



# European guidelines on cardiovascular disease prevention in clinical practice: executive summary

## Fourth 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)

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**Preamble**

Guidelines and Expert Consensus Documents summarize and evaluate all currently available evidence on a particular issue with the aim to assist physicians in selecting the best management strategies for a typical patient, suffering from a given condition, taking into account the impact on outcome, as well as the risk–benefit ratio of particular diagnostic or therapeutic means. Guidelines are not substitutes for textbooks. The legal implications of medical guidelines have been discussed previously.

A great number of Guidelines and Expert Consensus Documents have been issued in recent years by the European Society of Cardiology (ESC) as well as by other societies and organizations. Because of the impact on clinical practice, quality criteria for development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines and Expert Consensus Documents can be found on the ESC web site (<http://www.escardio.org/knowledge/guidelines/rules>).

In brief, experts in the field are selected and undertake a comprehensive review of the published evidence for management and/or prevention of a given condition. A critical evaluation of diagnostic and therapeutic procedures is performed, including assessment of the risk–benefit ratio. Estimates of expected health outcomes for larger societies are included, where data exist. The level of evidence and the strength of recommendation of particular treatment options are weighed and graded according to predefined scales, as outlined in the tables below.

The experts of the writing panels have provided disclosure statements of all relationships they may have which might be perceived as real or potential sources of conflicts of interest. These disclosure forms are kept on file at the European Heart House, headquarters of the ESC. Any changes in conflict of interest that arise during the writing period must be notified to the ESC. The Task Force report was entirely supported financially by the ESC and was developed without any involvement of industry.

The ESC Committee for Practice Guidelines (CPG) supervises and coordinates the preparation of new Guidelines and Expert Consensus Documents produced by Task Forces, expert groups, or consensus panels. The Committee is also responsible for the endorsement process of these Guidelines and Expert Consensus Documents or statements. Once the

document has been finalized and approved by all the experts involved in the Task Force, it is submitted to outside specialists for review. The document is revised, and finally approved by the CPG and subsequently published.

After publication, dissemination of the message is of paramount importance. Pocket-sized versions and personal digital assistant (PDA)-downloadable versions are useful at the point of care. Some surveys have shown that the intended end-users are sometimes not aware of the existence of guidelines, or simply do not translate them into practice, so this is why implementation programmes for new guidelines form an important component of the dissemination of knowledge. Meetings are organized by the ESC, and directed towards its member National Societies and key opinion leaders in Europe. Implementation meetings can also be undertaken at national levels, once the guidelines have been endorsed by the ESC member societies, and translated into the national language. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Thus, the task of writing Guidelines or Expert Consensus documents covers not only the integration of the most recent research, but also the creation of educational tools and implementation programmes for the recommendations. The loop between clinical research, writing of guidelines, and implementing them in clinical practice can then only be completed if surveys and registries are performed to verify that real-life daily practice is in keeping with what is recommended in the guidelines. Such surveys and registries also make it possible to evaluate the impact of implementation of the guidelines on patient outcomes. Guidelines and recommendations should help the physicians to make decisions in their daily practice; however, the ultimate judgement regarding the care of an individual patient must be made by the physician in charge of his/her care.

Classes of recommendations	
<b>Class I</b>	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, and effective
<b>Class II</b>	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure
<b>Class IIa</b>	Weight of evidence/opinion is in favour of usefulness/efficacy
<b>Class IIb</b>	Usefulness/efficacy is less well established by evidence/opinion
<b>Class III</b>	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful

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



## Introduction

The rationale for an active approach to the prevention of atherosclerotic cardiovascular disease (CVD) is based on five key points:

### Why develop a preventive strategy in clinical practice?

1. Cardiovascular disease (CVD) is the major cause of premature death in Europe. It is an important cause of disability and contributes substantially to the escalating costs of health care
2. The underlying atherosclerosis develops insidiously over many years and is usually advanced by the time that symptoms occur
3. Death from CVD often occurs suddenly and before medical care is available, so that many therapeutic interventions are either inapplicable or palliative
4. The mass occurrence of CVD relates strongly to lifestyles and to modifiable physiological and biochemical factors
5. Risk factor modifications have been shown to reduce CVD mortality and morbidity, particularly in high risk subjects

By the early 1990s there was a plethora of similar yet confusingly different national and international guidelines for the prevention of CVD. In order to try to define the areas of agreement, the ESC, the European Atherosclerosis Society and the European Society of Hypertension agreed to collaborate, resulting in a set of recommendations for the prevention of coronary heart disease (CHD) that was published in 1994.<sup>1</sup> These guidelines were revised in 1998 and 2003 by the second and third Joint Task Forces.<sup>2,3</sup> A strength of the guidelines is that, from the outset, it was stressed that CVD is usually the product of multiple interacting risk factors. This resulted in the production of risk charts that attempt to simplify the estimation of total CVD risk, and a realization that risk management requires attention to all modifiable risk factors.

It was appreciated that the original partners needed assistance from other bodies and experts, in particular in the fields of behavioural medicine and diabetes. In addition, it is acknowledged that much practical preventive advice is delivered by family doctors, nurses, and through voluntary bodies such as Heart Foundations. These considerations are reflected in the expanded partnership represented in the present guidelines, and in the list of experts whose input has been sought.

The Third Joint Task Force Guidelines saw a change from CHD to CVD prevention, to reflect the fact that atherosclerosis may affect any part of the vascular tree. A new risk chart called SCORE (Systematic COronary Risk Evaluation) was developed which was based on 12 European cohort studies and allowed the estimation of 10-year risk of cardiovascular death. Separate charts were produced for high and low risk regions of Europe. More explicit clinical priorities were developed. Less emphasis was placed on the terms 'primary' and 'secondary' prevention since risk is a continuum—asymptomatic persons may have investigational evidence of atherosclerotic disease. A rigorous external review process was undertaken.

The Fourth Joint Task Force has taken note of feedback in several areas:

- (1) More detailed guidance was sought from the World Organization of National Colleges, Academies and academic associations of general practitioners/family physicians (WONCA, or the 'World Organization of Family Doctors' for short) and from the ESC Working Group on Cardiovascular Nursing, since these bodies represent the professionals that are heavily engaged in the practical delivery of preventive advice in many European countries.
- (2) The current ESC approach to grading evidence was examined in detail. Concern was expressed that the present system, while logical, tends to give priority to drug treatments since these are more amenable to double-blind randomized controlled trials than lifestyle measures, even if observational studies indicate powerful benefits from, for example, smoking cessation. For this reason, the gradings have not been included in the present documents, and further debate on this topic is strongly recommended.
- (3) All risk estimation systems, including SCORE, will overestimate risk in countries that have experienced a decline in CVD mortality, and underestimate risk if mortality has increased. The development of national guidance has always been recommended by the Task Force and, as part of this process, recalibration of the SCORE charts to allow for time trends in both mortality and risk factor distributions in individual countries is recommended. In the Third Joint Guidelines, the need to address the problem of a high relative but low absolute risk in younger persons was dealt with by extrapolating a young person's risk to age 60 to flag persons who will become at high absolute risk. If interpreted too literally, this approach might result in excessive use of drug treatments in young people. In the present guidelines, this approach has been replaced with a simple relative risk chart to be used in conjunction with the SCORE absolute risk chart.
- (4) A re-examination of the SCORE data sets indicated that the impact of self-reported diabetes on risk may have been underestimated. The issue of predicting total events as well as just CVD mortality also receives more attention, as do gender issues, central obesity, high-density lipoprotein (HDL) cholesterol, heart rate, renal impairment, and manifestations of CVD other than CHD.

### What's new in the Fourth Joint Task Force Guidelines on the Prevention of CVD?

- Increased input from general practice and cardiovascular nursing
- Increased emphasis on exercise, weight, and lifestyle
- More detailed discussion on the limitations of present systems of grading evidence
- Re-defined priorities and objectives
- Revised approach to risk in the young
- Total events considered as well as mortality
- More information from SCORE on total events, diabetes, HDL cholesterol, and body mass index (BMI)
- New sections on gender, heart rate, BMI/waist circumference, other manifestations of CVD, and renal impairment

These Guidelines attempt to find areas of broad agreement among different professional bodies and scientific disciplines. With the help of WONCA, a particular effort has been made to

harmonize the advice that may be given to primary care and second-line care health professionals. The production of more detailed guidelines by the partner societies is encouraged; as examples, reference is made to the ESH/ESC guidelines on the management of arterial hypertension<sup>4</sup> and to the guidelines on diabetes, pre-diabetes and CVD by the ESC/EASD.<sup>5</sup> Implicit in this partnership process is that these will be compatible with the generic Joint Guidelines.

The development of national guidance on CVD prevention is also specifically encouraged. The Joint Guidelines should be regarded as a framework from which national guidelines can be developed to suit local political, economic, social, and medical circumstances. The production of guidelines is only one step in the process of prevention, and the development of national multidisciplinary implementation partnerships is recommended; the section on implementation addresses some of the issues involved.

It should be appreciated that the Fourth Joint Task Force Guidelines are for the use of physicians and other health professionals engaged in clinical practice. Therefore, they give the highest priority to those individuals at highest CVD risk because such persons gain most by active risk factor management. However, they should be complemented by national and European public health strategies aimed at whole populations in a co-ordinated and comprehensive effort to reduce the enormous burden of CVD that afflicts European populations. In this way, we hope that the guidelines will promote higher quality of care to help reduce this burden and CVD in Europe. These issues inform a major new initiative, the publication of the European Health Charter, available through [www.heartcharter.eu](http://www.heartcharter.eu). The Charter was produced by the ESC, European Union (EU), and the European Heart Network, in partnership with the World Health Organization (WHO). The relationship between the Charter and the present Guidelines may be summarized:

#### The European Heart Health Charter and the Guidelines on cardiovascular disease prevention

- The European Heart Health Charter advocates the development and implementation of comprehensive health strategies, measures and policies at European, national, regional, and local level that promote cardiovascular health and prevent CVD
- These guidelines aim to assist physicians and other health professionals to fulfil their role in this endeavour, particularly with regard to achieving effective preventive measures in day-to-day clinical practice
- They reflect the consensus arising from a multi-disciplinary partnership between the major European professional bodies represented

## The scope of the problem: past and future

### Scientific background

CVDs were the direct cause of >4 million deaths in Europe around the year 2000 (1.9 million in the EU), accounting for 43% of all deaths of all ages in men and for 55% in women (*Table 1* from [www.ehnheart.org](http://www.ehnheart.org)).<sup>7</sup> CVDs were also the major cause of hospital discharges, with an average rate of 2557 per 100 000 population around the year 2002. Out

**Table 1** All deaths from circulatory disease in Europe. All ages. Year 2000 or circa

All causes	Men	4 519 403
	Women	4 336 346
All circulatory	Men	1 963 644
	Women	2 307 945
CHD	Men	967 258
	Women	983 229
Stroke	Men	504 307
	Women	775 571
Other	Men	492 079
	Women	637 405

of these, 695 per 100 000 were caused by CHD and 375 per 100 000 by stroke, but more than half were due to other forms of chronic heart disease. The estimated total cost of CVDs in the EU countries was €168 757 million in 2003.<sup>8</sup>

CVD mortality rates vary with age, gender, socio-economic status, ethnicity, and geographical region. Mortality rates increase with age, and are higher in men, in people of low socio-economic status, in Central and Eastern Europe, and in immigrants of South Asian origins. There are marked socio-economic gradients in CVD morbidity and mortality within European countries, which are partially explained by socio-economic differences in conventional risk factors, such as smoking, blood pressure (BP), blood cholesterol, and glucose.

Total CVD mortality has been falling consistently, both in middle life and at older ages, since 1970 in Western Europe.<sup>9</sup> In Central and Eastern Europe, they started to decline only in recent years, and they remain very high in such countries. There is still nearly a 10-fold gradient in male CHD mortality between Eastern Europe and France at ages 35–74, and up to a 6-fold difference in stroke mortality. Declines in CHD mortality are related to population-wide behavioural changes in nutrition and smoking in both Western and Eastern Europe. The incidences of CHD<sup>10</sup> and stroke have also been declining in Western Europe, but increasing in other countries, principally in Eastern Europe and Spain.

### Practical aspects: coronary artery disease

Changes in CHD mortality at the end of the 20th century were mostly explained by changes in incidence rather than changes in short-term case fatality of acute myocardial infarction (AMI).<sup>11</sup> Major emphasis is needed in the control of risk factors and of the determinants of incident CHD. The reduction in blood pressure noted at population level is only partly attributable to an increase in the proportion of hypertensive subjects receiving treatment, suggesting that despite the importance of medication to individuals, other determinants of BP lowering are more powerful in whole populations. Risk factor control in high risk patients and in patients with established CHD remains poor, especially regarding obesity, smoking, and BP, and mostly so in diabetic patients, in spite of issued guidelines indicating the need for reinforcing dissemination and implementation of cost-effective prevention actions in an organized way.<sup>12</sup>

As survival after acute events improves, prevalent CHD increases, especially in older women. It is known that diabetes is a more powerful risk factor for women, and, thus, control of risk factors among diabetic patients becomes a

special priority. As the prevalence of overweight and obesity increases worldwide, an increase in the prevalence of type 2 diabetes and hence all its complications may be anticipated. Consequently, control of the growing epidemic of obesity should be a priority.

The clinical manifestations of CVD may be very different. Hospital statistics reveal only the tip of the iceberg, since sudden cardiac death occurring outside the hospital still represents a large proportion of all cardiovascular deaths.

### Heart failure

Pump failure of the heart is a common cause of death in the elderly, although this not always reflected in mortality statistics because of the limitations of coding rules. Hospital admission rates for heart failure have been increasing in the USA and in Europe. Hypertension, obesity, and diabetes are major risk factors. Although a small proportion of clinical cases are due to valve disease (often linked with CHD), or to cardiomyopathy, epidemiological studies suggest that, in well developed countries, the majority of cases are due to ischaemia.<sup>13</sup>

### Aortic aneurysm and dissection

Aortic aneurysm is also atherosclerotic in nature, and increasing mortality trends have been shown in some European countries.<sup>14</sup> It is a potentially preventable cause of death, particularly when confined to the abdominal aorta. The prevalence is 5% in men aged 60 years or more, and 1–2% in women. Screening for this condition has been suggested since elective surgical repair carries a 5–8% 30-day mortality in comparison with 50% mortality for ruptured aneurysm; a trial of screening conducted in the UK has shown encouraging results.<sup>15</sup>

### Peripheral arterial disease

It is known that coronary and peripheral vessels are affected by the same disease process, requiring the same treatment modalities. Peripheral arterial disease (PAD) occurs almost as frequently in women as in men.<sup>16</sup> The correlation of PAD with CHD, myocardial infarction (MI), and stroke reflects the widespread nature of atherosclerosis. However, some minor differences have emerged from epidemiological studies regarding the risk factors for these diseases. Smoking appears to be more important in the aetiology of PAD than in CHD.<sup>17</sup> A positive family history, hypertension, diabetes, dyslipidaemia including increased total and low-density lipoprotein (LDL) cholesterol and decreased HDL cholesterol, increased fibrinogen and C-reactive protein (CRP), advanced age, and physical inactivity seem to be common risk factors.

As in CHD, effective risk factor management is essential. Risk reduction can be achieved through lifestyle modification, particularly physical activity and exercise, smoking cessation, and therapies such as use of statins, antiplatelet therapies, antithrombotic strategies, angiotensin-converting enzyme (ACE) inhibitors, and  $\beta$ -blockers.<sup>16,18,19</sup> The beneficial effects of statins in these patients have been shown in large trials.<sup>20</sup> Statins not only lower the risk of PAD and vascular events, but they also improve the symptoms associated with PAD. There is also evidence that statins reduce surgical mortality and improve graft patency and limb salvage in PAD patients.<sup>21</sup>

### Stroke

The incidence of stroke increases exponentially with age, affecting about 25 per 100 000 in the age group 35–44 years and 1500 per 100 000 in age group 75–84 years annually. Stroke is the third leading cause of death in many countries. Intracerebral haemorrhage and subarachnoid haemorrhage contribute 10 and 5% of strokes, respectively. Ischaemic stroke may be due to large vessel disease, small vessel disease, emboli from the heart or from the aortic arch, or other rarer identified causes, while a large proportion still remains undetermined.<sup>22</sup>

The most important risk factor is hypertension, followed by smoking and diabetes. Others are sedentary lifestyle, overuse of alcohol, and illicit drugs, elevated cholesterol, use of oral contraceptives or postmenopausal hormones, overweight, low socio-economic status (SES), and atherosclerotic stenosis of extracranial vessels.

### Practical aspects: prevention and management of stroke

Antihypertensive treatment reduces risk of both ischaemic and haemorrhagic stroke, and stroke prevention is the most important effect of antihypertensive treatment. Smoking should be discouraged and physical activity encouraged. Alcohol intake in low amounts may not be harmful. With regard to statin therapy, stroke survivors should be treated in the same way as those with other manifestations of CVD. Carotid endarterectomy in symptomatic patients with stenosis of the internal carotid artery reducing the lumen >70% reduces the risk of recurrent stroke.

Prophylactic antithrombotic treatment: Within the therapeutic range of international normalized ratio (INR) 2–3, anticoagulation reduces stroke risk in patients with atrial fibrillation. Antiplatelet therapy is indicated in patients with non-cardioembolic ischaemic stroke. Aspirin is the most widely used drug in doses of 75–150 mg a day. The combination of aspirin and dipyridamole gives an additional risk reduction. Clopidogrel has an effect similar to aspirin in patients with ischaemic cerebrovascular disease. Combination of clopidogrel and aspirin is not recommended for stroke survivors. For a more comprehensive review, readers are referred to the European Stroke Initiative.<sup>23</sup>

## Prevention strategies and policy issues

### Scientific background

Three strategies for the prevention of CVD can be distinguished: **population, high-risk and secondary prevention**. The three strategies are necessary and complement each other. The population strategy in particular is critical to reducing the overall incidence of CVD since it aims to reduce risk factors at population level through lifestyle and environmental changes that affect the whole population without requiring the medical examination of individuals. This type of strategy is mostly achieved by establishing *ad hoc* policies and community interventions.

The strategies aimed to diminish the total cardiovascular risk of individuals are the high risk primary prevention and the secondary prevention strategies. The former deals with healthy persons belonging to the upper part of the



risk distribution, and the second with patients with established cardiovascular organ damage or disease. To prevent one single cardiovascular event, it will be necessary to intervene in many subjects with no apparent benefit to them (*prevention paradox*). Furthermore, the number of subjects in whom an intervention is needed to prevent one case will vary in different populations or population subgroups (e.g. in women) depending on their underlying prevalences and distribution of risk factors, and the incidence rate of disease.

### Practical aspects: policy issues

The Fourth Task Force aligns and fully endorses the initiatives of major international organizations in taking steps to implement measures at the population level, such as those for tobacco control established by the WHO Framework Convention for Tobacco Control,<sup>24</sup> the EU initiative on obesity,<sup>25</sup> the WHO Global Strategy on diet, physical activity, and health,<sup>26</sup> and the Osaka Declaration on Heart Health which can be summarized as:

1. Increase awareness of governments that the health agenda is not just an agenda of health departments.
2. Let scientists and health professionals contribute to the marketing of the heart health agenda.
3. Let schools for health professionals provide training in methods for community organizing, social marketing, and advocacy.
4. Let departments of health, non-governmental organizations (NGO's), and professional organizations develop plans to make the case for heart health resources at the political level
5. Let the WHO continue to strengthen the capacity for heart health promotion in all WHO regions and member states.

Likewise, the EU Council on Employment, Social Policy, Health, and Consumer Affairs in June 2004 and an EU Heart Health Conference that resulted in the Luxembourg Declaration of 29 June 2005 defined the characteristics that are necessary to achieve cardiovascular health:

- Avoidance of tobacco
- Adequate physical activity (at least 30 min per day)
- Healthy food choices
- Avoiding overweight
- BP below 140/90 mmHg
- Total cholesterol below 5 mmol/L (~200 mg/dL).

The Fourth Task Force encourages health professionals of all countries to participate actively in the design and implementation of such national and international policies and community interventions.

### Prevention in clinical practice

There is no evidence that mass screening for detection of early stages of CHD or stroke is a cost-effective way to prevent disease. For opportunistic detection of biological risk factors or of lifestyles to detect persons at high risk, the following are necessary:

- accurate and adequate systems of measurement are routinely available
- real time for advice or treatment as appropriate
- continuity of care
- patient access to treatments, regardless of SES.

Programmes for secondary prevention of CHD have proven to be effective in improving processes of care, readmissions to hospital, functional status, and overall mortality, especially if they incorporate exercise programmes. However, their effect sizes are quite modest and their cost-effectiveness on a large scale remains uncertain.<sup>27,28</sup>

## How to evaluate scientific evidence

### Scientific background

Evidence-based medicine (EBM) has been defined as the integration of individual clinical expertise with the best available clinical evidence from systematic research. It involves asking answerable questions, searching for the best evidence, critically appraising the evidence, applying the evidence to individual patient care, and evaluating the process.<sup>29</sup> Despite over a decade of educational effort, it is rare for clinicians to practise EBM as intended, with many considering that the major issue is finding the evidence.<sup>30</sup>

This report aims to provide guidelines under the auspices of the Fourth Joint Task Force of the ESC and other European Societies on Cardiovascular Disease Prevention. The Task Force wishes these guidelines to be as evidence based as possible. Good guidelines are a major mechanism for improving the delivery of health care and improving patient outcomes.<sup>31</sup> It has been shown that guidelines based on credible evidence are more likely to be adopted.<sup>32</sup>

### Desirable attributes of clinical guidelines

- Validity
- Reproducibility
- Reliability
- Clinical applicability
- Clinical flexibility
- Clarity
- Meticulous documentation of the evidence
- Regular review of the guidelines should be scheduled
- Involvement of key groups affected by the guidelines

### What is 'evidence'?

The evaluation of interventions and diagnostic methods can make use of a wide range of sources of evidence: experience, retrospective case review, case reports, case series, historic and geographic comparisons, drug (and post-marketing) surveillance studies, pharmacoepidemiological databases, cross-sectional studies, case-control studies, cohort studies, randomized controlled trials, and systematic reviews of trials and of observational studies. Traditionally, hierarchies of evidence have been promoted as a means of prioritizing recommendations. These generally put systematic reviews at the top of the hierarchy and case reports at

the bottom. However, this approach may be misleading as the quality of evidence ultimately depends on the question to be answered.

It is clear that different questions require different scientific methods, and that reliance on one source of evidence to the exclusion of others is likely to be misleading. This is particularly true in CVD prevention. Lifestyle measures such as smoking cessation, exercise, and healthy eating are less amenable to double blind randomized controlled trials than are drug treatments, and to promote slavish adherence to the primacy of the randomized controlled trial may result in guidelines that promote excessive usage of drugs. Systematic reviews and randomized controlled trials are not the most appropriate method for identifying rare hazards of treatment. Case reports may provide the first hint that a treatment is hazardous, but they require confirmation in large prospective surveillance surveys.

### Grading of evidence

In using evidence to produce guidance or recommendations for clinical or public health practice, it is important to distinguish between the *quality of the evidence* (is it robust, little likelihood of bias, generalizable, etc.) and the *strength of a recommendation* underpinned by the evidence. Not all high quality evidence merits a strong recommendation.

Guideline developing bodies have generally used the 'hierarchy of evidence approach'. Application of the hierarchy of evidence method requires explicit judgements to be made about the quality of the evidence (e.g. completeness, potential for bias, adequacy of outcomes assessed, etc.) Critically, both the benefits and the hazards of interventions need to be taken into account in producing clinical guidance. While such an approach provides transparency, there are also disadvantages, as outlined above. There have also been difficulties in the implementation of these graded recommendations. For example, in implementing a guideline, some recommendations that are crucial to the overall improvement of care may be underpinned by little or no strong evidence. If a decision to implement only high grade recommendations was undertaken on the grounds of resource constraints, then important elements of the guideline may be overlooked. Consequently, there is interest in developing a system that retains the desirable ability to maintain transparency but avoids perversity in implementation.

The WHO have established a working group to develop such a system, called GRADE. Evidence is graded based on the outcomes relevant to the question being answered. This is appraised in four domains: study design, study quality, consistency, and directness (generalizability). Based on the scoring of these attributes, the quality of evidence for the specific outcome is defined as high, moderate, low, or very low grade.<sup>33</sup> This system cannot tackle the implementation problems discussed above but provides a clear judgement of whether the benefits of an intervention outweigh the adverse effects. This provides a transparent method of prioritizing interventions for implementation. As experience in using this system grows, it will probably become a more widely used tool for the generation of clinical guidance.

### The problems of evidence and guidance

We have attempted to ensure that the most appropriate evidence is used to underpin recommendations. For population prevention programmes, observational epidemiological findings are an important first step in considering causality. Behaviours such as smoking cessation and exercise are less amenable to randomized controlled trials than drug treatments. Clearly, systematic reviews of observational studies are preferable to citation of single observational studies. However, it is important to be aware that the increased precision provided by pooling data may be spurious if the control for confounding and other biases is weak in the index studies.<sup>34</sup>

A growing concern in epidemiology is that with some associations causation has been wrongly attributed. This appears to be the case for antioxidant vitamins, where observational studies suggested a reasonable protective effect, but randomized controlled trials have shown that the interventions may even be harmful.<sup>35,36</sup> A further concern for us is the nature of available evidence. Much of the evidence concerns drug treatments rather than lifestyle interventions or health system improvements.

In examining the effects of interventions, we have given prominence to Cochrane systematic reviews where they exist as these are conducted to a rigorous standard and are updated periodically. We have used other systematic reviews where these exist and have only cited individual trials where they make particular points of interest, or are sufficiently large to provide a clear answer to a clinical question. Where we feel the evidence is scant, we have stated this.

When examining effect sizes, we have not used numbers needed to treat as these have quite marked problems,<sup>37</sup> particularly in preventive cardiology where baseline rates of CVD vary markedly throughout Europe. Consequently a number needed to treat would be needed for countries with low, medium, and high risk. Moreover, numbers needed to treat for different age groups and for men and women would be required. Relative risk reductions on treatment are applicable to all European populations, age groups, and men and women as, in general, most treatments have the same relative benefits at different levels of risk.

### Practical aspects

In this report, we have attempted to follow an evidence-based approach. We have defined the following questions:

- What is the evidence that specific risk factors cause CVD?
- What is the evidence that these risk factors vary in importance among those with and without established CVD?
- What is the evidence that interventions for populations lead to reductions in risk factors and CVD outcomes?
- What is the evidence that interventions for individuals lead to reductions in risk factors and CVD outcomes?

We have systematically and critically reviewed the relevant literature to answer each question posed. Certain difficulties are apparent with regard to the current ESC hierarchical grading system. The present system is likely to favour drug treatments over major lifestyle measures because the latter are less amenable to double-blind



randomized controlled trials. For this reason, after prolonged debate, the Task Force has not included the table of the grades that it prepared. However, it is anticipated that this issue will require further debate.

Efforts have been made to implement the guidelines through the various participating societies. Previous guidelines have been evaluated by means of EUROASPIRE I and II.<sup>38,39</sup>

## Priorities, total risk estimation, and objectives

### Introduction

At the outset, it is stressed that these guidelines are just that, and not didactic rules. They should be interpreted in the light of the clinician's own knowledge and judgement, the patient's view, and in the light of local conditions and practicalities and as new knowledge becomes available. Indeed the development of national guidelines is strongly encouraged, with objectives, priorities, and implementation strategies that are adapted to suit local conditions, both medical and economic.

The priorities suggested 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. As noted elsewhere, although such individuals gain most, most deaths in a community come from those at lower levels of risk, simply because they are more numerous compared with high risk individuals who, paradoxically, develop fewer events in absolute terms—the Rose Paradox.<sup>40</sup> Thus a strategy for individuals at high risk must be complemented by public health measures to reduce, as far as is practicable, population levels of cardiovascular risk factors and to encourage a healthy lifestyle.

The encouragement of total risk estimation as a crucial tool to guide patient management has been a cornerstone of the Guidelines since the first (1994) edition.<sup>1</sup> 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.

Although clinicians often ask for thresholds to trigger intervention, this is problematic since **risk is a continuum** and there is no exact point where, for example, a drug is automatically indicated. This issue is dealt with in more detail, 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 overall objectives of cardiovascular prevention are to reduce mortality and morbidity in those at high absolute risk and to assist those at low absolute risk to maintain this state, through a healthy lifestyle. Here, the risk charts are helpful—if BP is hard to control fully, for example, total risk can still be reduced by stopping smoking or perhaps reducing cholesterol levels further. Although thresholds for total cardiovascular risk included in this guideline are arbitrary, targets for individual risk factors are even more problematic in that they will always be open to debate, are not always achievable, and, notably, because they seem to promote a uni-risk factor approach to prevention. Yet clinicians ask for guidance, so an attempt to define desirable

levels of individual risk factors has been made in the context of more specific objectives.

### Priorities

Individuals at highest risk gain most from preventive efforts, and this guides the following priorities:

#### What are the priorities for CVD prevention in clinical practice?

1. Patients with established atherosclerotic CVD
2. Asymptomatic individuals who are at increased risk of CVD because of
  - 2.1 Multiple risk factors resulting in raised total CVD risk ( $\geq 5\%$  10-year risk of CVD death)
  - 2.2 Diabetes type 2 and type 1 with microalbuminuria
  - 2.3 Markedly increased single risk factors especially if associated with end-organ damage
3. Close relatives of subjects with premature atherosclerotic CVD or of those at particularly high risk

What are the objectives of cardiovascular disease prevention?

#### What are the objectives of CVD prevention?

1. To assist those at low risk of CVD to maintain this state lifelong, and to help those at increased total CVD risk to reduce it
2. To achieve the characteristics of people who tend to stay healthy:
  - 2.1 No smoking
  - 2.2 Healthy food choices
  - 2.3 Physical activity: 30 min of moderate activity a day
  - 2.4 BMI  $< 25 \text{ kg/m}^2$  and avoidance of central obesity
  - 2.5 BP  $< 140/90 \text{ mmHg}$
  - 2.6 Total cholesterol  $< 5 \text{ mmol/L}$  ( $\sim 190 \text{ mg/dL}$ )
  - 2.7 LDL cholesterol  $< 3 \text{ mmol/L}$  ( $\sim 115 \text{ mg/dL}$ )
  - 2.8 Blood glucose  $< 6 \text{ mmol/L}$  ( $\sim 110 \text{ mg/dL}$ )

3. To achieve more rigorous risk factor control in **high risk** subjects, especially those with established CVD or diabetes:
  - 3.1 Blood pressure under  $130/80 \text{ mmHg}$  if feasible
  - 3.2 Total cholesterol  $< 4.5 \text{ mmol/L}$  ( $\sim 175 \text{ mg/dL}$ ) with an option of  $< 4 \text{ mmol/L}$  ( $\sim 155 \text{ mg/dL}$ ) if feasible
  - 3.3 LDL cholesterol  $< 2.5 \text{ mmol/L}$  ( $\sim 100 \text{ mg/dL}$ ) with an option of  $< 2 \text{ mmol/L}$  ( $\sim 80 \text{ mg/dL}$ ) if feasible
  - 3.4 Fasting blood glucose  $< 6 \text{ mmol/L}$  ( $\sim 110 \text{ mg/dL}$ ) and HbA1c  $< 6.5\%$  if feasible
4. To consider cardioprotective drug therapy in these high risk subjects especially those with established atherosclerotic CVD

In general, a middle aged person with a 10-year risk of CVD death of 5% or more is regarded as at high risk. Examination of the FINRISK MONICA data (which contribute substantially to the SCORE high risk population charts) suggests that the equivalent total (fatal + non-fatal) CVD risk is about 10%—more in younger men and less in women and the elderly. The likelihood of requiring medication in addition increases with increasing risk.

**Total risk estimation**

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

The importance of total risk estimation before management decisions are made is illustrated in *Table 2* and *Figure 1*. The figure illustrates that the effect of 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 2* shows that a person with a total cholesterol of 8 mmol/L can be at 10 times lower risk than someone with

a total cholesterol of 5 mmol/L if the latter is a male hypertensive smoker. Randomized controlled drug trials of single risk factors do not give sufficient data to address these issues fully. While audits such as EuroAspire<sup>38,39</sup> 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 on 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.

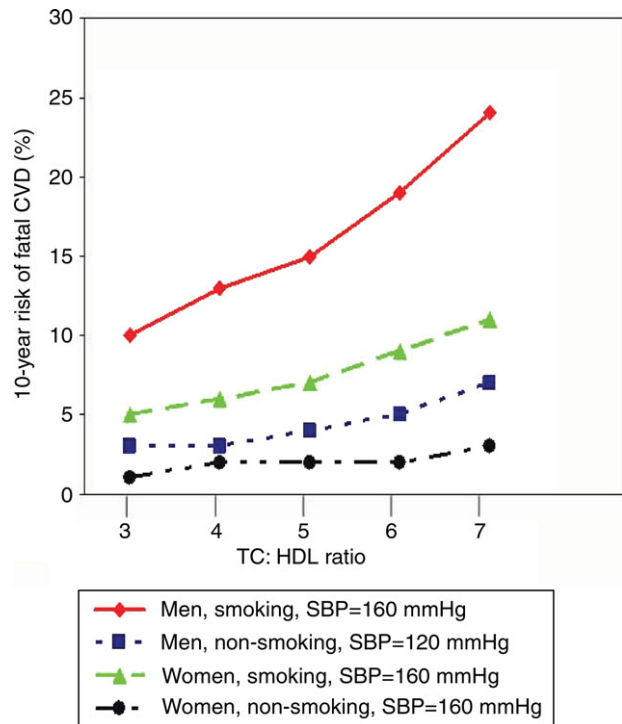
For these considerations to impact on clinical practice, it is essential for the clinician to be able to assess risk rapidly and with sufficient accuracy to allow logical management decisions.

**How do I assess risk?**

**How do I assess CVD risk quickly and easily?**

- Those with-
  - known CVD
  - type 2 diabetes or type 1 diabetes with microalbuminuria,
  - very high levels of individual risk factors

are already at INCREASED CVD RISK and need management of all risk factors
- For all other people, the SCORE risk charts can be used to estimate total risk—this is critically important because many people have mildly raised levels of several risk factors that, in combination, can result in unexpectedly high levels of total CVD risk



**Figure 1** The relationship of total cholesterol (TC):HDL cholesterol ratio to 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. SBP = systolic blood pressure.

**Table 2** Impact of combinations of risk factors on risk

Sex	Age (years)	Cholesterol (mmol/L)	BP (mmHg)	Smoker	Risk (%)
F	60	8	120	No	2
F	60	7	140	Yes	5
M	60	6	160	No	8
M	60	5	180	Yes	21

The need to assess total risk easily and quickly led to the development of the risk chart used in the 1994 and 1998 Guidelines.<sup>1,2,41</sup> There were several problems with this chart. First, it was derived from American data from the Framingham study and the applicability of the chart to all European populations was uncertain. Secondly, the data set used was fairly small. Thirdly, the definitions of non-fatal CHD events differed from those used in many other studies, making it difficult to validate the chart. Finally, estimation of the risk of other manifestations of atherosclerosis such as stroke or aneurysm of the abdominal aorta was not possible.

The 2003 Guidelines<sup>3</sup> used a new system for risk estimation called SCORE,<sup>42</sup> based on data from 12 European cohort studies, and includes 205 178 subjects examined at baseline between 1970 and 1988 with 2.7 million years of follow-up and 7934 cardiovascular deaths.

Risk charts such as SCORE are intended to facilitate risk estimation in ostensibly healthy persons. Patients who have had a clinical event such as an acute coronary syndrome or stroke, who have type 2 diabetes or type 1 diabetes with microalbuminuria, or who have a markedly increased level of a single risk factor have already declared themselves to be at markedly increased risk and 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:

- 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 allows re-calibration to take into account time trends in CVD mortality. Any risk estimation system will overpredict in countries in which mortality has fallen and underpredict in those in which it has risen. Recalibration to allow for secular changes can be undertaken if good quality, up-to-date mortality and risk factor prevalence data are available. Data quality does not permit this for non-fatal events. For these reasons, the CVD mortality charts were produced and have, indeed, been re-calibrated for a number of European countries. Country-specific versions of HeartScore are available for Belgium, Germany, Greece, The Netherlands, Poland, Spain, and Sweden. Nevertheless it is essential to address the issue of total risk.

In the 2003 Guidelines,<sup>3</sup> a 10-year risk of CVD death of 5% or more 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 this 2007 Guideline is that everyone with a 10-year risk of CVD death of 5% or more has an *increased risk*. Naturally 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 FINRISK, which has data on non-fatal events defined according to the MONICA project.<sup>43</sup> 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 about 10%, more (15%) in younger men and somewhat less in women. The 'multiplier' to convert CVD mortality to total events is also smaller in older people, presumably because a first event is more likely to be fatal.

As noted in the Introduction, clinicians often ask for thresholds to trigger certain interventions, but this is 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 very high relative risk. In the 2003 Guidelines,<sup>3</sup> it was suggested to extrapolate risk to age 60 to stress that a high absolute risk would occur if preventive action were not taken. It was not intended that such a young person should be necessarily treated as if they were 60, but a literal interpretation of this suggestion could lead to

excessive drug treatment in younger persons. 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.

- Another problem relates to old people. In some age categories, the vast majority, especially of men, will have estimated CVD death risks exceeding the 5–10% threshold, based on age (and gender) only, even when other CVD risk factor levels are relatively low. This could lead to excessive usage of drugs in the elderly. Preventive treatments in the elderly should be evidence based unless clearly indicated.
- As before, charts are presented for both total cholesterol and the cholesterol:HDL cholesterol ratio. They look remarkably similar. However, subsequent work on the SCORE database, as yet unpublished, has shown that HDL cholesterol can contribute substantially to risk prediction if entered as an independent variable.
- 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, interactive version of SCORE, HeartScore (available through [escardio.org](http://escardio.org)), is not so constrained. It presently replicates SCORE in 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 CRP and homocysteine levels), their contribution to absolute CVD risk estimations of individual patients (in addition to the older risk factors) is generally modest.
- 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 approximately five in women and three in men.

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

#### Advantages in using the SCORE risk chart

- Intuitive, easy to use tool
- Takes account of the multifactorial nature of CVD
- Estimates risk of all atherosclerotic CVD, not just CHD
- 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 higher and reducible relative risk.



### How do I use the SCORE charts to assess total CVD risk in asymptomatic persons?

1. Use the low risk chart in Belgium\*, France, Greece\*, Italy, Luxembourg, Spain\*, Switzerland, and Portugal; use the high risk chart in other countries of Europe  
 \* Updated, re-calibrated charts are now available for Belgium, Germany, Greece, The Netherlands, Poland, Spain, and Sweden
2. Find the cell nearest to the person's age, cholesterol, and BP values, bearing in mind that risk will be higher as the person approaches the next age, cholesterol or BP category
3. Check the qualifiers
4. Establish the absolute 10-year risk for fatal CVD

Note that a low absolute risk in a young person may conceal a high relative risk; this may be explained to the person by using the relative risk chart. As the person ages, a high relative risk will translate into a high absolute risk. More intensive lifestyle advice will be needed in such persons.

### Risk estimation using SCORE: qualifiers

- The charts should be used in the light of the clinician's knowledge and judgement, especially with regard to local conditions
- As with all risk estimation systems, risk will be overestimated in countries with a falling CVD mortality rate, and underestimated if it is rising
- At any given age, risk appears lower for women than men. This is misleading since, ultimately, more women than men die from CVD. Inspection of the charts shows that their risk is merely deferred by 10 years
- Risk may be higher than indicated in the chart in:
  - Sedentary or obese subjects, especially those with central obesity
  - Those with a strong family history of premature CVD
  - The socially deprived
  - Subjects with diabetes—risk may be 5-fold higher in women with diabetes and 3-fold higher in men with diabetes compared with those without diabetes
  - Those with low HDL cholesterol or high triglycerides
  - Asymptomatic subjects with evidence of pre-clinical atherosclerosis, for example a reduced ankle-brachial index, or on imaging such as carotid ultrasonography or CT scanning

The SCORE risk charts are shown in Figures 2–6, including a chart of relative risks.

The relative risk chart in Figure 6 is useful in explaining to a younger person that, even if their absolute risk is low, it may still be 10–12 times higher than that of a person of a similar age with low risk factors.

### Conclusions

The priorities defined in this section are for clinical use and reflect the fact that those at highest risk of a CVD event gain most from preventive measures. This approach should complement public actions to reduce community risk factor levels and promote a healthy lifestyle.

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 difficulty in imposing arbitrary thresholds or targets upon a continuous variable such as risk is acknowledged. Nevertheless, specific objectives are defined in terms of desirable levels of individual risk factors. This must be seen as an aid to clinicians in planning risk management strategies with their patients. The primacy of managing total risk rather than focusing on individual risk factors is stressed.

Priorities, risk estimation, and the definition of objectives reflect an attempt to make complex issues simple and

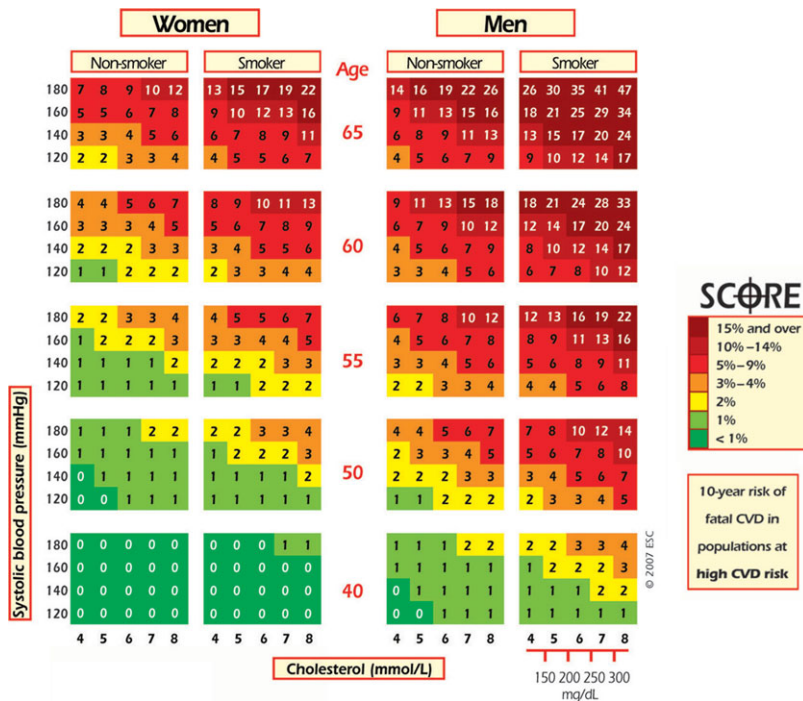


Figure 2 SCORE chart: 10-year risk of fatal CVD in populations at high CVD risk based on the following risk factors: age, gender, smoking, systolic blood pressure, and total cholesterol. © The European Society of Cardiology.

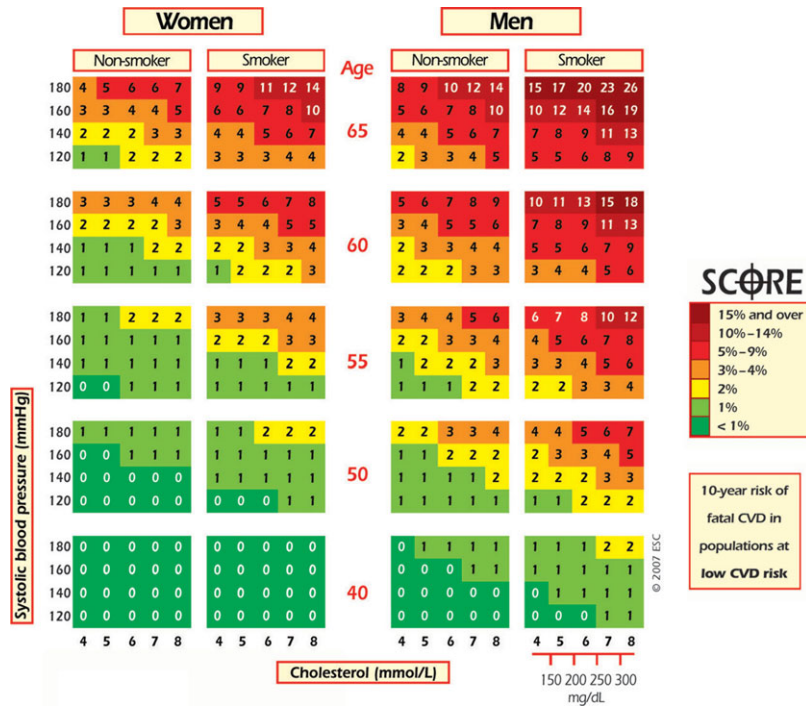


Figure 3 SCORE chart: 10-year risk of fatal CVD in populations at low CVD risk based on the following risk factors: age, gender, smoking, systolic blood pressure, and total cholesterol. © The European Society of Cardiology.

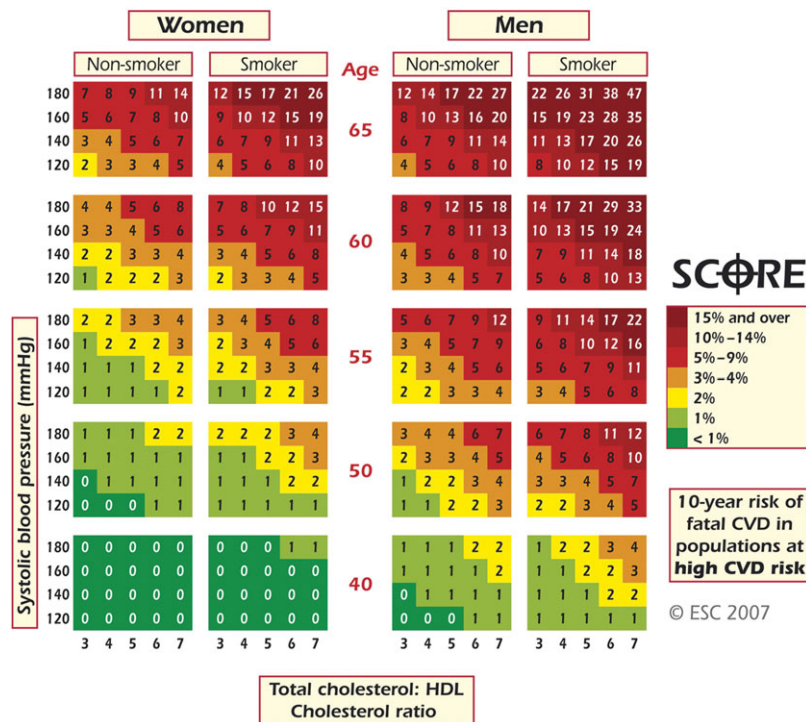


Figure 4 SCORE chart: 10-year risk of fatal CVD in populations at high CVD risk based on the following risk factors: age, gender, smoking, systolic blood pressure, and total cholesterol:HDL cholesterol ratio. © The European Society of Cardiology.

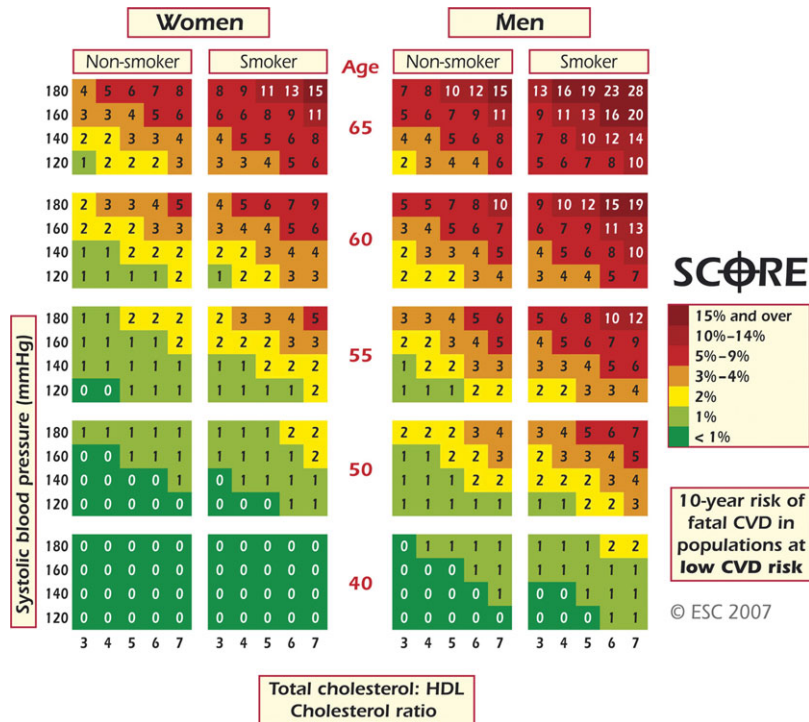


Figure 5 SCORE chart: 10-year risk of fatal CVD in populations at low CVD risk based on the following risk factors: age, gender, smoking, systolic blood pressure, and total cholesterol:HDL cholesterol ratio. © The European Society of Cardiology.

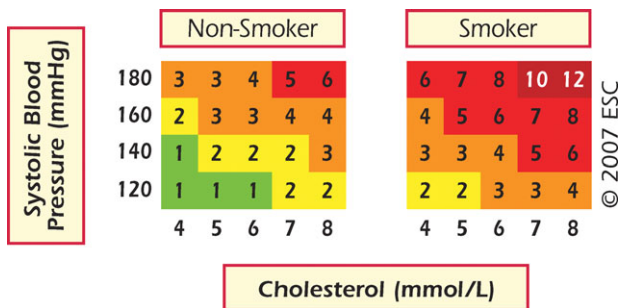


Figure 6 Relative risk chart. © The European Society of Cardiology.

accessible. Their very simplicity makes them vulnerable to criticism. Above all they must be interpreted in the light of the physician's detailed knowledge of their patient and in the light of local guidance and conditions.

The flow chart on p. 2389 gives a short summary of the recommendations.

## Principles of behaviour change and management of behavioural risk factors

### Scientific background

Physicians and other health professionals in the primary and out-patient care setting are in a unique position to

contribute significantly to the improved prevention and management of CVD. Physicians are generally perceived by the general public as the most reliable and credible source of information on health and advice. Patients usually want to receive as much information as possible from physicians, and often prefer to receive assistance from them in order to change behaviours such as smoking, nutrition and diet, and physical activity, rather than attend special programmes elsewhere.

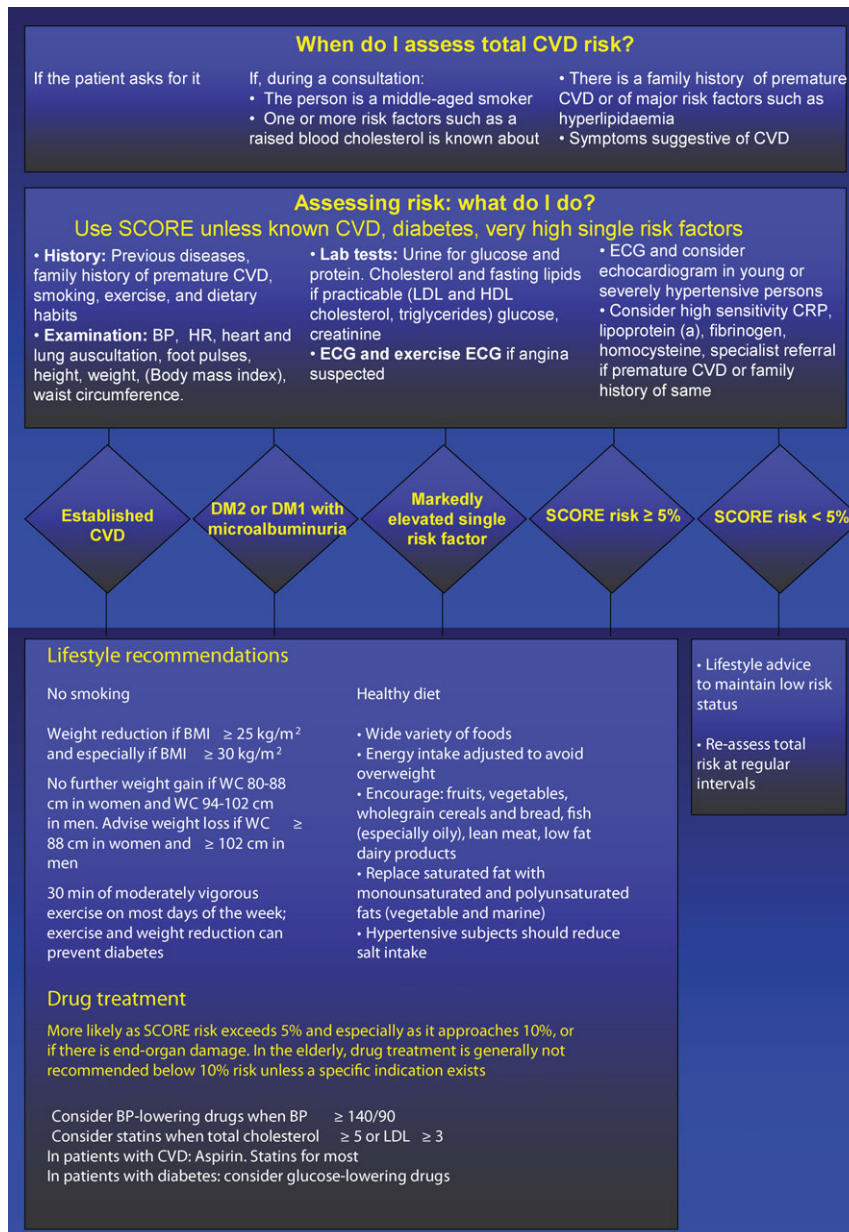
### The physician/caregiver–patient interaction as a means towards behavioural change

A friendly and positive physician–patient interaction is a powerful tool to enhance patients' coping with stress and illness and adherence to recommended lifestyle change and medication.

Social support provided by caregivers, including physicians, and shared decision making can help patients maintain healthy habits and adhere to medical advice.

Previous negative, unsuccessful attempts to change behaviour, however, often result in a lower self-efficacy for future change in that behaviour, and often lead to another failure. A crucial step in changing negative experiences to positive is to set realistic goals, and goal setting combined with self-monitoring of the chosen behaviour are the main tools to achieve a positive outcome. This in turn will increase self-efficacy for the chosen behaviour, and thereafter new goals could be set. Moving forward in small





consecutive steps is one of the key points in long-term behaviour change.

### Specialized and multimodal interventions

A number of specialized psychosocial intervention strategies have been demonstrated to have positive effects on risk factors, but the specific content and approaches taken by these interventions vary. Even if they intend to target only one behavioural risk factor, group-based behavioural interventions often contain elements which affect multiple risk factors. Interventions adding psychosocial and psychoeducational components to standard cardiological care can significantly improve quality of life and diminish cardiovascular risk factors.<sup>44-46</sup>

### Practical aspects: management of behavioural risk factors

**Managing total CVD risk- TIPS TO HELP BEHAVIOUR CHANGE**

- Spend enough time with the patient
- Speak to the patient in their own language
- Develop a sympathetic alliance with the patient
- Listen carefully and recognize strengths and weaknesses in the patient's attitude to illness and lifestyle change
- Ensure the patient understands the relationship between lifestyle and disease
- Accept the patient's personal views of his/her disease and allow expression of worries and anxieties
- Acknowledge that changing life-long habits can be difficult and that gradual change that is sustained is often more permanent
- Gain commitment to lifestyle change
- Involve the patient in identifying the risk factors to change
- Explore potential barriers to change

- Use a combination of strategies including reinforcement of patient's own capacity for change
- Make sure that the patient has understood your advice and has the means to follow it
- Help design a lifestyle change plan
- Be realistic and encouraging: 'ANY increase in exercise is good and can be built on'
- Reinforce the patient's efforts to change
- Monitor progress through follow-up contacts; repeated efforts may be required
- Involve other health care staff wherever possible
- In patients with manifest CVD or very high risk, psychosocial and/or psychoeducational components should be added to standard cardiological care
- Use a multimodal team approach, involving experts in behavioural medicine, mental health, nutrition, etc and expert counselling if barriers to behavioural change become obvious
- If feasible, intervention programmes should be individualized

### Managing total CVD risk:

#### Why do people find it hard to change their lifestyle?

- **Socio-economic status:** Low SES, including low educational level and low income, impedes the ability to adopt lifestyle change
- **Social isolation:** People living alone are more likely to have unhealthy lifestyles
- **Stress:** Stress at work and at home makes it more difficult for people to adopt and sustain a healthy lifestyle
- **Negative emotions:** Depression, anxiety and hostility impede lifestyle change
- **Complex or confusing advice**

Increased physician awareness of these factors facilitates empathy, counselling, and the provision of sympathetic, simple, and explicit advice

### Managing total CVD risk: SMOKING

**All smokers should be professionally encouraged to permanently stop smoking all forms of tobacco**  
The 5 As can help-

- A -ASK systematically identify all smokers at every opportunity
- A- ASSESS: Determine the person's degree of addiction and his/her readiness to cease smoking
- A- ADVISE: Unequivocally urge all smokers to quit
- A- ASSIST: Agree on a smoking cessation strategy including behavioural counselling, nicotine replacement therapy, and/or pharmacological intervention
- A- ARRANGE a schedule of follow-up visits

Quitting smoking is a complex and difficult process, because the habit is strongly addictive both pharmacologically and psychologically. Quitting can be facilitated with professional assistance. The physician's firm and explicit advice that a person should stop smoking completely is the most important factor in getting the smoking cessation process started. The momentum for smoking cessation is particularly strong at the time of diagnosing atherothrombotic CVD and in connection with an invasive treatment, such as coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, or vascular surgery. The physician's advice is equally important in helping healthy high risk individuals to attempt to quit smoking. Assessing whether the person is willing to try to quit, brief reiteration of the cardiovascular and other health hazards of smoking, and agreeing on a specific plan with a follow-up arrangement are the decisive first steps and essential features of the brief initial advice of smoking cessation in clinical practice.

Both individual and group behavioural interventions are effective in helping smokers to quit.<sup>51</sup> However, the quality of physician-patient communication seems to be more relevant than the quantity of counselling sessions or the intervention format (group vs. individual). Support by the partner and family is very important in smoking cessation. Involvement of the family in the smoking cessation process and getting other smoking family members to quit smoking together with the patient is of great help.

Nicotine chewing gum and transdermal nicotine patches have been widely used in helping quitters to go through the difficult initial weeks or months of smoking cessation.

Antidepressant medication in aiding long-term smoking cessation has been shown to be effective. Bupropion and nortriptyline can aid smoking cessation.

Another new pharmacological agent that may be of help in smoking cessation is varenicline, a nicotine acetylcholine receptor agonist. Among long-term smokers, treatment with varenicline was associated with a smoking cessation rate of 23% at 1 year as compared with 15 and 10.3% in the groups treated with bupropion and placebo, respectively. Reports that it may be more effective than bupropion or placebo need confirmation.

## Smoking

### Scientific background

There is overwhelming evidence for an adverse effect of smoking on health.<sup>47</sup> This adverse effect of smoking is related to the amount of tobacco smoked daily and to the duration of smoking. The effects of smoking on CVD interact synergistically in the presence of other CVD risk factors such as age, gender, arterial hypertension, and diabetes.

Passive smoking has been shown to increase the risk of CHD and other smoking-related diseases.<sup>48</sup>

The benefits of smoking cessation have been extensively reported.<sup>49,50</sup> Some of the advantages are almost immediate; others take more time. Stopping smoking after an MI is potentially the most effective of all preventive measures. Sufficient efforts should be devoted to this end.

### Practical aspects: prevention and management of smoking

The assessment of smoking status should be done at every opportunity.

Stopping smoking should be encouraged in all smokers. There is no age limit to the benefits of smoking cessation.

## Nutrition

### Scientific background

Fatty acids regulate cholesterol homeostasis and concentrations of blood lipoproteins, and affect the levels of other cardiovascular risk factors, such as BP, haemostasis, and body weight, through various mechanisms. There are strong, consistent, and graded relationships between saturated fat intake, blood cholesterol levels, and the mass occurrence of CVD. The relationships are accepted as causal. *n*-3 fatty acids, in contrast, showed protective effects on fatal events in patients who had suffered a previous MI. Sodium intake, especially in the form of sodium chloride, influences arterial BP and therefore the risk of arterial hypertension, stroke, CHD, and heart failure. Intervention trials with vitamin supplements have failed to demonstrate any protection against CHD. Besides micro- and macronutrients, dietary patterns, including fruit and vegetables, monounsaturated fatty acid-rich oil (such as olive oil), and low fat dairy products, have been associated with decreased incidence of cardiovascular events.

### Practical aspects: management

Dietetics is an integral part of cardiovascular patient risk management. All patients having a CVD and those individuals at high risk should be given professional advice on the food and dietary options which reduce the cardiovascular risk. A varied and energy-balanced regimen together with regular exercise is critical to the preservation of a good cardiovascular health.

**Managing total CVD risk:  
HEALTHY FOOD CHOICES**

All individuals should be advised about food choices that are associated with a lower CVD risk. High risk persons should receive specialist dietary advice if feasible.

General recommendations should suit the local culture-

- A wide variety of foods should be eaten
- Energy intake should be adjusted to avoid overweight
- Encourage: Fruits, vegetables, wholegrain cereals and bread, fish (especially oily), lean meat, low fat dairy products
- Replace saturated fats with the above foods and with monounsaturated and polyunsaturated fats from vegetable and marine sources to reduce total fat to <30% of energy, of which less than 1/3 is saturated
- Reduce salt intake if blood pressure is raised by avoiding table salt and salt in cooking, and by choosing fresh or frozen unsalted foods. Many processed and prepared foods, including bread, are high in salt.

Dietetic recommendations should be defined individually, taking into account the subject’s risk factors—dyslipidaemia, hypertension, diabetes, and obesity.

## Overweight and obesity

### Scientific background

As societies develop a higher standard of living, cardiovascular mortality initially increases. This is followed by a

reduction in both major risk factors such as blood cholesterol and high BP which, together with improvements in therapy, translate into reduced cardiovascular mortality. The exceptions to these trends are body weight and diabetes which tend to increase as other risk factors decline. Obesity is becoming a worldwide epidemic in both children and adults.<sup>52</sup> Currently it is estimated that, worldwide, over 1 billion people are overweight, and over 300 million are obese. Over one-third of children are overweight or obese.

### Body weight and risk

It is now clear that fat, and in particular intra-abdominal visceral fat, is a metabolically active endocrine organ that is 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. Fat is associated with increased secretion of free fatty acids, hyperinsulinaemia, insulin resistance, hypertension, and dyslipidaemia.<sup>53,54</sup> This impacts on CVD risk factors and hence on risk. The mechanical effects of overweight impact on non-cardiovascular causes of morbidity and mortality. The health effects of increasing body weight are summarized in *Table 3*.

Interestingly, the effects of multivariate adjustment on the association between lipid levels and risk and between body weight and risk are different. Raised blood cholesterol or a reduced HDL cholesterol level 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.

**Table 3** Impact of increasing body weight on risk factors, morbidity, and mortality

Risk factors	Morbidity	Mortality
Raised BP	Type 2 diabetes	Increased total and cardiovascular mortality
Raised total and LDL cholesterol	Insulin resistance Coronary heart disease	
Reduced HDL cholesterol	Stroke	
Increased waist circumference	Osteoarthritis (knee)	
Sleep apnoea	Cancer	
Obesity hypoventilation syndrome	Low back pain due to obesity	
Physical inactivity	Breathlessness	
	Polycystic ovary syndrome	
	Infertility	
	Cholelithiasis	
	Asthma (exacerbation)	
	Venous thromboembolic pulmonary embolism	
	Inflammation	
	Autonomic nervous system dysfunction	



## Which index of obesity is the best predictor of cardiovascular risk and cardiovascular risk factors—body mass index (BMI), waist circumference (WC), or waist–hip circumference ratio (WHR)?

Recent studies have demonstrated that regional distribution of adipose tissue may be more important in determining cardiovascular risk than total body weight. Excess central (visceral abdominal) fat in particular has been shown to be strongly associated with metabolic and cardiovascular risk.<sup>55</sup> This has led to increased interest in anthropometric measures of risk. Most data are available for BMI, waist–hip circumference ratio (WHR), and, more recently, simple waist circumference (WC). Such measures of risk are cheap and universally available. WC, while simple, may be more prone to measurement error than BMI. The optimal level for measurement of WC is midway from the lower rib margin to the anterior superior iliac crest. The evidence supporting each measure in estimating risk is now considered.

BMI has been extensively used to define the groups of body weight [ $\text{kg}/\text{height (m)}^2$ ] using classifications suggested by the National Institutes of Health and the WHO. In adults, overweight is defined by an increased BMI ranging from 25 to  $29.9 \text{ kg}/\text{m}^2$  and obesity by  $\text{BMI} \geq 30 \text{ kg}/\text{m}^2$ . Increasing BMI is highly associated with CVD.

The association between both increasing WC and WHR and greater risk of development of CVD has been demonstrated in cohort and case–control studies.<sup>56</sup> In general, these have shown that the measurement of WC in addition to BMI gives additional information for CVD risk estimation. The association between increasing WC or WHR and the presence of other cardiovascular risk factors or the metabolic syndrome has been shown in many cross-sectional studies.<sup>57</sup> There is no consistent information on which of these anthropometric measures is superior.

Both the WHO report on obesity<sup>58</sup> and the American National Heart, Lung, and Blood Institute (NHLBI) expert panel on obesity<sup>59</sup> recommend the use of WC as an additional indicator of metabolic risk factors, within each category of BMI. Of various definitions,<sup>58,59</sup> the WHO cut-off points are the most widely accepted in Europe; two action levels are recommended. Action level 1— $\text{WC} \geq 94 \text{ cm}$  in men and  $\geq 80 \text{ cm}$  in women—represents the threshold at which no further weight should be gained. Action level 2— $\text{WC} \geq 102 \text{ cm}$  in men and  $\geq 88 \text{ cm}$  in women represents the threshold at which weight reduction should be advised. The cut-off points have been calculated based on white people, and it is apparent that different cut-off points for anthropometric measurements are required in different races and ethnicities.<sup>60</sup>

In conclusion, there is no solid evidence for superiority of either variable in the prediction of risk factors. WC has the advantage of simplicity, may be a slightly better estimator of risk than BMI, but is probably more prone to measurement error.

## Imaging and fat distribution

Several measurements have been described for assessing the anatomical distribution of fat, such as computed tomography (CT), ultrasound (US), and magnetic resonance imaging (MRI). They allow changes in intra-abdominal fat to be monitored. However, they are expensive and time consuming, and are to be regarded as specialist

research tools rather than everyday risk assessment tools at this time.

Anthropometric measurements such as WC and WHR provide a useful estimation of the proportion of abdominal or upper-body fat, but they do not distinguish between accumulations of deep abdominal (visceral) fat and subcutaneous abdominal fat. CT can be considered the gold standard not only for adipose tissue evaluation but also for multicompartiment body measurement;<sup>61</sup> the subcompartments of adipose tissue volume, visceral and subcutaneous adipose tissue, can be accurately measured with errors of 1.2 and 0.5%, respectively.

MRI provides results similar to CT without exposure to ionizing radiation, the main problem with CT multislice measurements. It demonstrates good reproducibility for total and visceral adipose tissue volumes.<sup>62</sup>

Several studies demonstrated a highly significant correlation between the intra-abdominal adipose tissue determined by CT and by US.<sup>63,64</sup>

Sagittal abdominal diameter is derived either from a CT abdominal scan<sup>65</sup> or by using a sagittometer placed over the abdomen perpendicular to the length axis of the trunk at the iliac crest level (L4–5) with the subject in the supine position on a firm bench with the knees bent.<sup>66</sup> Sagittal abdominal diameter correlates strongly with visceral fat volume as measured by CT.<sup>67</sup> CT scanning is expensive and involves exposure to radiation. It is not as yet recommended for routine clinical risk assessment.

## Practical aspects: management of obesity and overweight

Intentional weight loss in obese patients can improve or prevent many of the obesity-related risk factors for CHD. Reduction in BP occurs before attainment of desirable body weight.

### Managing total CVD risk: BODY WEIGHT

- Increasing body weight is associated with increased total and CVD mortality and morbidity, mediated in part through increases in blood pressure and blood cholesterol, reduced HDL cholesterol, and an increased likelihood of diabetes
- Weight reduction is recommended for obese people ( $\text{BMI} \geq 30 \text{ kg}/\text{m}^2$ ) and should be considered for those who are overweight ( $\text{BMI} \geq 25$  and  $< 30 \text{ kg}/\text{m}^2$ )
- Men with a waist circumference of 94–102 cm and women with a waist circumference of 80–88 cm are advised not to increase their weight. Men above 102 cm and women above 88 cm are advised to lose weight
- Restriction of total calorie intake and regular physical exercise are the cornerstones of weight control. It is likely that improvements in central fat metabolism occur with exercise even before weight reduction occurs

## Physical activity and body weight

There is sufficient evidence available from intervention studies supporting the role of physical activity and moderate to vigorous exercise in promoting weight loss.<sup>68</sup> Recent research has indicated that exercise may have beneficial effects before a training effect is apparent<sup>69,70</sup> and may impact on abdominal fat metabolism before weight loss occurs.<sup>69,70</sup> This information may be valuable in motivating high risk persons to initiate exercise.

## Diet and behavioural interventions

Many different diets and behavioural interventions have been proposed for the treatment of obesity. The control of overweight is dependent upon achieving the appropriate balance between energy intake and expenditure. The dietary approaches vary in their total energy content, macronutrient composition (protein, carbohydrates, and lipids), energy density, and glycaemic index.<sup>71</sup> The low fat diet is considered the standard approach to weight reduction and has a more favourable effect on LDL cholesterol. Total fat intake should be kept between 25 and 35% of energy. The reduction in saturated fats is the preferred target due to its effects on the lipoprotein profile. Intake of saturated and trans fatty acids should be <7%.<sup>72</sup>

The low carbohydrate diet has become popular and in the short term decreases body weight greatly and also has a good effect on plasma triglycerides and HDL cholesterol.<sup>73</sup> However, its long-term safety is still under investigation. Alcohol is a major source of calories and reduction may be an important part of weight control.

Behaviour modification inducing long-term lifestyle change leading to a gradual weight loss is the basis of all obesity treatment. According to a recent Cochrane review, behavioural and cognitive-behavioural therapy helps to lose additional weight when added to diet and exercise programmes.<sup>74</sup> Behavioural interventions have also been shown to help maintain weight loss.<sup>75</sup>

## Drug treatment of overweight

In general, the contribution of drug treatments is modest and, in the past, some products have had serious side effects.

Orlistat inhibits intestinal lipases to prevent the hydrolysis and uptake of fat. Weight loss is usually modest, and gastrointestinal disturbance may occur. It should be used with a full and balanced diet.

Sibutramine enhances a feeling of satiety after food by an effect of its metabolites which inhibit noradrenaline and serotonin uptake. Both contraindications and side effects are appreciable.

Rimonabant is an endocannabinoid receptor inhibitor that appears capable of inducing a modest but sustained weight loss in combination with a calorie-controlled diet. It may improve glucose tolerance, beneficially affect lipid metabolism, and is associated with a modest reduction in BP. Possible adverse effects on depression are being monitored. It remains to be seen if its promising effects on weight and other risk factors will translate into hard evidence of reduced cardiovascular events.

## Physical activity

### Scientific background

- A lack of regular physical activity may contribute to the early onset and progression of CVD.
- Almost any increase in physical activity will result in health benefits.
- Assessment of physical activity is a key element of risk evaluation.

Physical inactivity is a significant public health problem in Europe: children have become less physically active and

only in a few countries do children have access to the recommended daily dose of physical activity. More than half of adolescents become physically inactive after leaving school.

Adults face a significant decrease in physical demands at their place of work and, during leisure time, fewer people are physically active. A sedentary lifestyle is associated with a doubling of the risk of premature death and with an increased risk of CVD.<sup>76,77</sup> Avoiding a sedentary lifestyle during adulthood may extend total life expectancy and CVD-free life expectancy (by 1.3–3.5 years).<sup>78</sup>

Physical training has a wide variety of beneficial effects on the course of atherosclerosis, resulting in a 20–25% reduction in overall mortality.<sup>79</sup> Yet, in Europe, a minority of CVD patients participate in exercise training programmes. Even fewer patients with chronic heart failure (CHF) are enrolled, although they may well benefit from adapted exercise training.

In the elderly population, approximately a quarter of the population suffer from CVD. Physiological and mental changes that come with increasing age may contribute to physical inactivity, but regular physical activity may effectively slow down the age-related changes, thereby improving physical functioning and extending disease-free survival.

### Estimating physical activity

For an assessment of physical activity, different methods are available: doubly labelled water, indirect calorimetry, direct observation, activity monitors (pedometers, accelerometers), heart rate monitors and questionnaires, or activity diaries. For physical fitness and exercise capacity, maximal incremental exercise testing is used.<sup>80</sup>

In clinical practice, the assessment should be combined with a total CVD risk estimation using the SCORE/HeartScore method. In individuals at low risk, a brief interview concerning the person's physical activity may suffice, but in high risk persons this may be completed with an exercise test. Assessment in adults with known CVD should be combined with exercise testing in order to detect myocardial ischaemia, stratify for risk, and give guidance on the clinical management.

### Managing total CVD risk: PHYSICAL ACTIVITY

- Stress that positive health benefits occur with almost any increase in activity; small amounts of exercise have an additive effect; exercise opportunities exist in the workplace, for example by using stairs instead of the lift
- Try to find leisure activities that are positively enjoyable
- 30 min of moderately vigorous exercise on most days of the week will reduce risk and increase fitness
- Exercising with family or friends tends to improve motivation
- Added benefits include a sense of well-being, weight reduction, and better self-esteem
- Continued physician encouragement and support may help in the long term

### Practical aspects: management

In the young population, the promotion of physical fitness is the shared responsibility of parents, school staff, health

care providers, politicians, and society as a whole: each child in Europe should have access to periods of physical activity each day. Here, more research is needed to find instruments for measuring physical fitness and activity, and to create programmes to improve and maintain physical activity.

The choice of lifestyle, including maintained physical fitness, remains the sole responsibility of the individual person. This may be supported by family and friends, work environment, access to attractive and affordable leisure time activities, and by health-promoting campaigns. Regular physical exercise within the resources of the work place is recommended. The ultimate goal is at least half an hour of physical activity on most days of the week as almost any increase in activity is associated with measurable health benefits.

The intensity may be defined in terms of target heart rate or perceived exertion. A heart rate during peak exercise of 60–75% of the average maximum heart rate is preferred. The Borg scale of perceived exertion may be applied, using the level of 'moderate exertion'. This may be easily achieved by a wide variety of activities such as brisk walking or jogging, cycling, swimming, gardening, aerobic dancing, tennis, golf, or even cross-country skiing.<sup>81</sup>

Recommendations for patients with known CVD have to be based on a comprehensive clinical judgement including exercise testing. A majority will benefit from a cardiac rehabilitation programme: in addition to supervised physical exercise in patient groups, this includes lifestyle advice and support as well as measures aimed at risk reduction. If patients prefer to perform the programme at home, they will need clear prescriptions, encouragement, and regular follow-up by their physician. For patients with mild to moderate heart failure, both dynamic interval training with moderate intensity and resistance training may be advantageous.

When counselling elderly persons, it is recommended to maintain daily physical activity on a moderate to submaximum level. Principles of behavioural change including social support, self-efficacy, and positive reinforcement should be applied, and programmes should start off at low intensity but gradually increase to moderate levels. Key elements of activity programmes for the elderly are a combination of endurance, strength, balance, and flexibility.

Even the elderly CVD patient may benefit from rehabilitation programmes: exercise training is safe, improves strength, aerobic fitness, endurance, and physical function, and there are no gender differences in the outcome.

Thus, the assessment, counselling, and support in the maintenance of physical activity are core tasks for physicians and other health workers engaged in the prevention of cardiovascular disease.

## Heart rate

### Scientific background

Elevated heart rate has been shown to be associated with increased risk of all-cause mortality, CVD mortality, and development of CVD in the general population, hypertensives, diabetics, and those with pre-existing coronary artery disease.<sup>82,83</sup> The relationship is also seen in animal

models. Levine demonstrated the semi-logarithmic inverse relationship between heart rate and life expectancy in mammalian species.<sup>84</sup> A reduction in the development of atherosclerosis has been demonstrated in cholesterol-fed monkeys after pharmacological or surgical reduction of heart rate.<sup>85</sup>

Most epidemiological studies have shown the relationship to be strong, graded, and independent of other factors including BP and physical activity. While virtually all of the studies demonstrated a significant effect in men, the relationship between CVD mortality and elevated heart rate in women and the elderly was non-significant after multivariate adjustment in some of the studies. Risk of sudden death in men is particularly associated with elevated resting heart rate.<sup>86</sup>

A low heart rate may be exerting its effect on CVD through anti-arrhythmic or anti-ischaemic effects. Other possible mechanisms are the direct effect on haemostasis of an elevated heart rate causing progression of atherosclerosis.

No trial has investigated the effect of lowering heart rate on prognosis in asymptomatic people. Meta-analyses of  $\beta$ -blocker and calcium channel blocker therapy in post-MI patients and in CHF have demonstrated their benefits in these patients.<sup>87,88</sup> Studies have shown that the benefit achieved is related to the level of heart rate reduction; however, it is uncertain if this is the only mechanism in the benefit of  $\beta$ -blockade.<sup>89</sup>

### Practical aspects: management

In the general population, avoidance of elevated heart rate through lifestyle measures can be recommended. These include regular physical activity, avoidance of psychological stress, and excessive use of stimulants such as caffeine. Pharmacological reduction of heart rate cannot be recommended in the asymptomatic population.

Both  $\beta$ -blockers and selective  $I_f$  channel blockers are effective in the treatment of angina.<sup>90</sup>  $\beta$ -Blockers are recommended in patients post-MI and in CHF patients in carefully titrated doses.

## Blood pressure

### Scientific background

Elevated BP is a risk factor for CHD<sup>91</sup>, heart failure, CVD, peripheral vascular disease, and renal failure in both men and women.<sup>91–94</sup> BP levels correlate inversely with cognitive function, and hypertension is associated with an increased incidence of dementia.<sup>95</sup> CHD and stroke mortality increase progressively and linearly from BP levels as low as 115 mmHg systolic and 75 mmHg diastolic upward.<sup>96</sup>

In addition, longitudinal data obtained from the Framingham Heart Study indicated that BP values in the 130–139/85–89 mmHg range are associated with a >2-fold increase in relative risk from CVD compared with those with BP levels below 120/80 mmHg.<sup>97</sup>

The classification of hypertension used in the 2003 and 2007 ESH/ESC guidelines has been retained (*Table 4*). Isolated systolic hypertension should be graded as the same as the systolic BP values indicated for systolic–diastolic hypertension. However, the association with a low diastolic



**Table 4** Definition and classification of blood pressure levels

Category	Systolic		Diastolic
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

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

BP (e.g. 60–70 mmHg), indicating a wide pulse pressure, should be regarded as higher risk.

#### Risk stratification and target organ damage

The decision to start pharmacological treatment depends not only on the BP level but also on total cardiovascular risk, which calls for a careful history, physical examination, and laboratory tests to identify (i) the presence of clinically established CVD; (ii) the co-existence of other cardiovascular risk factors; and (iii) the presence of subclinical CVD or end-organ damage—an intermediate stage in the continuum of cardiovascular risk. The presence of clinically established cardiovascular or renal disease markedly increases the risk of subsequent cardiovascular events at all levels of BP (Table 5).

The co-existence of other cardiovascular risk factors (smoking, increased plasma cholesterol, family history of

**Table 5** Factors influencing prognosis in hypertension

Risk factors	Target organ damage	Diabetes mellitus	Established CVD or real disease
<ul style="list-style-type: none"> <li>Systolic and diastolic BP levels</li> </ul>	<ul style="list-style-type: none"> <li>Electrocardiographic LVH (Sokolow–Lyons &gt; 38 mm; Cornell &gt; 2440 mm × ms)</li> </ul>	<ul style="list-style-type: none"> <li>Fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL)</li> </ul>	<ul style="list-style-type: none"> <li>Cerebrovascular disease: ischaemic stroke; cerebral haemorrhage; transient ischaemic attack</li> </ul>
<ul style="list-style-type: none"> <li>Levels of pulse pressure (in the elderly)</li> <li>Age (M &gt; 55 years; W &gt; 65 years)</li> </ul>	or:	<ul style="list-style-type: none"> <li>Postload plasma glucose &gt; 110 mmol/L (198 mg/dL)</li> </ul>	
<ul style="list-style-type: none"> <li>Smoking</li> </ul>	<ul style="list-style-type: none"> <li>Echocardiographic LVH<sup>a</sup> (LVMI M ≥ 125 g/m<sup>2</sup>, W ≥ 110 g/m<sup>2</sup>)</li> </ul>		
<ul style="list-style-type: none"> <li>Dyslipidaemia <ul style="list-style-type: none"> <li>TC &gt; 5.0 mmol/L (190 mg/dL)</li> </ul> </li> <li>or: <ul style="list-style-type: none"> <li>LDL-C &gt; 3.0 mmol/L (115 mg/dL)</li> </ul> </li> <li>or: <ul style="list-style-type: none"> <li>HDL-C: M &lt; 1.0 mmol/L (40 mg/dL), W &lt; 1.2 mmol/L (46 mg/dL)</li> </ul> </li> <li>or: <ul style="list-style-type: none"> <li>TG &gt; 1.7 mmol/L (150 mg/dL)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Carotid–wall thickening (IMT ≥ 0.9 mm) or plaque</li> <li>Carotid–femoral pulse wave velocity &gt; 12 m/s</li> </ul>		<ul style="list-style-type: none"> <li>Heart disease: myocardial infarction; angina; coronary revascularization; heart failure</li> </ul>
<ul style="list-style-type: none"> <li>Fasting plasma glucose 5.6–6.9 mmol/L (100–125 mg/dL)</li> <li>Abnormal glucose tolerance test</li> </ul>	<ul style="list-style-type: none"> <li>Ankle/brachial BP index &lt; 0.9</li> <li>Slight increase in plasma creatinine: <ul style="list-style-type: none"> <li>M: 115–133 μmol/L (1.3–1.5 mg/dL);</li> <li>W: 107–124 μmol/L (1.2–1.4 mg/dL)</li> </ul> </li> <li>Low estimated glomerular filtration rate<sup>b</sup> (&lt;60 mL min/1.73 m<sup>2</sup>) or creatinine clearance<sup>c</sup> (&lt; 60 mL/min)</li> </ul>		<ul style="list-style-type: none"> <li>Renal disease: diabetic nephropathy; renal impairment (serum creatinine M &gt; 133, W &gt; 124 μmol/L) proteinuria (&gt;300 mg/24 h)</li> </ul>
<ul style="list-style-type: none"> <li>Abdominal obesity [waist circumference &gt;102 cm (M), &gt;88 cm (W)]</li> <li>Family history of premature CV disease (M at age &lt; 55 years; W at age &lt; 65 years)</li> </ul>	<ul style="list-style-type: none"> <li>Microalbuminuria 30–300 mg/24 h or albumin creatinine ratio: ≥ 22 (M); or ≥ 31 (W) mg/g creatinine</li> </ul>		<ul style="list-style-type: none"> <li>Peripheral artery disease</li> <li>Advanced retinopathy: haemorrhages or exudates, papilloedema</li> </ul>

The cluster of three out of five factors among abdominal obesity, fasting blood glucose, BP ≥140/85 mmHg, low HDL cholesterol (M, <40 mg/dL or 1.03 mmol/L; W, <50 mg/dL or 1.29 mmol/L, and high triglycerides (≥150 mg/dL or 1.7 mmol/L) indicates the presence of a metabolic syndrome.

M = men; W = women; CVD = cardiovascular disease; IMT = intima-media thickness.

<sup>a</sup>Risk maximal for concentric LVH (left ventricular hypertrophy): increased LVMI (left ventricular mass index) with a wall thickness/radius ratio ≥0.42.

<sup>b</sup>MDRD formula.

<sup>c</sup>Cockcroft–Gault formula.

premature CVD) also greatly adds to the risk associated with a mild BP elevation (see SCORE risk charts).<sup>42</sup>

## Practical aspects: management of hypertension

### Who to treat?

The term 'treatment' should be taken to mean total management. This means detailed lifestyle advice for all those with raised BP, with the judicious use of medication in some. The decision to start antihypertensive drug treatment depends on the presence or absence of established CVD, diabetes, renal disease, target organ damage, and, of critical importance in all other persons, on the SCORE estimate of total CVD risk (Table 6), Persons in whom repeated BP measurements show grade 2 or 3 hypertension (i.e. systolic values  $\geq 160$  mmHg or diastolic values  $\geq 100$  mmHg) are generally regarded as candidates for antihypertensive treatment because a large number of placebo-controlled trials have conclusively demonstrated that, in patients with these BP values, BP reduction lowers cardiovascular morbidity and mortality<sup>98–101</sup>. However, the benefit may be modest in those at low total CVD risk. In particular, randomized controlled trial data are lacking to provide guidance with regard to drug treatment in, for example, younger women without other risk factors. The likely benefits of drug treatment should be weighed against side effects, cost, the use of medical resources, and turning healthy people into 'patients'.

In all grade 1–3 hypertensives, comprehensive risk factor assessment and appropriate lifestyle counselling should be provided after hypertension is diagnosed, while promptness in the initiation of pharmacological therapy depends on the level of total cardiovascular risk. Drug treatment should be initiated promptly in grade 3 hypertension, as well as in grade 1 and grade 2 hypertensives with increased or markedly increased total cardiovascular risk (i.e. in

hypertensive patients with established CVD or renal disease, TOD, diabetes, or a SCORE risk of  $\geq 5\%$ ). In grade 1 or 2 hypertensives with moderate total cardiovascular risk, drug treatment may be delayed for some time to allow evaluation of the effects of lifestyle advice on total risk.. However, even in these patients, lack of BP control after a suitable period of non-pharmacological measures should lead to instituting drug treatment in addition to lifestyle measures.

When initial BP is within the high normal range (130–139/85–89 mmHg), the decision on drug intervention depends heavily on total cardiovascular risk. In the case of diabetes or a history of cerebrovascular or coronary disease, evidence<sup>102–110</sup> justifies the recommendation to start antihypertensive drug administration (together with intense lifestyle changes) even in patients with BP in the high normal range, with associated CVD or diabetes.

### How to treat?

Lifestyle interventions include: weight reduction in overweight/obese individuals; reduction in the use of sodium chloride to  $<3.8$  g/day (sodium intake  $<1.5$  g/day, i.e. 65 mmol/day);<sup>111</sup> restriction of alcohol consumption to no more than 10–30 g of ethanol per day in men (1–3 standard measures of spirits, 1–3 glasses of wine, or 1–3 bottles of beer), and to no more than 10–20 g of ethanol per day in women (1–2 of these drinks/day); and regular physical activity in sedentary individuals. Hypertensives should be generally advised to eat more fruit and vegetables (4–5 servings per day, i.e. 300 g)<sup>112</sup> and to reduce intake of saturated fat and cholesterol.

### Antihypertensive drugs

The large number of randomized trials of antihypertensive therapy, both those comparing active treatment vs.

**Table 6** Management of total CVD risk–blood pressure

**In ALL cases, look for and manage all risk factors. Those with established CVD, diabetes or renal disease are at markedly increased risk, and a BP of  $<130/80$  is desirable if feasible. For all other people, check SCORE risk. Those with target organ damage are managed as 'increased risk'**

SCORE CVD risk	Normal $<130/85$	High Normal 130–139/ 85–89	Grade 1 140–159/ 90–99	Grade 2 160–179/ 100–109	Grade 3 $\geq 180/110$
Low $<1\%$	Lifestyle advice	Lifestyle advice	Lifestyle advice	Drug Rx if persists	Drug Rx
Moderate 1–4%	Lifestyle advice	Lifestyle advice	+consider drug Rx	Drug Rx if persists	Drug Rx
Increased 5–9%	Lifestyle advice	+consider drug Rx	Drug Rx	Drug Rx	Drug Rx
Markedly increased $\geq 10\%$	Lifestyle advice	+consider drug Rx	Drug Rx	Drug Rx	Drug Rx

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 diuretics (chlorthalidone and indapamide),  $\beta$ -blockers, calcium antagonists, ACE inhibitors, and angiotensin receptor antagonists can adequately lower BP, and significantly reduce cardiovascular morbidity and mortality. These drugs are thus all suitable for initiation and maintenance of antihypertensive treatment, either as monotherapy or in combination.

Two recent large-scale trials<sup>113–115</sup> and a meta-analysis<sup>116</sup> have concluded that  $\beta$ -blockers may have a reduced ability to protect against stroke, though being equally effective in reducing coronary events and mortality. Moreover, administration of  $\beta$ -blockers has been proven beneficial in patients with angina, heart failure, and a recent MI.<sup>87,117,118</sup> Thus,  $\beta$ -blockers should still be considered a valid option for initial and subsequent antihypertensive treatment strategies. However, they may induce weight gain,<sup>119</sup> have adverse effects on lipid metabolism,<sup>115</sup> and increase (compared with other drugs) the incidence of new-onset diabetes.<sup>120</sup> While these effects are modest, they may indicate caution in hypertensives with multiple metabolic risk factors including the metabolic syndrome and its major components.<sup>121,122</sup> This applies also to thiazide diuretics, which have dyslipidaemic and diabetogenic effects, particularly when used at high doses.<sup>120</sup> 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. These metabolic effects may be less with vasodilating  $\beta$ -blockers.<sup>123,124</sup>

Trials assessing intermediate end-points suggest other differences between various antihypertensive agents or compounds: ACE inhibitors and angiotensin receptor antagonists have been reported to be particularly effective in reducing left ventricular hypertrophy,<sup>125</sup> including the fibrotic component,<sup>126,127</sup> and microalbuminuria and proteinuria,<sup>106,128–130</sup> and in preserving renal function and delaying end-stage renal disease.<sup>130–133</sup> Calcium antagonists, beside being effective on left ventricular hypertrophy, appear particularly beneficial in slowing down progression of carotid hypertrophy and atherosclerosis.<sup>134–136</sup> Evidence concerning the benefits of other classes of antihypertensive agents is much more limited.

Combination treatment is frequently needed to control BP.<sup>137</sup> Drugs that have a long-lasting effect and a documented ability to lower BP effectively over 24 h with once-a-day administration are preferred. Simplification of treatment improves adherence to therapy,<sup>138</sup> while effective 24 h BP control is prognostically important in addition to office blood pressure control.<sup>139</sup> Long-acting drugs also minimize BP variability and this may offer protection against progression of target organ damage and risk of cardiovascular events.<sup>140–142</sup>

## Desirable blood pressure

The primary goal of treatment of the hypertensive patient is to achieve the maximum reduction in the long-term total risk of cardiovascular morbidity and mortality. This requires treatment of all the reversible risk factors identified,

including smoking, dyslipidaemia, or diabetes, and the appropriate management of associated clinical conditions, as well as treatment of the elevated BP *per se*.

If possible, BP should be reduced to below 140/90 mmHg in all hypertensive patients who qualify for drug treatment and lower if lack of side effects permits. In diabetic patients, antihypertensive treatment should be more intense, and a goal of <130/80 mmHg has been proposed. The same target is appropriate for subjects with established cardiovascular disease if feasible.

## Duration of treatment

Generally, antihypertensive therapy should be maintained indefinitely. In general clinical practice, hypertension is not well treated and only a minority of subjects achieve a BP of <140/90 mmHg.<sup>143</sup> Increasing compliance with antihypertensive treatment and achieving a wide BP control in the population thus represents a major challenge for clinical practice in the future.

## Plasma lipids

### Scientific background

The relationship between a raised plasma cholesterol and atherosclerotic vascular disease fulfils all of the criteria for causality. The evidence that reducing plasma cholesterol reduces risk is equally unequivocal. The higher the risk, the greater the benefit. A 10% reduction in plasma total cholesterol is followed by a 25% reduction in incidence of coronary artery disease after 5 years, and a reduction of LDL cholesterol of 1 mmol/L (~40 mg/dL) is accompanied by a 20% reduction in CHD events.<sup>144</sup> While the relationship between a reduced HDL cholesterol level and risk is strong, trial data do not yet permit the definition of a target level for HDL cholesterol. Raised plasma triglycerides signal the need to look for those other factors that may be associated with the so-called metabolic syndrome.

### Practical aspects: management

As with raised BP, the first principle of management is to assess and control all components of total CVD risk by means of appropriate advice with regard to smoking, exercise, nutrition, and BP control.

In general, total plasma cholesterol should be below 5 mmol/L (190 mg/dL), and LDL cholesterol should be below 3 mmol/L (115 mg/dL). In the highest risk subjects, especially those with clinically established atherosclerotic CVD and patients with diabetes, the treatment goals should be lower: total cholesterol <4.5 mmol/L (~175 mg/dL) with an option of <4 mmol/L (~155 mg/dL) if feasible, and LDL cholesterol <2.5 mmol/L (~100 mg/dL) with an option of <2 mmol/L (~80 mg/dL) if feasible. If these targets are not feasible, total risk can still be reduced by means of increased efforts to control other risk factors.

### Should statins be given to all persons with cardiovascular disease?

Relative risk reductions seem to be constant at all lipid levels, but absolute risk reductions are small in those with



low lipid levels, with little evidence of a reduction in total mortality. The universal use of statins may be unrealistic in some economies.

No specific treatment goals are defined for HDL cholesterol and triglycerides, but concentrations of HDL cholesterol  $<1.0$  mmol/L ( $\sim 40$  mg/dL) in men and  $<1.2$  mmol/L ( $\sim 45$  mg/dL) in women, and, similarly, fasting triglycerides  $>1.7$  mmol/L ( $\sim 150$  mg/dL), serve as markers of increased cardiovascular risk. Values of HDL cholesterol and triglycerides should also be used to guide the choice of drug therapy.

Asymptomatic people at high multifactorial risk of developing CVD, whose untreated values of total and LDL cholesterol are already close to 5 and 3 mmol/L, respectively, seem to benefit from further reduction of total cholesterol to  $<4.5$  mmol/L (175 mg/dL) and, if feasible, lower, and from further reduction of LDL cholesterol to  $<2.5$  mmol/L (100 mg/dL) and, if feasible, lower, with lipid-lowering drugs.

Table 7 summarizes the management of plasma lipids in clinical practice. The first step is to assess total cardiovascular risk and to identify these components of risk that are to be modified. If the 10-year risk of cardiovascular death is  $<5\%$  and will not exceed 5% if the individual's risk factor combination is projected to age 60, professional advice on diet, regular physical activity, and stopping smoking should be given to keep the cardiovascular risk low. Risk assessment should be repeated at 5-year intervals.

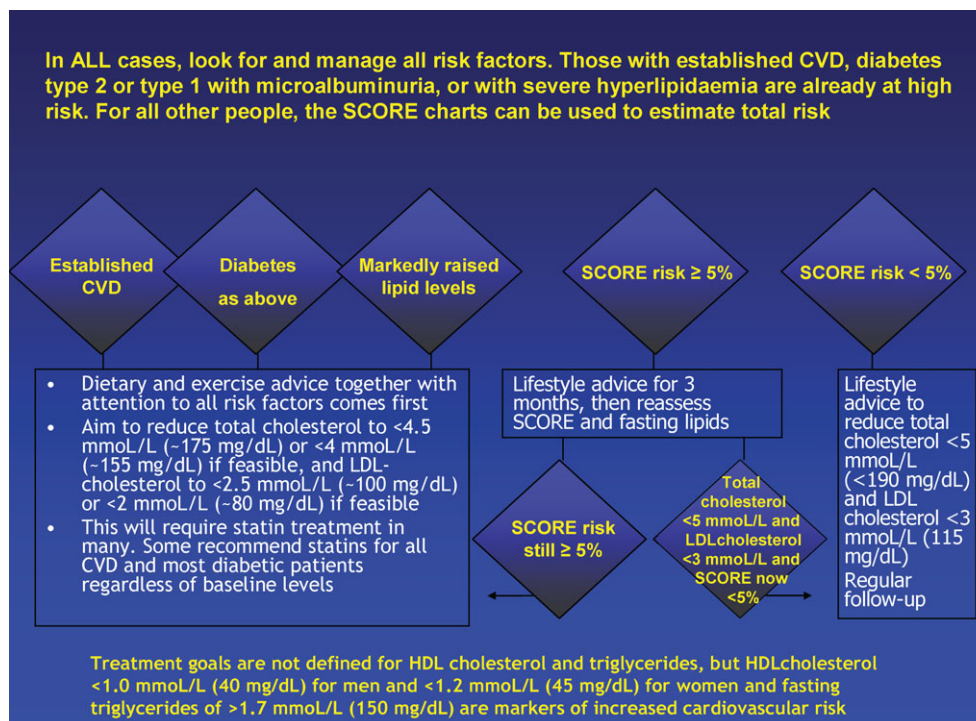
Note that assessment of total risk does not pertain to patients with familial hypercholesterolaemia, since total cholesterol  $>8$  mmol/L ( $\sim 320$  mg/dL) and LDL cholesterol  $>6$  mmol/L ( $\sim 240$  mg/dL) by definition places a patient at high total risk of CVD, especially as the raised cholesterol level will have been present since childhood. This high risk

justifies lipid-lowering therapy even in young asymptomatic subjects.

If the 10-year risk of cardiovascular death is  $\geq 5\%$ , or will become  $\geq 5\%$  if the individual's risk factor combination is projected to age 60, a full analysis of plasma lipoproteins (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) should be performed, and intensive lifestyle advice, particularly dietary and physical activity advice, should be given. If values of total and LDL cholesterol fall below 5 mmol/L ( $\sim 190$  mg/dL) and 3 mmol/L ( $\sim 115$  mg/dL), respectively, and the total CVD risk estimate has become  $<5\%$ , then these persons should be followed at yearly intervals to ensure that cardiovascular risk remains low without drugs. In contrast, if total CVD risk remains  $\geq 5\%$ , lipid-lowering drug therapy should be considered to lower total and LDL cholesterol even further. The goals in such persistently high risk individuals are to lower total cholesterol to  $<4.5$  mmol/L ( $\sim 175$  mg/dL) with an option of  $<4$  mmol/L ( $\sim 155$  mg/dL) if feasible, and to lower LDL cholesterol to  $<2.5$  mmol/L ( $\sim 100$  mg/dL) with an option of  $<2$  mmol/L ( $\sim 80$  mg/dL) if feasible. As stated earlier, these lower values are not goals of therapy for patients with higher untreated values. It has to be stressed that the benefits of cholesterol-lowering therapy depend on initial levels of risk: the higher the risk, the greater the benefit.

Since the lifelong CVD risk in diabetic patients may be as high as in non-diabetic individuals with prior CVD, particularly if they have some other risk factors or have microalbuminuria, earlier and intensive prevention using lipid-lowering drugs, even in type 2 diabetic patients with moderate risk, is needed.<sup>145,146</sup>

Table 7 Management of total CVD risk–lipids



Despite early observational studies indicating that plasma cholesterol is not associated with overall rates of stroke, and that lowering cholesterol does not lower the risk of stroke, most of the large statin trials reported significant reductions in stroke rates in patients with or at high risk of getting coronary artery disease<sup>147–149</sup> due to a reduction in the rates of ischaemic stroke.<sup>150</sup> Therefore, the patients with cerebrovascular disease as well as the patients with PAD merit the same degree of attention to treatment of plasma lipids as patients with coronary artery disease.

In all patients with an acute coronary syndrome, statin treatment should be initiated while the patients are in the hospital.<sup>151–153</sup> Such early drug treatment should nevertheless be combined with effective lifestyle changes and particularly dietary intervention after hospital discharge.

The benefits of statins appear to apply to both genders and most ages,<sup>145</sup> although the benefits in healthy, asymptomatic women are not proven.

The current armamentarium of lipid-lowering drugs includes inhibitors of hydroxy-3-methyl-glutaryl-CoA reductase (statins), fibrates, bile acid sequestrants (anion exchange resins), niacin (nicotinic acid), and selective cholesterol absorption inhibitors (e.g. ezetimibe). Statins have been shown not only to reduce hyperlipidaemia but also to reduce cardiovascular events and mortality as well as the need for coronary artery by-pass grafting and various forms of coronary angioplasty. Statins in the highest doses seem also to halt progression or induce regression of coronary atherosclerosis.<sup>105,154</sup> Therefore, they should be used as the drugs of first choice. These drugs are easy to use and all have proved safe in large trials.<sup>144</sup> Liver dysfunction is occasional and reversible. Rhabdomyolysis is rare; severe muscle pain requires immediate cessation of therapy. Because statins are prescribed on a long-term basis, possible interactions with other drugs (ciclosporin, macrolides, azole antifungals, calcium antagonists, protease inhibitors, sildenafil, warfarin, digoxin, nicotinic acid, fibrates, etc.) deserve particular attention, as many patients will receive pharmacological therapy for concomitant conditions during the course of statin treatment.<sup>155</sup>

Selective cholesterol absorption inhibitors can be used in combination with statins in patients not reaching treatment goals with statins. Bile acid sequestrants also decrease total and LDL cholesterol, but tend to increase triglycerides. Fibrates and nicotinic acid are used primarily for triglyceride lowering and increasing HDL cholesterol, while fish oils (omega-3 fatty acids) are used for triglyceride lowering.

In some patients, combination therapy with different lipid-lowering drugs is necessary to achieve the treatment goals. The combination of statins with fibrates has been associated with a moderately higher likelihood of myopathy and occasional rhabdomyolysis. Therefore, patients must be carefully selected and carefully instructed about warning symptoms. However, these adverse effects are very rare and should not be the reason to deny the combined treatment to patients who really need it.

In some patients, goals cannot be reached even on maximal lipid-lowering therapy, but they will still benefit from treatment to the extent to which cholesterol has been lowered. Increased attention to other risk factors offers an additional way to reduce total risk.

## Diabetes

### Scientific background

The extensive literature on diabetes and its precursor stages and CVD has been thoroughly reviewed in the recent guidelines on diabetes, pre-diabetes and cardiovascular disease created by the Joint Task Force of the ESC and the European Association for the Study of Diabetes. In addition to the full text of the present guidelines, the readers are referred to that document.<sup>5</sup>

### Practical aspects: management

In subjects with impaired glucose tolerance, it has been demonstrated that progression to diabetes can be prevented or delayed by lifestyle intervention. Even temporary interventions seem to have a long-lasting impact years after the intervention period.

In patients with type 1 diabetes as well as with type 2 diabetes, randomized trials consistently show that good metabolic control prevents microvascular complications. In relation to macrovascular disease the picture is less clear. In type 1 diabetes, long-lasting effects of optimized metabolic control on the risk of developing CVD have been demonstrated, but this could be an effect mediated through the effect on microvascular complications. In type 2 diabetes, the combined evidence from epidemiological studies and intervention trials strongly indicates an effect of glucose control on risk of CVD. Consequently, there is reason to aim for good glucose control in both types of diabetes. In type 1 diabetes, glucose control requires appropriate insulin therapy and concomitant professional dietary therapy. In type 2 diabetes, professional dietary advice, reduction of overweight, and increased physical activity should be the first treatment, followed by pharmacological treatment (oral hypoglycaemic treatment and insulin when needed) aiming at good glucose control. Recommended treatment targets for type 2 diabetes are given in *Table 8*. As to HbA<sub>1c</sub> and glucose targets, in patients who receive treatment with insulin or drugs stimulating insulin secretion (sulphonylureas, nateglinide, and repaglinide), special attention should be paid to avoidance of hypoglycaemic episodes, with guidance obtained from glucose self-monitoring. Targets for

**Table 8** Treatment targets in patients with type 2 diabetes

	Unit	Target
HbA <sub>1c</sub> (DCCT-aligned)	HbA <sub>1c</sub> (%)	≤ 6.5 if feasible
Plasma glucose	Fasting/pre-prandial mmol/L (mg/dL)	<6.0 (110) if feasible
	Post-prandial mmol/L (mg/dL)	<7.5 (135) if feasible
Blood pressure	mmHg	≤130/80
Total cholesterol	mmol/L (mg/dL)	<4.5 (175)
	mmol/L (mg/dL)	<4.0 (155) if feasible
LDL cholesterol	mmol/L (mg/dL)	<2.5 (100)
	mmol/L (mg/dL)	<2.0 (80) if feasible

blood pressure and lipids are generally more ambitious in patients with diabetes than in non-diabetic subjects.

## The metabolic syndrome

### Scientific background

The metabolic syndrome describes the clustering of cardiovascular risk factors in individuals with obesity or insulin resistance. It identifies individuals with increased risk of developing CVD in accordance with the clustering of risk factors, but does not indicate risk of CVD over and above the effect of the risk factors involved.

### Practical aspects: management

### The metabolic syndrome

- The term 'metabolic syndrome' refers to the combination of several factors that tend to cluster together central obesity— hypertension, low HDL cholesterol, raised triglycerides, and raised blood sugar— to increase risk of diabetes and CVD
- This implies that, if one component is identified, a systematic search for the others is indicated, together with an active approach to managing all of these risk factors
- Physical activity and weight control can radically reduce the risk of developing diabetes in those with the metabolic syndrome

The diagnosis of the metabolic syndrome is of greatest importance in non-diabetic subjects as an indicator of an increased risk of developing type 2 diabetes and CVD. The interest in the metabolic syndrome should, however, not displace the use of other similar risk scoring tools from their primary place in the identification of individuals at high risk of CVD. Among different definitions for the metabolic syndrome formulated by international and national expert groups, the original NCEP-ATP III definition and its revision recommended by the American Heart Association (AHA) and NHLBI<sup>156,157</sup> (see *Table 9*) and the definition created by the Consensus Panel of the International Diabetes Federation (IDF)<sup>158</sup> (see *Table 10*) have been developed for clinical use, but it is important to realize that the prevalence obtained with these definitions is far from similar, and individuals labelled as having the metabolic syndrome will to a substantial extent be different. The prevalence of the metabolic syndrome is clearly higher with the AHA/NHLBI revision of the NCEP-ATP III definition than with the original NCEP-ATP III definition and the IDF definition. This is mainly caused by the lowered cut-off for impaired fasting glycaemia in the two new definitions, but with the IDF definition the emphasis on central obesity defined by strict cut-offs also contributes. The original NCEP-ATP III definition is more robust in the prediction of CVD risk, with a higher positive predictive value than the revised NCEP-ATP III definition and the IDF definition.

Lifestyle has a strong influence on all the components of the metabolic syndrome and, therefore, the main emphasis

**Table 9** Original and revised NCEP-ATP III definitions of the metabolic syndrome

At least three of the following five components  
 Central obesity: waist circumference >102 cm in men, >88 cm in women  
 Elevated triglycerides:  $\geq 1.7$  mmol/L ( $\geq 150$  mg/dL)  
 Low HDL cholesterol: <1.03 mmol/L (<40 mg/dL) in men, <1.29 mmol/L (<50 mg/dL) in women  
 Raised blood pressure: systolic BP  $\geq 130$  mmHg and/or diastolic BP  $\geq 85$  mmHg, or treatment of previously diagnosed hypertension  
 Impaired fasting glycaemia: fasting plasma glucose  $\geq 6.1$  mmol/L (110 mg/dL) [ $\geq 5.6$  mmol/L ( $\geq 100$  mg/dL)]<sup>a</sup> or previously diagnosed type 2 diabetes

<sup>a</sup>The revised version recommended by the AHA/NHLBI uses the lower cut-off for impaired fasting glycaemia.

**Table 10** The IDF definition of the metabolic syndrome

Central obesity defined by ethnic-specific waist circumference criteria  $\geq 94$  cm in European men,  $\geq 80$  cm for European women and any two of the following four components:  
 Elevated triglycerides:  $\geq 1.7$  mmol/L ( $\geq 150$  mg/dL) or specific treatment for this lipid abnormality  
 Low HDL cholesterol: <1.03 mmol/L (<40 mg/dL) in men, <1.29 mmol/L (<50 mg/dL) in women or specific treatment for this lipid abnormality  
 Raised blood pressure: systolic BP >130 mmHg and/or diastolic BP >85 mmHg, or treatment of previously diagnosed hypertension  
 Impaired fasting glycaemia: fasting plasma glucose  $\geq 5.6$  mmol/L (100 mg/dL) or previously diagnosed type 2 diabetes

in the management of the metabolic syndrome should be in professionally supervised lifestyle changes, particularly efforts to reduce body weight and increase physical activity. Elevated BP, dyslipidaemia, and hyperglycaemia (in the diabetic range) may, however, need additional drug treatment as recommended in the present guidelines.

## Psychosocial factors

### Scientific background

There is increasing scientific evidence that psychosocial factors contribute independently to the risk of CHD even after statistical control for the effects of standard risk factors.<sup>159</sup> In addition to increasing the risk of a first event and worsening the prognosis in CHD, these factors may act as barriers to treatment adherence and efforts to improve lifestyle, as well as to promote health and well-being in patients and populations.

The following psychosocial risk factors have been shown to influence both the risk of contracting CHD and the worsening of clinical course and prognosis in patients with CHD:

- Low socio-economic status
- Social isolation and lack of social support
- Stress at work and in family life
- Negative emotions including depression and hostility.



It is now evident that psychosocial risk factors do not occur in isolation from one another, but tend to cluster in the same individuals and groups, for example, those with low SES. In addition to risky health behaviours such as smoking and unhealthy nutrition, persons with psychosocial risk factors such as depression are also more likely to express physiological characteristics such as autonomic, endocrine, and inflammatory changes that are involved in promoting CVD.

Evidence is also accumulating of therapeutic and preventive intervention methods that counteract psychosocial risk factors and promote healthy behaviours and lifestyle.<sup>44,45,160</sup> Several psychosocial interventions have been shown to have beneficial effects on distress and physiological risk factors,<sup>44,46</sup> and some studies also showed improved CVD outcomes, especially in white men and in patients who achieved the proximal goals of the intervention. Specific behavioural group treatments for women with CHD may be useful for reducing distress and exhaustion. In patients with CHD and severe co-morbid depression, selective serotonin re-uptake inhibitors can be given to treat depression and improve quality of life. Results from non-randomized trials indicate that these substances may also improve prognosis in depressed patients.

### Practical aspects: management of psychosocial risk factors in clinical practice

- Assess all patients for psychosocial risk factors, e.g. depression and hostility, low SES, social isolation, and chronic life stress by clinical interview or standardized questionnaires. A selection of screening instruments is given in Albus *et al.*<sup>161</sup>
- Core questions for the assessment of psychosocial risk factors include the following. It should be noted that these rather blunt questions will need to be phrased with sensitivity if a constructive rapport with the patient is to be established:
  - **Low SES.** Do you have no more than mandatory education? Are you a manual worker?
  - **Social isolation.** Are you living alone? Do you lack a close confidant? Do you lack any person to help you in case of illness?
  - **Work and family stress.** Do you have enough control over how to meet the demands at work? Is your reward appropriate for your effort? Do you have serious problems with your spouse?
  - **Depression.** Do you feel down, depressed, and hopeless? Have you lost interest and pleasure in life?
  - **Hostility.** Do you frequently feel angry over little things? If someone annoys you, do you regularly let your partner know? Do you often feel annoyed about habits other people have?
- Discuss relevance with patient in respect to quality of life and medical outcome.
- Use principles of enhanced communication and behavioural counselling as described above.
- Patients with low SES need special preventive effort.
- In patients at high risk or those with established CVD and psychosocial risk factors, prescribe multimodal, behavioural intervention, integrating individual or group counselling for psychosocial risk factors and coping with stress and illness.
- Refer to a specialist in the case of clinically significant emotional distress. Patients with clinical depression

should receive treatment with psychotherapy or anti-depressant medication, preferably selective serotonin re-uptake inhibitors, according to established guidelines. Those not accepting treatment should be closely followed and treatment offered again if depression persists for more than 4–6 weeks.

## Inflammation markers and haemostatic factors

### Scientific background

Risk factors may be classed into several hierarchical categories as follows: classical, established, emerging, and putative, and also as risk markers. The highest level of classification achieved thus far by the heterogeneous group of factors discussed in these guidelines is 'emerging', but many are under active investigation in clinical and epidemiological studies. These factors are associated with many different biological systems such as those regulating platelets, coagulation, fibrinolysis, endothelial function, and the inflammatory response. These interact in ways which remain incompletely understood, but in which scientific interest and achievement is considerable. In addition to their potential utility in long-term risk prediction of CVDs, close associations between inflammatory markers and obesity and diabetes have been demonstrated, which strengthens the case for their scientific investigation.

There is strong evidence from pathological<sup>162,163</sup> and epidemiological studies<sup>164–167</sup> that the circulating markers of activated inflammation and haemostasis are closely associated with the development of fatal and non-fatal MI. A large case series, based in a national primary care database, showed that first MI and stroke were each more common following recent respiratory or urinary tract infections, the risk being greatest within the first 3 days after diagnosis (relative risks 5.0 and 3.2, respectively), and falling during the following weeks.<sup>168</sup> A recent report from Europe, as part of the WHO's MONICA study, showed that population levels of certain haemostatic factors differed between participating centres and countries, and showed significant associations with the incidence of CHD in the centres.

Prospective epidemiological studies have also linked inflammatory markers with the development of type 2 diabetes mellitus, and interleukin-6 (IL-6), a pro-inflammatory cytokine, with CHF. Some studies have demonstrated that risk prediction for CHD, and for both CHD and stroke can be improved by the addition of these newer risk factors to risk models which include all established risk factors. A recent report in the USA proposed that CRP should be used as an 'option' in current guidelines,<sup>169</sup> but this proposal has been questioned both in the USA and in Europe.<sup>170,171</sup>

Incorporation of CRP and other emerging risk factors into routine practice for prediction of cardiovascular risk may be premature, therefore, and criteria for the rigorous evaluation of such factors have been proposed. These criteria include: applicability to all relevant clinical cardiovascular events; ability to predict in short, intermediate, and long-term follow-up; standardized measurements; examination of variability; the degree of correlation with established risk factors; and improvement in overall prediction, among other criteria. A number of meta-analyses of observational epidemiological studies have been conducted, e.g. for CRP<sup>172</sup> and for fibrinogen.<sup>173</sup> Such meta-analyses will

provide evidence of the possible utility of emerging risk factors in future clinical practice; but current investigations of determinants of inflammatory markers, which include physical activity, dietary factors, alcohol, and weight loss as protective factors, and infections such as periodontitis as a potentially treatable risk factor, encourage the detailed examination of this group of markers in future research.

Another important point regarding these meta-analyses is that CRP (as well as fibrinogen and possibly other biomarkers) is often seriously confounded by other unmeasured variables and subject to reverse causality (i.e. pre-clinical disease causes rises in CRP). Consequently, large-scale meta-analyses, like those cited above, fall into the trap of promoting the idea that the evidence of a causal link is strong. An alternative approach, examining genotypes directly, has been carried out by several groups, demonstrating that predicted associations between CRP genotypes that code for higher levels of circulating CRP are not associated with CVD or risk factors. However, a large meta-analysis of seven haemostatic genes showed that variants of factor V gene and of the prothrombin gene may be moderately associated with risk of coronary disease.<sup>174</sup>

## Genetic factors

Genetic information is divided into three categories: family history, phenotypes, and genotypes.

### Family history: scientific background

Some studies have established the importance of family history as a coronary risk factor for CHD, and have shown that the risk associated with family history of early CHD (in first-degree relatives, male <55 years and female <65 years) ranges between 1.5 and 1.7 and is independent of classical CHD risk factors.<sup>175,176</sup>

The risk of CHD increases with a positive history

- in a first degree relative (parents, son, daughter, brother or sister), in a second degree relative (grandparents, aunt or uncle), or in a third degree relative (cousin);
- as the number of family members with CHD increases; and
- the younger the age at which family members develop CHD.

### Family history: practical aspects

Risk factor assessment, and a family history of premature CHD, including a detailed history and a drawing of a pedigree, should therefore be carried out in the first degree relatives of any patient developing coronary disease before 55 years in men and 65 years in women. Lifestyle advice and, where appropriate, therapeutic management of risk factors should be offered to members of families where coronary disease is highly prevalent.

### Phenotypes: scientific background

The study of the genetic determinants of 'phenotypes' which are involved in the pathophysiology of CHD (dyslipidaemia, hypertension, endothelial dysfunction, diabetes, cardiac and vascular hypertrophy, and atherosclerosis) is likely to be clinically relevant, and each has its own genetic and environmental determinants.

For many of these phenotypes (measurable traits) there is a good evidence for a relatively strong genetic determination, which is usually estimated by 'heritability'. For example, for apoproteins and lipid traits, heritability varies between 40 and 60%;<sup>177</sup> for plasma Lp(a), heritability is >90%.<sup>178</sup> Since meta-analyses show that levels of Lp(a) are associated with a 1.6-fold greater risk of CHD,<sup>179</sup> an effect which is of similar magnitude to smoking, the Lp(a) gene would appear to be a major genetic factor for CHD.

The data suggest a moderate to high heritability for emerging risk factors such as intercellular adhesion molecule (ICAM), IL-6, phospholipase A2 (PLA2), etc.<sup>180,181</sup>

### Genotypes: scientific background

The levels of CHD risk traits are influenced by both environmental and genetic factors. The concept of gene-environment interaction is necessary to understand how genetic information can be used for accurate risk assessment,<sup>182</sup> and this is likely to be of major research importance in the future. Genetic polymorphisms are defined as sequence variants that occur at a frequency >1%. These include single nucleotide polymorphisms (SNPs) as well as insertion/deletion and copy number variants which have recently been reported to be very common.<sup>183</sup>

A large number of 'candidate' genes have already been investigated in relation to CHD traits and to risk of CHD itself.

Several variants in genes involved in lipid metabolism [e.g. apolipoprotein E (APOE), apolipoprotein B (APOB), lipoprotein lipase (LPL), cholesterol ester transfer protein (CETP)], coagulation [plasminogen activator inhibitor 1 (PAI1), glycoprotein IIb/IIIa (GIIb/IIIa), factor V (FV)], and different aspects of endothelial function [endothelial nitric oxide synthase (eNOS), methylenetetrahydrofolate reductase (MTHFR) and ACE]<sup>184</sup> appear to be associated with statistically significant, although rather modest effects on risk.

### DNA-based tests for risk prediction

Currently available CHD risk prediction algorithms based on classical risk factors<sup>185,186</sup> have a very low prediction rate, for example 11% in a 10-year follow-up of UK healthy men, and adding risk genotypes may improve this.<sup>187</sup>

Modelling has suggested<sup>188</sup> that only around 20 genes are needed to explain 50% of the burden of a disease in the population if the predisposing genotypes are common (>25%), even if the individual risk ratios are relatively small (i.e. increasing risk by only 20–50%).

### Practical aspects

#### DNA-based tests for risk prediction

At the moment, DNA-based tests do not add significantly to diagnostic utility or patient management. In the long term, understanding disease aetiology in terms of genetic determinants may be useful in identifying high risk individuals and adapting therapeutic management to the individual's genetic make-up.

#### Pharmacogenetics

Currently, there are few data either for the most effective choice of available drugs based on an individual's genetic make-up, or for the avoidance of dangerous side effects in the field of CVD.

The full potential of this field will only be realized with much further work.

### Severe familial dyslipidaemias and coronary heart disease

There are many extremely rare inherited conditions where plasma lipids are abnormal and CHD risk is altered. Here we focus on only the three most common of these.

#### Familial hypercholesterolaemia (FH)

*Scientific background:* FH has an estimated prevalence of 1/500.<sup>189</sup> It is characterized by hypercholesterolaemia due to increased LDL levels, xanthomas, premature CHD, and a family history of one or more of these. Angina, heart attacks, or death typically occur in men between 30 and 50 years, and in women between 50 and 70 years,<sup>190</sup> and those who smoke, are hypertensive, or have other risk factors are at particularly high risk. Several methods with different sensitivity and specificity have been developed for the clinical diagnosis of FH,<sup>191–193</sup> but the ‘gold standard’ is a combination of clinical and biochemical factors and the presence of a detectable disease-causing DNA change, which gives the highest clinical utility.

FH is an autosomal dominant inherited disorder and is usually caused by a mutation in the LDL receptor gene (*LDLR*). To date, > 700 different mutations have been identified worldwide (see <http://www.ucl.ac.uk/fh>), although the spectrum within a single country is much smaller.<sup>194,195</sup> Screening for deletions and rearrangements of the *LDLR* gene using a technique called multiplex ligation-dependent probe amplification (MLPA)<sup>196</sup> has become available, and it is known that up to 5% of FH patients may have such a deletion.<sup>197</sup>

A specific mutation occurs in the apolipoprotein B 100 gene (*APOB*), the ligand for the LDL receptor, in approximately 3% of FH patients in the UK, North Europe, and the USA. The disorder has been designated familial defective apolipoprotein B 100 (FDB).<sup>198</sup> FDB is milder than *LDLR-FH* but hypercholesterolaemia occurs in childhood and early CHD occurs in some subjects.

Recently, defects in a third gene called protein convertase subtilisin/kexin type 9 (*PCSK9*), causing monogenic hypercholesterolaemia, have been identified.<sup>199</sup> These mutations could cause increased degradation of LDL receptors, reduced numbers of receptors on the surface of the cell, and monogenic hypercholesterolaemia.

Using currently available routine clinical genetic diagnostic techniques,<sup>192–194</sup> it is possible to demonstrate a mutation in the *LDLR*, *PCSK9*, or *APOB* gene in up to 80–90% of clinically diagnosed patients, but this is usually only available in a research setting. Such specialist services are available in several European countries,<sup>194,195,200–202</sup> but each country should have its own programme for genetic testing for FH because the spectrum of mutations varies between countries.

Current data strongly suggest that DNA testing for FH complements cholesterol measurement in cascade screening to identify affected subjects unambiguously.<sup>203,204</sup>

*Practical aspects:* Because of their high CHD risk, patients with FH should be aggressively treated with statins at a young age. Lifestyle advice should be offered and supported. Cascade testing to identify affected relatives should be undertaken. It is likely that, for optimal diagnostic

and management results, both phenotypic and genotypic diagnosis should be used.

#### Familial combined hyperlipidaemia (FCH)

*Scientific background:* This is the most common of the severe hyperlipidaemias, with a prevalence of perhaps 1/100.<sup>205</sup> FCH is likely to be more polygenic/multifactorial than FH. A major gene determining the FCH phenotype has been found in Finnish families, identified as the gene for upstream regulatory factor 1 (*USF1*)—a major controller of lipid and glucose homeostasis.<sup>206</sup>

Despite no specific mutation within the *USF1* gene being identified in FCH patients, a common haplotype composed of several SNPs is associated with risk of developing FCH.<sup>207</sup>

*Practical aspects:* Because of their high CHD risk, patients with FCH should be treated with lipid-lowering therapy and lifestyle advice. There is currently little experience to support the clinical utility of cascade testing to identify affected relatives, but this is likely to be beneficial.

#### Familial high-density lipoprotein deficiency syndromes

*Scientific background:* The inverse and independent association between HDL cholesterol and the risk of fatal and non-fatal CHD events has been established by clinical and epidemiological studies. A low HDL cholesterol level < 35 mg/dL (0.9 mmol/L) has become part of the multiparametric algorithms used for CVD risk estimation.<sup>185,186</sup>

Patients with HDL cholesterol levels below the 5th percentile within a given population can be assumed to have monogenic HDL deficiency.<sup>208</sup>

*Practical aspects:* Rule out secondary causes and perform a careful physical examination in patients with the virtual absence of HDL. Family studies should be initiated, to demonstrate the vertical transmission of the low HDL cholesterol phenotype. Since currently there is no routinely used drug available to increase HDL cholesterol levels in patients with familial low HDL cholesterol, these patients should be treated for additional risk factors.

### New imaging methods to detect asymptomatic individuals at high risk for cardiovascular events

#### Scientific background

One of the major objectives of a CVD detection programme should be to identify those apparently healthy individuals who have asymptomatic arterial disease in order to slow the progression of atherosclerotic disease, to induce regression, and in particular to reduce the risk of clinical manifestations. The revolution in technology has clearly influenced the decision making of cardiovascular patients, and this can be clearly applied to the early detection of the disease even in asymptomatic patients.

For coronary artery disease, the consequences of coronary atherosclerosis can be objectively assessed non-invasively, using a variety of techniques such as bicycle or treadmill exercise ECG testing, stress echocardiography, or radio-nuclide scintigraphy. These techniques are routinely used in diagnostic work-up programmes in the clinic; they have rarely been used in the population as screening tools. More recently, new techniques have become available to detect coronary lesions.



MRI has been evaluated as a means of assessing the presence or absence of coronary artery stenosis. The value of this technique in detecting coronary artery stenosis is still in question. Sensitivity, specificity, and robustness of this technique are not high enough to perform screening for coronary stenoses in asymptomatic people.

A potentially more useful approach for risk stratification is to perform *in vivo* imaging of the arterial wall using MRI. *In vitro*, MRI is able to differentiate between the plaque components of carotid, aortic, and coronary artery specimens obtained at autopsy. For the present moment, MRI is a promising research tool, but its use is limited to only a small number of research laboratories at this time. Thus, MRI is not yet appropriate for use in identifying patients at high risk for coronary artery disease.

Coronary calcifications represent atherosclerosis of coronary arteries. Normally, they occur exclusively as atherosclerotic lesions within the intima layer and are not found in healthy coronary vessel walls. On the other hand, atherosclerotic diseased coronary arteries do not necessarily always show calcifications. The extent of coronary calcifications correlates with the extent of the total coronary plaque burden. It should be noted that coronary calcification is an indicator neither for stability nor instability of an atherosclerotic plaque.

Recent developments in technology of the classic CT resulted in multislice CT devices.<sup>215</sup> With the use of MS-CT it is possible to obtain a clear definition of the coronary vessels in most patients. However, the highest value of this technique seems to be its negative predictive value, reaching close to 98% in some studies. This very high negative predictive value of the technique leads to the consideration of using MS-CT for screening in certain subsets of the high risk population. Still, we need prospective studies to determine clearly which population may benefit most from this technology.

Although calcium scanning is widely applied today, it should not be uncritically used as a screening method. There is a need for prospective studies that will show the clear benefit on each individual subgroups in which an MS-CT scan is useful.

Population-based studies have shown a correlation between the severity of atherosclerosis in one arterial territory and involvement of other arteries. Atherosclerotic lesions of carotid arteries in the legs are more accessible for non-invasive examinations than those in coronary or intra-cerebral arteries. Therefore, early detection of arterial disease in apparently healthy individuals has also focused on the peripheral arterial territory and on the carotid arteries. Recently, plaque characteristics as assessed by carotid ultrasound were found to be predictive of subsequent cerebral ischaemic events. Patients with echolucent stenotic plaques had a much higher risk of stroke and cerebrovascular events than subjects with other plaque types.

An ankle-brachial index (ABI)  $<0.9$  reflects  $\geq 50\%$  stenosis between the aorta and the distal leg arteries. Because of its high sensitivity and specificity (both  $>90\%$ ), an ABI  $>0.90$  is considered a reliable sign of peripheral vascular disease. 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.

Recently it has been shown that the extent of atherosclerosis of retinal arteries correlates with the extent of the total coronary plaque burden. Atherosclerosis of retinal arteries also strongly correlates with plasma total cholesterol, LDL cholesterol, triglycerides, and apoprotein B levels. Since ophthalmoscopy is a non-invasive technique, is easy to perform, and has no adverse effects, it might be used to detect asymptomatic individuals at high risk for cardiovascular events.<sup>216,217</sup>

## Gender issues: cardiovascular disease prevention in women

### Scientific background

More women than men die from CVD, although they do so at an older age. CHD is slightly more common as a cause of death in women, and stroke markedly more common. In contrast, breast cancer accounts for only 3% of all deaths in women. CVD risk in women is deferred by 10 years compared with that of men. A 55-year-old woman is identical in terms of risk to a 45-year-old man. The decline in CVD mortality in recent years has been greater in men than in women, and CVD incidence has actually increased in women, especially in the oldest groups.<sup>209,210</sup>

- Systolic hypertension becomes more frequent in older women.
- The use of oral contraceptives increases the CVD risk associated with smoking.
- Total cholesterol levels peak at around 60 years of age in women, about 10 years later than in men.<sup>211</sup>
- Diabetes carries a considerably greater risk of fatal CVD in women.
- Obesity is more prevalent in middle-aged and elderly women.

In general, women are disadvantaged at all stages of the clinical evolution of CVD.<sup>212</sup> Risk management advice, particularly with regard to drug therapy, is hampered by defective evidence, as women are frequently under-represented in therapeutic trials, and there may be gender differences in therapeutic response.<sup>213</sup> Aspirin reduces the risk of stroke in women but not the risk of an AMI.<sup>214</sup> For women without CVD, lipid lowering may not affect total or CHD mortality. For women with known CVD, treatment of hyperlipidemia is effective in reducing CHD events, CHD mortality, non-fatal MI, and revascularization, but does not affect total mortality.

### Practical aspects

- (1) European and national public health policy needs to address the problem of inadequate recognition of the size of the problem of CVD in women and to reflect this through publicity and education of both the public and the medical profession.
- (2) Clinicians should make a specific point of assessing risk in female patients.
- (3) The principles of total risk estimation and management are the same for both sexes, with particular emphasis on the evaluation of smoking, overweight, the use of oral contraceptives, and glucose tolerance in women.

- (4) A low absolute risk in a young woman may conceal a large relative risk that will result in high absolute risk as she ages. Therefore, effective management of lifestyle change is in general more important than drug treatment in order to avoid a high absolute risk in older life.
- (5) Extrapolating the results of lipid-lowering trials to young or middle-aged women without other risk factors may lead to substantial overuse of cholesterol-lowering drugs.
- (6) Hormone replacement therapy has not been associated with a reduction in cardiovascular risk, although it might be indicated for menopausal symptomatic relief.

## Renal impairment as a risk factor in cardiovascular disease prevention

### Renal impairment and cardiovascular risk

- Risk of CVD rises progressively from microalbuminuria with preserved GFR to end-stage renal disease, when it is 20–30x that of the general population
- Applies to apparently healthy people and to those with hypertension, CVD, and heart failure
- Associated with high blood pressure, hyperlipidaemia, metabolic syndrome, uric acid, homocysteine, and anaemia
- Particularly vigorous risk factor control needed

### Scientific background

Renal impairment is associated with the development of CVD and death. The increased risk is already present by the time microalbuminuria develops. The risk progressively increases as renal function deteriorates, and end-stage renal disease (ESRD) is associated with a CVD risk up to 20–30 times that of the general population.<sup>218</sup> The association between impaired renal function and increased CVD risk is seen in the general population, hypertensives, and patients with pre-existing CVD. The development of renal impairment is associated with risk factors including age, hypertension, dyslipidaemia, and the metabolic syndrome, which are also CVD risk factors.<sup>219,220</sup> Therefore, the two diseases can develop in parallel. Once ESRD has developed, other factors such as alterations in calcium phosphate homeostasis and anaemia also contribute to CVD risk.<sup>221,222</sup> In heart failure patients, renal function is independently associated with risk of death, CVD death, and hospitalization.

### Practical aspects: management

The estimated glomerular filtration rate (eGFR) and presence of either microalbuminuria (30–300 mg/24 h) or macroalbuminuria (>300 mg/24 h) are used to assess the stage of renal impairment. An eGFR <60 mL/min is

associated with significant CVD risk. Microalbuminuria often accompanies reduced eGFR, and the combination of the two is associated with an additive effect on CVD risk.

An early attempt to control CVD risk factors in patients with renal impairment is needed. Patients with renal impairment and CHD or heart failure may not be treated with all appropriate medications.<sup>223</sup> Particular attention to ensuring these patients are prescribed all necessary therapeutic interventions will improve survival.<sup>224</sup>

## Cardioprotective drug therapy

### Scientific background

The use of prophylactic drugs which have been shown to reduce morbidity and mortality in clinical trials should be considered, in addition to drugs used for treatment of elevated blood pressure, lipids, and glucose.

### Antiplatelet therapies

In patients with atherosclerotic disease, platelet-modifying drugs result in a significant reduction in all causes of mortality, vascular mortality, and non-fatal MI and stroke.<sup>225</sup> Addition of clopidogrel has been proven to be beneficial in acute coronary syndromes.<sup>226</sup> In chronic stable atherosclerotic disease, combination of aspirin and clopidogrel is not associated with a significant benefit in terms of MI, stroke, or CVD death, but is associated with an increased bleeding risk. In asymptomatic individuals, aspirin reduced MI and death from CHD, but increased haemorrhagic strokes and gastrointestinal (GI) bleeding.

### β-Blockers

Meta-analyses have demonstrated the benefit of β-blockers in those post-MI, in terms of all-cause mortality, reinfarction, and CHD death.<sup>87</sup> (DAVIT trials show that verapamil can be considered as an alternative in those post-MI with contraindications to β-blockers.) In CHF patients, β-blocker therapy has been shown to reduce all-cause mortality.

### ACE inhibitors

In heart failure patients or those with left ventricular dysfunction, ACE inhibitors have been shown to reduce risk of death, recurrent MI, and progression to persistent heart failure.<sup>227</sup> ACE inhibitor treatment also reduced risk of death after AMI. Studies assessing the benefit of ACE inhibitors in those with stable coronary disease without left ventricular dysfunction have yielded varying results. In PROGRESS, patients with previous CVD, BP lowering using ACE inhibitor/diuretic combination showed significant reductions in stroke and coronary disease events. In HOPE, in diabetics aged over 55 with one additional risk factor and without left ventricular dysfunction or uncontrolled hypertension, ACE inhibitors reduced risk of death and MI.<sup>106</sup>

### Anticoagulation

Systemic anticoagulation is indicated, particularly in combination with aspirin, in patients post-MI whose risk of thromboembolism is increased.<sup>228</sup>

## Practical aspects: management

### When to prescribe cardioprotective drugs in addition to those used to treat blood pressure, lipids, and diabetes

- Aspirin for virtually all with established CVD, and in persons at >10% SCORE risk once blood pressure has been controlled
- $\beta$ -blockers after myocardial infarction and, in carefully titrated doses, in those with heart failure
- ACE inhibitors in those with left ventricular dysfunction and in diabetic subjects with hypertension or nephropathy
- Anticoagulants in those at increased risk of thromboembolic events, particularly atrial fibrillation

### Antiplatelet therapy: aspirin

Indicated in:

- (1) All with established CVD (including diabetics) unless contra-indicated; lifelong treatment with low dose (75–150 mg daily) is recommended.
- (2) Asymptomatic individuals, aspirin should only be considered when the 10-year risk of CVD mortality is markedly increased and the BP is controlled.

### Antiplatelet therapy: clopidogrel

Indicated in:

- (1) Cases of aspirin allergy.
- (2) In addition to aspirin, in acute coronary syndromes for 9–12 months.
- (3) Combination of aspirin and clopidogrel is not routinely recommended in chronic stable atherosclerotic disease.

### $\beta$ -Blockers

Indicated in:

- (1) Patients post-MI (including diabetics).
- (2) CHF patients.
- (3) Angina to relieve the symptoms of myocardial ischaemia.
- (4) As an antihypertensive (other antihypertensives preferred in diabetics).

### ACE inhibitors

Indicated in:

- (1) Treatment of heart failure or left ventricular dysfunction.
- (2) Diabetics to reduce BP to target or if type 1 (and possibly type 2) nephropathy.
- (3) To reduce BP to target. Angiotensin receptor blockers can be used in patients with an indication for ACE inhibitors but who cannot tolerate ACE inhibitors.

### Calcium channel blockers

Indicated for:

- (1) Reducing BP to target.
- (2) Post-MI if  $\beta$ -blockers are contra-indicated.

**Table 11** Indications for antithrombotic therapy in patients with atrial fibrillation

Risk category	Recommended therapy	
No risk factors	Aspirin, 81 to 325 mg daily	
One moderate risk factor	Aspirin, 81 to 325 mg daily, or warfarin (INR 2.0 to 3.0, target 2.5)	
Any high risk factor or more than 1 moderate risk factor	Warfarin (INR 2.0 to 3.0, target 2.5) <sup>a</sup>	
Less validated or weaker risk factors	Moderate risk factors	High risk factors
Female gender	Age $\geq$ 75 years	Previous stroke, TIA or embolism
Age 65 to 74 y	Hypertension	Mitral stenosis
Coronary artery disease	Heart failure	Prosthetic heart valve <sup>a</sup>
Thyrotoxicosis	LV ejection fraction 35% or less	
	Diabetes mellitus	

<sup>a</sup>If mechanical valve, target international normalized ratio (INR) greater than 2.5.

<sup>b</sup>LV = left ventricular; TIA = transient ischaemic attack.

### Diuretics

Indicated for:

- (1) Reducing BP to target. (Alternative antihypertensives are preferred in type 2 diabetes or those at high risk of developing type 2 diabetes.)

### Anticoagulation

Indicated in:

- (1) History of thromboembolic events
- (2) Left ventricular thrombus
- (3) Persistent or paroxysmal atrial fibrillation – see ESC guidelines on atrial fibrillation<sup>229</sup> (Table 11)
- (4) Consider in:
  - (i) large anterior MI
  - (ii) left ventricular aneurysm
  - (iii) paroxysmal tachyarrhythmias
  - (iv) post-MI CHF

## Implementation strategies

### Scientific background

Several studies have been carried out to evaluate the effect of different implementation strategies of guidelines on clinical practice.

EUROASPIRE I (1995/96)<sup>39</sup> and II (2000/01)<sup>38</sup> surveys both showed a high prevalence of unhealthy lifestyles, modifiable risk factors, and inadequate use of drug therapies to achieve



BP and lipid goals in patients with established CHD, with wide variations in medical practice between countries.

Many surveys have shown similar results, some also showing great variance between countries.

There is considerable potential throughout Europe in coronary patients and their families to raise the standard of preventive cardiology through more lifestyle intervention, control of other risk factors and optimal use of prophylactic drug therapies in order to reduce the risk of recurrent disease and death. Similar results have been shown for stroke.

Although the availability of systematic reviews and guidelines reduces the need for doctors to read original studies, they still find it difficult to keep up with such syntheses. Even if doctors are aware of the evidence and are willing to change, to alter well established patterns of care is difficult, especially if the clinical environment is not conducive to change.

### Barriers to the implementation of guidelines

It is essential that clinical guidelines are in concordance with priorities in the health system and with ethical values most clinicians can agree upon. If not, this may be an important reason why many clinicians do not follow guidelines.<sup>230</sup>

The implementation of these guidelines should be based on national surveys to adjust them to the stratification of risk factors and premature CVD death in the individual country and bring them in accordance with priorities set by the health authorities and the professional bodies. The workload put on the health system should be affordable and should not imply that resources should be allocated to prevention strategies when the outcome for the population is better by alternative use.

#### What would make the practice of CVD prevention easier?

- Simple, clear, credible guidelines
- Sufficient time
- Positively helpful government policies (defined prevention strategy with resources, and incentives including remuneration for prevention as well as treatment)
- Educational policies that facilitate patient adherence to advice

Analyses of the barriers to changing practice, have shown that obstacles to change in practice can arise at different stages in the health care organization, or the wider environment. Most theories on implementation of evidence in health care emphasize the importance of developing a good understanding of such obstacles to develop an effective intervention.

### Doctor–patient relationship

The preventive interventions must be based on a patient-centred approach, where the doctor pays full attention to appraise and meet the patient's concerns, beliefs, and

values, and respects the patient's choice even if it is not in concordance with the doctor's first proposal. The changing of lifestyle or taking medication often means for the rest of the patient's life, so the decision must be owned by the patient. Therefore, treatment goals should be set in collaboration with the patient, taking into account the values and priorities of the patient. If the treatment goals are unaffordable, it may lead to frustration and clinical neglect, both by the doctor and by the patient. The doctor should explore the patient's important values, beliefs, and expectations regarding the prevention measures to be taken.

### Practical aspects

#### Important arenas for training

There is a need for training of doctors in patient-centred preventive care, with emphasis on

- patient-centred methods in the consultation process
- the motivation to change—how to support and strengthen the patient's decision to adopt healthy habits
- how to evaluate multifactorial risk and use risk charts
- how to communicate risk and the effects of interventions
- how to discuss treatment goals and follow-up.

### Implementation strategies

- (1) On the European (international) level:
  - (a) Publication of the guidelines in relevant journals.
  - (b) Presentation at international conferences arranged by the participating societies.
  - (c) Involvement in policy at European Union level through, for example, the Luxembourg Declaration and the development of the European Heart Health Charter.
- (2) On the national level:
  - (a) If not already existing, implementation demands a leading expert group of national organizations representing similar groups to the European Task Force. The group should have acceptance and support from national health authorities.
  - (b) Adjustment and application of national standards, in accordance with the European Guidelines.
  - (c) Further implementation should be organized by the National Colleges in accordance with the local needs, see below.

Implementation strategies should consist of a package of different measures, working in combination:

- (1) A public health approach, with emphasis on smoking cessation, healthier food and better access to physical activity in all ages should be implemented—to support and complement the individual-oriented high risk strategy of doctor-initiated prevention.
- (2) A public information campaign of the Fourth Joint CVD Prevention Guidelines and the corresponding national Guidelines with two main topics:
  - (a) Information on the concept of multiple risk assessment and treatment, and the intervention thresholds.
  - (b) What people can do to reduce risk.

The message should encourage people at high risk to realize their risk and go to see a doctor, but should reassure people with low risk that they can stay healthy without the doctor's help.

(3) An information and education programme aimed at practising doctors (GPs, internists, and others). It should consist of a selection of the effective strategies mentioned above:

- (a) Lectures and CME activities with interactive participation.
- (b) Audit and feedback, preferably combined with outreach visits by trained colleagues.
- (c) Dissemination of electronic versions, applicable to hand-held equipment.
- (d) Dissemination of simple, one-sheet versions of risk algorithms and treatment recommendations.



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