle

In the usual care setting, compliance with lifestyle recommendations and treatment regimens starts to decline within 6 months of discharge from hospital. Adherence to behavioural advice (diet, exercise, and smoking cessation) after an ACS was associated with a substantially lower risk of recurrent cardiovascular events compared with non-adherence [250]. Cardiac rehabilitation after cardiac events or interventions in a specialized centre helps to maintain long-term adherence to the optimal treatment programme by educating the patient and repeatedly emphasizing the importance of maintaining the prescribed treatments and recommended lifestyle.

5.6.2 Cardiac Rehabilitation is Cost-Effective

Cardiac rehabilitation is considered a cost-effective intervention following an acute coronary event; it improves prognosis by reducing recurrent hospitalizations and healthcare expenditure while prolonging life [561]. Cardiac rehabilitation after a cardiac event is a Class I recommendation from the ESC, the AHA, and the American College of Cardiology [139, 205, 562, 563].

Whereas the core components and goals of cardiac rehabilitation are standardized and documented in a position paper [205], the structure and type of cardiac rehabilitation units vary in different countries. Traditions of the healthcare system and cost considerations play important roles. Residential cardiac rehabilitation centres, where the patient is removed from his or her usual environment and lives in an idealized environment for 2–3 weeks to become familiar with the necessary medication and train a healthy lifestyle,

is one option in several European countries, and is usually followed by ambulatory training sessions in the home environment. Other countries favour ambulatory rehabilitation units where the patient participates once or twice per week in a rehabilitation session over a period of several months and tries to implement the lifestyle recommendations in his or her usual environment, including after returning to work.

A 3-year, multicentre RCT was conducted to compare a long-term, reinforced, multifactorial educational and behavioural intervention co-ordinated by a cardiologist vs. usual care after a standard cardiac rehabilitation programme (residential or ambulatory) following myocardial infarction in a cardiac rehabilitation centre. The intervention proved effective in improving risk factors and increasing medication adherence over time, with significant improvement in lifestyle habits (i.e. exercise, diet, psychosocial stress, and body weight). Clinical endpoints were also reduced by the intensive intervention: cardiovascular mortality, non-fatal myocardial infarction, and stroke by 33 % (P=0.02), and cardiac death plus non-fatal myocardial infarction by 36 % (P=0.02), total stroke by 32 %, and total mortality by 21 % (P=not significant) [564].

5.6.3 Challenges for Cardiac Rehabilitation: Female Gender and Co-Morbidities

Expected outcomes of all the cardiac rehabilitation interventions are improved clinical stability and symptom control, reduced overall cardiovascular risk, higher adherence to pharmacological advice, and a better health behaviour profile, all leading to superior quality of life and improved prognosis. However, dedicated long-term efforts beyond the early phase are necessary to maintain compliance with medications and lifestyle.

A particular challenge for the rehabilitation programmes are older and female [205, 565] patients and patients with specific co-morbid conditions, such as transient ischaemic attack or stroke, chronic obstructive pulmonary disease, and chronic renal failure. A new challenge all over Europe is how to meet the needs of ethnic minorities with sometimes different cultural values, and sometimes lack of fluency in the language of their country of residence [205]. The success of the rehabilitative and secondary preventive efforts depends on a high level of individual care and support with a careful clinical evaluation beyond cardiovascular function, including psychosocial assessment and evaluation of co-morbid conditions.

5.6.4 Repeated Sessions Improve Compliance

From a large observational study, it was suggested that the number of rehabilitation sessions attended (i.e. duration and intensity of the intervention and motivation of the participant) correlated with improved prognosis [67]. This was supported by the results of the Global Secondary Prevention

Strategies to Limit Event Recurrence After MI (GOSPEL) study, where a long-term intervention was more effective than a short-term course [564].

Whether the rehabilitation course is applied in an ambulatory setting or as a residential course is probably of lesser importance; the duration of the programme, the educational level, and the motivation of the patient are also important for long-term outcome [205].

The participation rate in a rehabilitation programme after a cardiac event is far lower than desirable: only ~30 % of eligible patients in Europe participate in such a programme, with considerable variation reported between countries [5]. Although cardiac rehabilitation is cost-effective from the perspective of society, it will be a major challenge in the future to improve this low rate of participation throughout Europe.

Most important new information

- Cardiac rehabilitation is cost-effective in reducing risk of cardiovascular events.

Remaining gaps in the evidence

- The optimal length of a cardiac rehabilitation programme remains unknown.

5.7 Non-Governmental Organization Programmes

Key message

- Non-governmental organizations are important partners to healthcare workers in promoting preventive cardiology.

The EHN is a Brussels-based alliance of heart foundations and like-minded non-governmental organizations throughout Europe, with member organizations in 26 countries. The EHN plays a leading role in prevention—in particular heart disease and stroke—through advocacy, networking, education, and patient support, so they may no longer be the major cause of premature death and disability throughout Europe [566].

To achieve its aim, the EHN dedicates itself to influencing European policy-makers in favour of a heart-healthy lifestyle; creating and nurturing ties between organizations concerned with heart health promotion and CVD prevention; gathering and disseminating information relevant to heart health promotion; and strengthening membership capacity.

The EHN works through expert groups, focusing on: nutrition for a healthy heart; tobacco policy and discouraging smoking; occupational health and psychosocial factors; and physical activity as a natural part of daily life.

The EHN facilitates networking amongst its member organizations that work actively to support heart and stroke patients. Approximately half of the organizations' members

fall within this category. Cardiovascular patient 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 they promote cardiac rehabilitation.

5.8 Action at the European Political Level

Key message

- The European Heart Health Charter marks the start of a new era of political engagement in preventive cardiology.

In 2002, the Board of the ESC marked its future involvement in health policy by declaring a strategy for member states to reduce deaths from CVD by 40 %. It was clear that for medical professionals to impact political decision-making on EU and national levels, it would be necessary to build strong alliances with other non-governmental health organizations, primarily the EHN, but also local health authorities and the EU. The work was initiated by providing accurate expertise and alarming statistics on the huge burden and inequity of CVD across Europe, and resulted in a call to action from member states and the European Commission to tackle CVD.

This initiative was followed by partnership with the Irish presidency in 2004. It was concluded that most cases of CVD are preventable through lifestyle changes and appropriate use of medications already in existence. The following EU Council Conclusions on CVD was the first political statement on the EU level acknowledging the need to improve CVD health in Europe. Successful collaborations with the Luxemburg, Austrian, and Portuguese presidencies paved the way, together with the EHN, to create a European Heart Health Charter. This charter was launched in June 2007 at the European Parliament, and was endorsed by the European Commission and WHO Region Europe. This development paved the way for a European Parliament Resolution on Action to Tackle Cardiovascular Disease, the strongest political agreement so far on the need for CVD prevention in Europe [566]. The charter outlines universal targets and goals for CVD prevention and provides the actions to be taken in order to reach these goals. It has been translated into 26 languages and officially adopted by 30 EU member nations and other European countries [6].

In the following period, the ESC perceived the prospect from policy-makers that combining efforts with other diseases could make a voice stronger and more influential. In order to succeed, the political challenge of bringing together science from different horizons to convey a single message benefiting all of the diseases represented in the group had to be overcome. In June 2009, the ESC invited medical organizations representing diabetes, respiratory diseases, and cancer to reflect on common health determinants, identify areas with sufficient evidence to support recommendations, and

discuss future collaboration. Four risk factors were identified as presenting enough commonalities to justify joint actions: tobacco, nutrition, alcohol consumption, and physical inactivity. Thus the European Chronic Disease Alliance was established. This alliance currently comprises 10 not-for-profit European organizations representing >100 000 health professionals. It addresses all major non-communicable chronic diseases, including heart disease, stroke, hypertension, diabetes, kidney disease, cancer, respiratory disease, and liver disease [172]. The alliance, which will facilitate a population-wide risk factor control, has the potential of a large impact on public health and healthcare savings.

In conclusion, the authors of the guidelines hope that this document will advocate a real partnership among politicians, physicians, allied health personnel, scientific associations, heart foundations, voluntary organizations, and consumers' associations to foster both health promotion at the population level and primary and cardiovascular prevention at the clinical level, using the complete spectrum of evidence in medicine from experimental trials to observations in populations.

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