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European guidelines on cardiovascular disease prevention in clinical practice

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Preamble

Guidelines and Expert Consensus documents aim to present all the relevant evidence on a particular issue in order to help physicians to weigh the benefits and risks of a particular diagnostic or therapeutic procedure. They should be helpful in everyday clinical decision-making. A great number of Guidelines and Expert Consensus Documents have been issued in recent years by different organisations, the European Society of Cardiology (ESC) and by other related societies. By means of links to web sites of National Societies several hundred guidelines are available. This profusion can put at stake the authority and validity of guidelines, which can only be guaranteed if they

have been developed by an unquestionable decision-making process. This is one of the reasons why the ESC and others have issued recommendations for formulating and issuing Guidelines and Expert Consensus Documents. In spite of the fact that standards for issuing good quality Guidelines and Expert Consensus Documents are well defined, recent surveys of Guidelines and Expert Consensus Documents published in peer-reviewed journals between 1985 and 1998 have shown that methodological standards were not complied with in the vast majority of cases. It is therefore of great importance that guidelines and recommendations are presented in formats that are easily interpreted. Subsequently, their

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implementation programmes must also be well conducted. Attempts have been made to determine whether guidelines improve the quality of clinical practice and the utilisation of health resources.

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 of these Guidelines and Expert Consensus Documents or statements.

1) Executive summary

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

- CVD is the major cause of premature death in most European populations; it is an important source of disability and contributes in large part to the escalating costs of health care
- the underlying pathology is usually atherosclerosis, which develops insidiously over many years and is usually advanced by the time symptoms occur
- death, myocardial infarction and stroke nevertheless frequently occur suddenly and before medical care is available, and many therapeutic interventions are therefore inapplicable or palliative
- the mass occurrence of CVD relates strongly to lifestyles and modifiable physiological factors
- risk factor modifications have been unequivocally shown to reduce mortality and morbidity, especially in people with either unrecognised or recognised CVD.

Cardiovascular disease is generally due to a combination of several risk factors, and, in recognition of the multifactorial nature of this group of diseases, the European Atherosclerosis Society, the European Society of Cardiology, and the European Society of Hypertension agreed in the early 1990s to collaborate to suggest guidelines for prevention of coronary heart disease in clinical practice. The result was a set of recommendations published in 1994. A revision of these early guidelines was published in 1998 by the Second Joint Task Force, which set lifestyle, risk factor and therapeutic goals for coronary prevention. In this 2nd report the original three societies were joined by the European Society of General Practice/Family Medicine, the European Heart Network and by the International Society of Behavioural Medicine.

Since completion of this report, important new data have been published. Therefore the Third Joint Task Force provides a second revision of the joint European guidelines. The Task Force has been joined by the European Association for the Study of Diabetes and by the International Diabetes Federation Europe. These new guidelines differ from the previous ones in several important aspects:

- 1) From coronary heart disease (CHD) to CVD prevention. The etiology of myocardial infarction, ischaemic stroke and peripheral arterial disease is similar, and,

indeed, recent intervention trials have shown that several forms of therapy prevent not only coronary events and revascularisations but also ischaemic stroke and peripheral artery disease. Hence, decisions about whether to initiate specific preventive action can be guided by estimation of risk of suffering any such vascular event, not just a coronary event, and preventive actions can be expected to reduce risk, not only of coronary heart disease, but also of stroke and peripheral arterial disease.

- 2) In order to assess the risk for development of CVD different multifactorial risk models have been developed. The Task Force recommends using the SCORE Model and Risk Charts as recently developed. The risk assessment using the SCORE database can be easily adapted to national conditions, resources and priorities and takes into account the heterogeneity in CVD mortality across European populations. A core element of the model is that risk is now defined in terms of the absolute 10 year probability of developing a fatal cardiovascular event.
- 3) Explicit clinical priorities. As in the 1994 and 1998 recommendations, the first priority of practitioners is patients with established cardiovascular disease and subjects who are at high risk of developing CVD. Subjects at high risk may also be recognised by new imaging techniques which allow visualisation of sub-clinical atherosclerosis.
- 4) All new and published knowledge from the field of preventive cardiology was considered, particularly results from recent clinical trials showing clinical benefit of dietary changes, of good management of risk factors and of the prophylactic use of certain drugs. This includes data on usage of certain drugs in elderly subjects and in subjects at high risk with a relatively low total cholesterol level.

These guidelines are specifically intended to encourage the development of national guidance on cardiovascular disease prevention. Implementation of these guidelines is possible only through collaboration between very different professional groups at the national level. The guidelines should be considered as the framework in which all necessary adaptations can be made in order to reflect different political, economic, social and medical circumstances.

The Third Joint Task Force recognises that these guidelines, which are targeted at those at highest CVD risk, should be complemented by strategies aimed at whole

populations at the national and European level as a contribution to a public health policy to reduce the enormous burden of cardiovascular disease in European populations.

Medical priorities

Preventive efforts are most efficient when they are directed at those at highest risk. The present recommendations therefore define the following priorities for CVD prevention in clinical practice:

- 1) Patients with established coronary heart disease, peripheral artery disease and cerebrovascular atherosclerotic disease.
- 2) Asymptomatic individuals who are at high risk of developing atherosclerotic cardiovascular diseases because of:
 - a) Multiple risk factors resulting in a 10 year risk of $\geq 5\%$ now (or if extrapolated to age 60) for developing a fatal CVD event.
 - b) Markedly raised levels of single risk factors: cholesterol ≥ 8 mmol/l (320 mg/dl), LDL cholesterol ≥ 6 mmol/l (240 mg/dl), blood pressure $\geq 180/110$ mmHg.
 - c) Diabetes type 2 and diabetes type 1 with microalbuminuria.
- 3) Close relatives of:
 - a) Patients with early onset atherosclerotic cardiovascular disease.
 - b) Asymptomatic individuals at particularly high risk.
- 4) Other individuals encountered in routine clinical practice.

Objectives of cardiovascular prevention

The objectives of these guidelines are to reduce the incidence of first or recurrent clinical events due to coronary heart disease, ischaemic stroke and peripheral artery disease. The focus is prevention of disability and early deaths. To this end, the current guidelines address the role of lifestyle changes, the management of major cardiovascular risk factors and the use of different prophylactic drug therapies in the prevention of clinical CVD.

Intermediate end-points such as left ventricular hypertrophy, carotid artery plaques and to a lesser extent endothelial dysfunction as well as alteration in the electrical stability of the myocardium have been shown to increase the risk of cardiovascular morbidity, indicating that sub-clinical organ damage has clinical relevance. Accordingly such measurements may be incorporated in more sophisticated models to assess the risk for future CVD events.

Total cardiovascular risk as a guide to preventive strategies: the SCORE system

Patients with established cardiovascular disease have declared themselves to be at high total risk of a further vascular event. Therefore, they require the most intensive lifestyle intervention, and where appropriate drug therapies.

In asymptomatic, apparently healthy subjects, preventive actions should be guided in accordance with the total CVD risk level. Those at highest total risk should be identified and targeted for intensive lifestyle interventions and when appropriate, drug therapies. Several models have been developed to assess the risk for CVD in asymptomatic subjects. Using different combinations of risk factors these models are all based on a multifactorial risk analysis in populations which have been followed for several years.

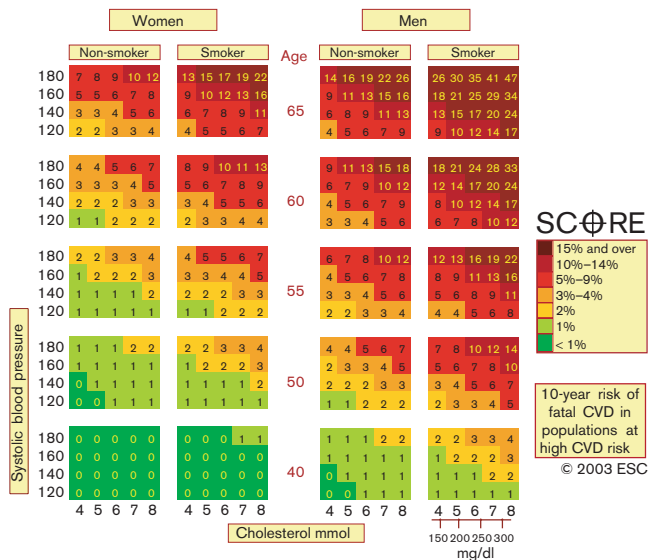
These guidelines recommend a new model for total risk estimation based on the SCORE (Systematic Coronary Risk Evaluation) system. The new risk chart based on the SCORE study represents several advantages compared to the previous chart. The SCORE risk assessment system is derived from a large dataset of prospective European studies and predicts any kind of fatal atherosclerotic end-point i.e. fatal CVD events over a 10 year period. In SCORE the following risk factors are integrated: gender, age, smoking, systolic blood pressure (SBP) and either total cholesterol or the cholesterol/HDL ratio. Since this chart predicts fatal events the threshold for being at high risk is defined as $\geq 5\%$, instead of the previous $\geq 20\%$ in charts using a composite coronary endpoint. Using SCORE it is now possible to produce risk charts tailored for individual countries provided reliable national mortality information is available.

Practitioners should use total CVD risk estimates when decisions are taken to intensify preventive actions i.e. when dietary advice should be more specified, when the physical activity prescription should be more individualized, when drugs should be prescribed, dosages adapted or combinations started to control risk factors. These decisions should usually not be based on the level of any one risk factor alone, neither should they be linked to only one arbitrary cut point from the continuous total CVD risk distribution.

Total CVD risk can easily be derived from printed charts (see illustrations in Figs 1 and 2 and instructions on how to use the charts in Tables 1 and 2) or from the web where in addition the SCORECARD system will provide physicians and patients with information on how total risk can be reduced by interventions (both lifestyles and drugs) that have been proven to be efficacious and safe in descriptive cohort studies and/or in randomised controlled trials.

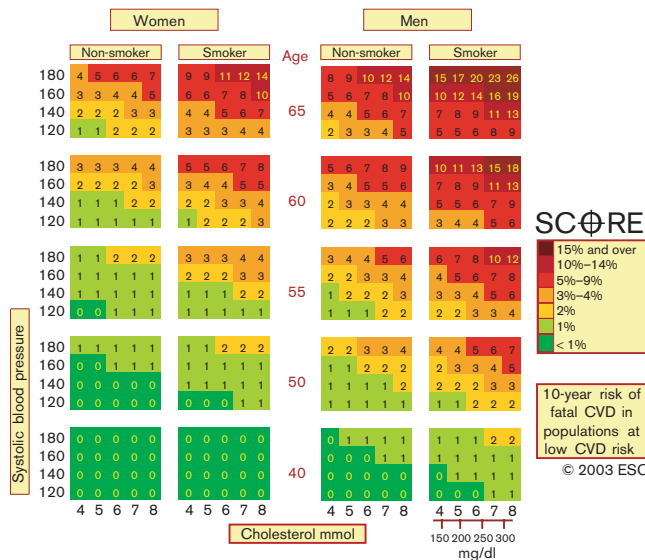
Both the SCORE and the SCORECARD system also allows the estimation of total CVD risk to be projected to age 60 which may be of particular importance for guiding young adults at low absolute risk at the age of 20 or 30 but already with an unhealthy risk profile which will put them at much higher risk when they grow older. Furthermore, both systems allow the use of relative risk estimates which, in addition to total absolute risk, may be of interest in particular cases.

Fig. 1



Ten year risk of fatal CVD in high risk regions of Europe by gender, age, systolic blood pressure, total cholesterol and smoking status

Fig. 2



Ten year risk of fatal CVD in low risk regions of Europe by gender, age, systolic blood pressure, total cholesterol and smoking status

Table 1 Instructions on how to use the charts

- The low risk chart should be used in Belgium, France, Greece, Italy, Luxembourg, Spain, Switzerland and Portugal; the high risk chart should be used in all other countries of Europe
- To estimate a person's total ten year risk of CVD death, find the table for their gender, smoking status and age. Within the table find the cell nearest to the person's systolic blood pressure (mmHg) and total cholesterol (mmol/l or mg/dl)
- The effect of lifetime exposure to risk factors can be seen by following the table upwards. This can be used when advising younger people
- Low risk individuals should be offered advice to maintain their low risk status. Those who are at 5% risk or higher or will reach this level in middle age should be given maximal attention
- To define a person's relative risk, compare their risk category with that of a non smoking person of the same age and gender, systolic blood pressure < 140 mmHg and total cholesterol < 5 mmol/l (190 mg/dl)
- The chart can be used to give some indications of the effect of changes from one risk category to another, for example when the subject stops smoking or reduces other risk factors

Table 2 Qualifiers

Note that total CVD risk may be higher than indicated in the chart:

- as the person approaches the next age category
- in asymptomatic subjects with pre-clinical evidence of atherosclerosis (eg CT scan, ultrasonography)
- in subjects with a strong family history of premature CVD
- in subjects with low HDL cholesterol levels, with raised triglyceride levels, with impaired glucose tolerance, and with raised levels of C-reactive protein, fibrinogen, homocysteine, apolipoprotein B or Lp(a)
- in obese and sedentary subjects

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

Magnetic resonance imaging (MRI) allows *in vivo* imaging of the arterial wall and differentiation of plaque components. Coronary calcifications can be detected and quantified by computed tomography (EB-CT or MS-CT). The resulting calcium score is an important parameter to detect asymptomatic individuals at high risk for future CVD events, independent of the traditional risk factors. Furthermore, carotid intima-media thickness, measured by ultrasound, is a risk factor for cardiac events and stroke. Left ventricular hypertrophy, either detected by ECG or by echocardiography has also been shown to be an independent risk factor for CVD mortality and morbidity in

hypertensive subjects. Each of these measurements has its limitations, yet they may be included in sophisticated models for risk assessment, which may be more precise than current models based on classical risk factors.

Management of CVD risk in clinical practice Behavioural risk factors

Changes in many patterns of individual behaviour are necessary in a large majority of patients with established CVD or at high risk of CVD, but recent surveys suggest a serious gap between recommendations for behavioural change and the advice actually provided by physicians in routine clinical practice. The management of behavioural risk factors is similar for patients with CVD and high risk

people, but changing risk behaviours (unhealthy diet, smoking, sedentary lifestyle), which have lasted for many years, needs a professional approach.

For many people it can be difficult to change lifestyle according to a physician's advice. This difficulty pertains especially to people and patients who are socially and economically disadvantaged, who exercise little control over a monotonous and unrewarding job, who are in a stressful family situation, or who live alone and lack social support.

Moreover, negative emotions, including depression, anger and hostility, may constitute barriers to preventive efforts, both in patients and in high-risk people.

The physician can recognise these barriers by using a simple set of questions. Although the physician's awareness is helpful and in some cases sufficient, persistent and severe negative emotions can require expert consultation and behavioural or pharmacological treatment. As psychosocial risk factors are independent of standard risk factors, efforts to relieve stress and counteract social isolation should be emphasised whenever possible.

Strategic steps that may be used to enhance the effectiveness of behavioural counselling include (adapted from the Report of the US Preventive Services Task Force):

- develop a therapeutic alliance with the patient
- ensure that patients understand the relationship between behaviour, health and disease
- help patients to understand the barriers to behavioural change
- gain commitments from patients to behavioural change
- involve patients in identifying and selecting the risk factors to change
- use a combination of strategies including reinforcement of patients' own capacity for change
- design a lifestyle modification plan
- monitor progress through follow-up contact
- involve other health care staff wherever possible

Stop smoking tobacco

All smokers should be professionally encouraged to permanently stop smoking all forms of tobacco. Strategies that may help can be summarised into the following 5 A's:

- **Ask:** systematically identify all smokers at every opportunity
- **Assess:** determine the patient's degree of addiction and his/her readiness to cease smoking
- **Advise:** urge strongly all smokers to quit
- **Assist:** agree on a smoking cessation strategy including behavioural counselling, nicotine replacement therapy and/or pharmacological intervention
- **Arrange** a schedule of follow-up visits

Make healthy food choices

Making healthy food choices is an integral part of total risk management. All individuals should receive professional advice on food and food choices to compose a diet associated with the lowest risk of cardiovascular disease.

A sound diet reduces risk by several mechanisms including weight reduction, lowering of blood pressure, effects on lipids, control of glucose and reduction of the propensity to thrombosis.

General recommendations (to be specified according to local culture):

- foods should be varied, and energy intake must be adjusted to maintain ideal body weight
- the consumption of the following foods should be encouraged: fruits and vegetables, whole grain cereals and bread, low fat dairy products, fish and lean meat.
- oily fish and omega-3-fatty acids have particular protective properties
- total fat intake should account for no more than 30% of energy intake, and intake of saturated fats should not exceed a third of total fat intake. The intake of cholesterol should be less than 300 mg/day
- in an isocaloric diet, saturated fat can be replaced partly by complex carbohydrates, partly by monounsaturated and polyunsaturated fats from vegetables and marine animals

Patients with arterial hypertension, diabetes, and hypercholesterolemia or other dyslipidemias should receive specialist dietary advice.

Increase physical activity

Physical activity should be promoted in all age groups – from children to the elderly – and all patients and high risk people should be professionally encouraged and supported to increase their physical activity safely to the level associated with the lowest risk of CVD. Although the goal is at least half an hour of physical activity on most days of the week, more moderate activity is also associated with health benefits.

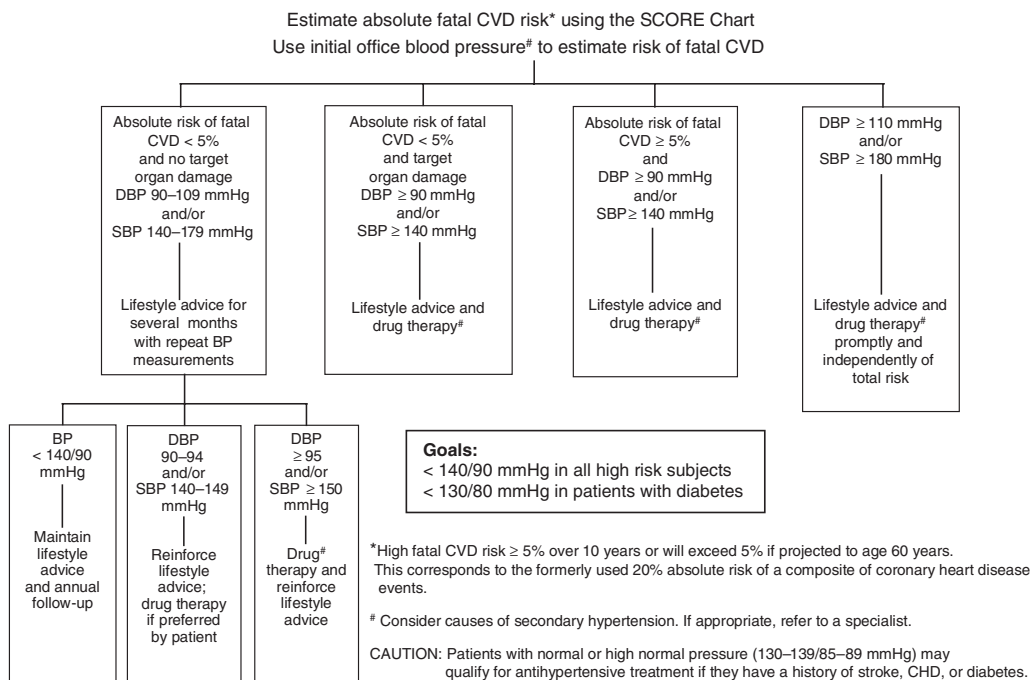
Healthy people should be advised to choose enjoyable activities which fit into their daily routine, preferably 30–45 min, 4–5 times weekly at 60–75% of the average maximum heart rate. For patients with established CVD, advice must be based on a comprehensive clinical judgement including the results of an exercise test. Detailed recommendations for CVD patients have been given by other expert committees.

Management of other risk factors

Overweight and obesity

Avoiding overweight or reducing existing overweight is important in patients with established CVD as well as in

Fig. 3



Guide to blood pressure management.

high risk people. Weight reduction is strongly recommended for obese people (BMI ≥ 30 kg/m²) or overweight individuals (BMI ≥ 25 and < 30 kg/m²) and for those with increased abdominal fat as indicated by waist circumference > 102 cm in men and > 88 cm in women.

Success in weight reduction is more likely if supported professionally, but it also requires strong motivation by the individual.

Blood pressure

The risk of cardiovascular diseases increases continuously as blood pressure rises from levels that are considered to be within the normal range. The decision to start treatment, however, depends not only on the level of blood pressure, but also on an assessment of total cardiovascular risk and the presence or absence of target organ damage. In patients with established CVD the choice of antihypertensive drugs depends on the underlying cardiovascular disease.

A guide to blood pressure management in asymptomatic people is given in Fig. 3. The decision to lower blood pressure with drugs depends not only on the total cardiovascular risk but also on presence of target organ damage. Drug therapy should be initiated promptly in individuals with a sustained SBP ≥ 180 mmHg and/or a diastolic blood pressure (DBP) ≥ 110 mmHg regardless of their total cardiovascular risk assessment.

Individuals at high risk of developing CVD with sustained SBP of ≥ 140 mmHg and/or DBP ≥ 90 mmHg also require drug therapy. For such individuals, drugs should be used to lower blood pressure to < 140/90 mmHg. Similar elevation of blood pressure in low risk people without target organ damage should be followed closely, and lifestyle advice should be given. Drug treatment might be considered after asking the patients' preference.

With few exceptions, individuals with SBP < 140 mmHg and/or DBP < 90 mmHg do not need drug therapy. Patients with a high or very high cardiovascular risk profile and patients with diabetes can benefit from reducing blood pressure below the goal of SBP < 140 mmHg and/or DBP < 90 mmHg.

Antihypertensive drugs should not only lower blood pressure effectively. They should have a favourable safety profile and be able to reduce cardiovascular morbidity and mortality.

Five classes of drugs currently meet these requirements: diuretics, beta-blockers, ACE inhibitors, calcium-channel blockers and angiotensin II antagonists.

In many clinical trials blood pressure control has been achieved by the combination of two or even three drugs, and drug combination therapy is often also necessary in routine clinical practice. In patients with several diseases

requiring drug therapy, polypharmacy can become a major problem and good clinical management is required to resolve it. In all patients, blood pressure reduction should be obtained gradually. For most patients, the goal of therapy is blood pressure less than 140/90 mmHg, but for patients with diabetes and individuals at high total CVD risk, the blood pressure goal should be lower.

Plasma lipids

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). For patients with clinically established CVD and patients with diabetes the treatment goals should be lower: total cholesterol < 4.5 mmol/l (175 mg/dl) and LDL cholesterol < 2.5 mmol/l (100 mg/dl).

No specific treatment goals are defined for HDL cholesterol and triglycerides, but concentrations of HDL cholesterol and triglycerides are used as markers of increased risk. HDL cholesterol < 1.0 mmol/l (< 40 mg/dl) in men and < 1.2 mmol/l (46 mg/dl) in women, and similarly, fasting triglycerides > 1.7 mmol/l (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.

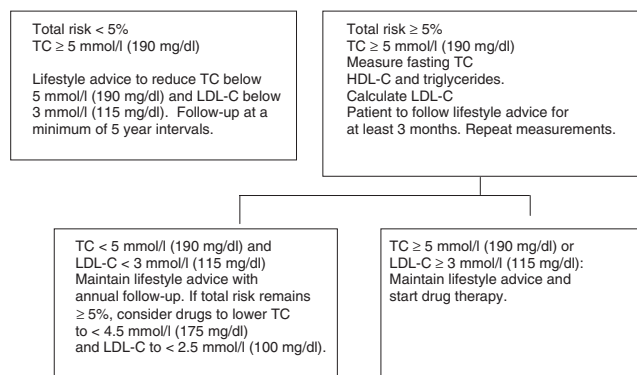
Asymptomatic people at high multifactorial risk of developing cardiovascular disease, whose untreated values of total and LDL cholesterol are already close to 5 and 3 mmol/l respectively, seem to benefit from further reduction of total cholesterol to < 4.5 mmol/l (175 mg/dl), and from further reduction of LDL cholesterol to < 2.5 mmol/l (100 mg/dl), with moderate doses of lipid lowering drugs. However, these lower values are not goals of therapy for patients with higher untreated values because high-dose therapy, the merits of which have not yet been documented, would be needed to reach such lower goals.

In asymptomatic individuals (see Fig. 4), 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 concerning a balanced diet, 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 hypercholesterolemia, since total cholesterol > 8 mmol/l (320 mg/dl) and LDL cholesterol > 6 mmol/l (240 mg/dl) by definition places a patient at high total risk of CVD.

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 should be performed, and intensive lifestyle advice, par-

Fig. 4

Estimate total fatal CVD risk using the SCORE chart. Use initial total cholesterol (or ratio of total to HDL cholesterol) to estimate risk. (TC: total cholesterol, LDL-C: LDL cholesterol, HDL-C: HDL cholesterol)



Guide to lipid management in asymptomatic subjects.

ticularly dietary advice, should be given. If values of total and LDL cholesterol fall below 5 mmol/l (190 mg/dl) and 3 mmol/l (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 (175 mg/dl) and to lower LDL cholesterol to < 2.5 mmol/l (100 mg/dl). As stated earlier, these lower values are not goals of therapy for patients with higher untreated values.

The first clinical trials which documented the clinical benefits (improved survival) of lipid lowering therapy with statins were restricted to individuals < 70 years and total cholesterol > 5 mmol/l. Recently published trials indicate that such treatment can also be effective in the elderly and in subjects with lower cholesterol levels.

Some individuals require combination therapy. In patients with several diseases requiring drug therapy, polypharmacy can become a major problem and good clinical management is required to resolve it. In some patients, goals cannot be reached even on maximal therapy, but they will still benefit from treatment to the extent to which cholesterol has been lowered.

Diabetes

It has been demonstrated that progression to diabetes can be prevented or delayed by lifestyle intervention in individuals with impaired glucose tolerance.

In patients with type 1 and type 2 diabetes, there is convincing evidence from randomised controlled trials that

Table 3 Treatment goals in patients with type 2 diabetes

		Goal
HbA _{1c} (DCCT-standardized)	HbA _{1c} (%)	≤ 6.1
Venous plasma glucose	Fasting/preprandial	≤ 6.0
	mmol/l mg/dl	< 110
Self-monitored blood glucose	Fasting/preprandial	4.0–5.0
	mmol/l	70–90
	mg/dl	
	Postprandial	4.0–7.5
	mmol/l	70–135
	mg/dl	< 130/80
Blood pressure	mmHg	< 4.5 (175)
Total cholesterol	mmol/l (mg/dl)	< 2.5 (100)
LDL cholesterol	mmol/l (mg/dl)	

good metabolic control prevents microvascular complications. Regarding the prevention of cardiovascular events, there are also good reasons 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 aiming at good glucose control.

Drug therapy must be added if these measures do not lead to a sufficient reduction of hyperglycemia. Recommended treatment targets for type 2 diabetes are given in Table 3.

Treatment goals for blood pressure and lipids are generally more ambitious in patients with diabetes (see above).

The metabolic syndrome

In clinical practice, the definition given by the US National Cholesterol Education Program can be provisionally used for the identification of individuals with the metabolic syndrome. The diagnosis of the metabolic syndrome is made, when three or more of the following features are present:

- 1) Waist circumference > 102 cm in males, > 88 cm in females.
- 2) Serum triglycerides ≥ 1.7 mmol/l (≥ 150 mg/dl).
- 3) HDL cholesterol < 1 mmol/l (< 40 mg/dl) in males or < 1.3 mmol/l (< 50 mg/dl) in females.
- 4) Blood pressure ≥ 130/85 mm Hg.
- 5) Plasma glucose ≥ 6.1 mmol/l (≥ 110 mg/dl).

People with the metabolic syndrome are usually at high risk of cardiovascular disease. Lifestyle has a strong influence on all the components of the metabolic syndrome and therefore the main emphasis 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 blood pressure, dyslipidemia and hyperglycemia (in the diabetic range) may, however, need additional drug treatment as recommended in the present guidelines.

Other prophylactic drug therapies

In addition to drugs needed to treat blood pressure, lipids and diabetes, the following drug classes should also be considered in the prevention of CVD in clinical practice:

- aspirin or other platelet-modifying drugs in virtually all patients with clinically established CVD
- betablockers in patients following myocardial infarction or with left ventricular dysfunction due to CHD
- ACE inhibitors in patients with symptoms or signs of left ventricular dysfunction due to CHD and/or arterial hypertension
- anti-coagulants in those patients with CHD who are at increased risk of thromboembolic events

In asymptomatic high risk people there is evidence that low dose aspirin can reduce the risk of cardiovascular events in people with diabetes, in people with well controlled hypertension and in men at high multifactorial CVD risk.

Screening close relatives

Close relatives of patients with premature coronary heart disease (men < 55 years and women < 65 years) and persons who belong to families with familial hypercholesterolemia or other inherited dyslipidemias should be examined for cardiovascular risk factors, because all of these persons are at increased risk of developing cardiovascular disease.

2) Introduction

2.1 The scope of the problem: past and future

CVDs are the major causes of death in adults in their middle and older years in most European countries. Cardiovascular diseases result in substantial disability and loss of productivity and contribute in large part to the escalating costs of healthcare, especially in the presence of an ageing population.

CVD (including CHD and stroke) accounts for 49% of all deaths in Europe and for 30% of all deaths before the age of 65 years. One in eight men and one in 17 women die from CVD before the age of 65 years [1].

In 2000 CVD also accounted for 22% of all disability-adjusted life years (DALY's) lost in Europe [2]. Furthermore, there are enormous differences in disease experience between countries and within countries over time.

There is up to 10-fold difference in premature CVD mortality between western Europe and countries in central and eastern Europe, with the highest rates in the east.

For the period 1970–2000 major differences in the annual change of CVD mortality in men aged 45–74 years were observed between countries. But in almost all countries, even in those where the age standardised mortality rates

from CVD have gradually declined, the prevalence of CVD is on the increase. CVD is strongly related to age and this together with an improved CVD treatment and survival rate means that an increasing number of subjects in Europe are living with impaired cardiovascular health. Europe has the oldest population in the world. In the coming years this demographic picture will rapidly change to even higher ages with a projection of one in three Europeans aged 65 and over by 2050. Therefore the prevalence of patients who are at risk for recurrent disease (reinfarction, recurrent stroke, heart failure, sudden death) is on the increase and the overall burden of CVD is anticipated to increase in the forthcoming decade.

Female gender is considered as a protection against CVD. Indeed, the age-specific incidence rates are 3–6 times higher in men compared to women [1,3] but attenuation of this difference occurs in all populations at older age. Nevertheless, even in older age incidence rates for women are lower than for men.

However, it should be realised that CVD kills ultimately as many women as men. The onset of CVD events may be delayed by some 10 years but when CVD strike women, their prognosis is not better, on the contrary [4,5]. Although differences exist between genders in the prevalence of certain risk factors, all of the major risk factors raise the risk of CVD also in women. Of special interest is the synergetic effect of oral contraceptives and smoking on CVD risk. The relative importance of certain factors, such as diabetes and triglycerides, may also be slightly different between genders. From all this the Task Force concluded that one should use gender specific risk estimation models but make no distinction in preventive actions when it comes to lifestyle changes or risk factor management.

There are also marked socio-economic gradients in CHD morbidity and mortality within European countries [6,7]. These differences are partly explained by socio-economic differences in conventional risk factors, such as smoking, blood pressure, blood cholesterol and glucose. However, specific psychosocial factors related to the work environment and reflecting social support and coping style are believed to be rather potent in explaining the socio-economic gradient.

In seeking to prevent CVD in European populations the objectives are to reduce morbidity, and also mortality, and thus improve quality of life and the chances of a longer life expectancy. The development of CVD is strongly related to lifestyle characteristics and associated risk factors and there is overwhelming scientific evidence that lifestyle modification and risk factor reduction can retard the development of CVD both before and after the occurrence of a clinical event. In 1994 a Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of

Hypertension published joint recommendations on the prevention of CHD in clinical practice [8]. These joint recommendations represented the first important step in specialist collaboration to make common cause on the prevention of coronary disease. Whilst recognising the powerful political, economic and social determinants of atherosclerotic diseases in populations, and therefore the need for a population strategy in coronary prevention, the Joint European Societies recommendations focused on prevention of CHD in clinical practice.

The highest priority for prevention was given to patients with established coronary heart disease or other atherosclerotic disease. The next priority for prevention was given to apparently healthy subjects at high risk for developing CHD. In this context the risk was defined as multifactorial, namely the total risk of developing CHD based on an assessment of all major risk factors, and coronary risk charts were developed for the physician to estimate total risk at a glance.

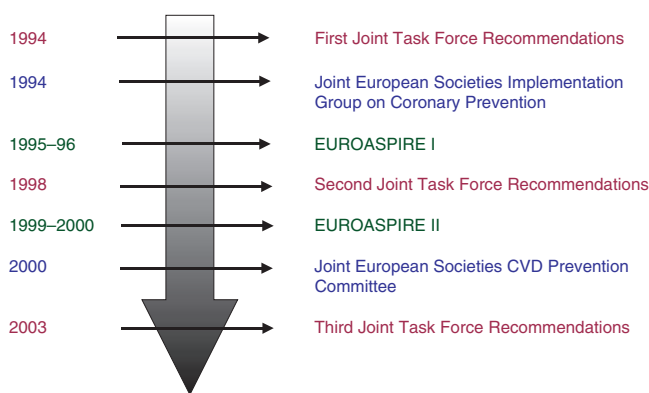
These charts illustrate how an individual with a number of modest risk factors may be at considerably greater risk than another person with one very high risk factor. Traditionally, risk factor guidelines have been concerned with unifactorial assessment – in the management of hypertension, hyperlipidaemia or diabetes – and this has resulted in undue emphasis being placed on individually high risk factors rather than the overall level of risk based on a combination of risk factors. Therefore, these joint recommendations emphasised the importance of matching the intensity of risk factor management with the hazard for developing CVD, based on a multifactorial total CVD risk assessment, rather than the level of one risk factor alone. This approach acknowledges three important facts: that CHD has a multifactorial aetiology, that risk factors can have a multiplicative effect, and that as physicians we are dealing with the whole person, not with isolated risk factors.

The third priority for prevention was the close relatives of patients with early onset CHD, or other vascular disease, and those of high risk individuals in the population. The relatives are themselves at increased risk of cardiovascular disease compared to the general population, particularly the first degree blood relatives of patients with premature CHD. In addition, members of a family, and especially an adult partner, sharing the same household, can favourably influence the adoption of a healthy lifestyle.

Developments in CVD prevention in Europe from 1994 onwards are summarised in Fig. 5.

After the publication of the First Joint Task force report in 1994 a Joint Implementation Group has taken several initiatives to disseminate the recommendations: to have

Fig. 5



Recent developments in CVD prevention in Europe.

them adapted or adopted by National Task Forces and translated into different European languages with the ultimate goal of having them implemented in daily clinical practice.

In 1995 a European survey was undertaken to describe how secondary prevention was realised in practice (EUROASPIRE I). These results demonstrate an unacceptable gap between the recommendations and what was achieved in the patients [9].

A Second Joint Task Force was then asked to update the report of 1994 and this was done in close collaboration with an even larger number of Scientific Societies by adding to the original three the European Heart Network, the European Society for General Practice/Family Medicine and the International Society of Behavioural Medicine.

These new recommendations, presented at the ESC Congress in Vienna in 1998 and published shortly after [10], unite secondary and primary prevention by setting common lifestyles and risk factor goals for patients with established atherothrombotic disease and for those at high risk of developing these diseases.

To promote the development of national guidance on coronary prevention a European Forum was convened at the Heart House in February 1999 which was attended by 162 representatives from 41 European countries. At the same time a European Coordinator for CHD prevention was appointed by the ESC. Regional follow-up meetings on coronary prevention have been organised in Prague, Barcelona, Munster, Bucharest and Istanbul. There are many examples of national efforts illustrating a common approach to the principles of prevention based on the Second Joint Task Force recommendations but with appropriate modifications to reflect the different ways in which medicine is practised in Europe.

This concept of devolved responsibility is central to the European efforts as each country needs to develop multi-professional national guidance on coronary prevention and to ensure it is effectively communicated, implemented and evaluated.

In the meantime the importance of comprehensive risk factor intervention in patients with established atherothrombotic disease and in high risk subjects has been emphasised by several other expert groups in different places of the world [11-14]. Thus, there is unanimity on the clinical priorities for coronary prevention and the need to target those at highest risk on the basis of a comprehensive multifactorial risk assessment.

Although this valuable consensus has emerged between professional societies, the reality of clinical practice has fallen short of these recommendations.

In 1999-2000 a second EUROASPIRE survey was carried out in 15 European countries [15]. These results show that there is still considerable potential to improve risk factor management in coronary patients; the comparison with results from EUROASPIRE I reveals little improvement over time [16].

All this underlines the need for a continuous process of guidance, implementation and evaluation. This is not new in medicine; it was already realised by pioneers in cardiology such as René Laënnec who introduced cardiac auscultation. He stated 200 years ago:

“Do not fear to repeat what has already been said. Men need the truth dinned to their ears many times and from all sides. The first rumour makes them prick up their ears, the second registers and the third enters.”

*Laënnec, RTH (1781-1826)
Regius Professor of Medicine, Collège de France.*

When in 2001 the Third Joint Task Force was asked to update the previous recommendations, the platform of Scientific Societies that makes the Third Joint Task Force was enlarged by inviting the European Association for the Study of Diabetes and the International Diabetes Federation Europe to join.

Indeed, it is now well recognised that atherothrombotic diseases are the greatest health threat to patients with diabetes. In EUROASPIRE II 20% of all patients were known diabetics, another 9% were undetected with diabetes and another 23% had impaired glucose tolerance [15]. The mortality follow-up of the EUROASPIRE I cohort revealed that apart from smoking, diabetes is the most important risk factor for total, CVD and CHD mortality in these coronary patients (EUROASPIRE I Mortality follow-up study, unpublished results).

The Third Joint Task Force decided at the beginning to focus not only on the prevention of coronary heart disease but also on the prevention of other clinical manifestations of atherothrombotic disease including thrombotic stroke and peripheral artery disease.

The recommendations are dealing with prevention of cardiovascular disease in clinical practice. However, the Third Task force recognises the importance of population strategies at the national, regional and global level. This approach is complementary to the prevention in clinical practice and is briefly addressed in the introduction.

One of the criticisms of the recommendations of the First and Second Joint Task Forces is related to the model that was used for total coronary risk estimation. This was based on the results from the Framingham Study [17]. The strengths and limitations of this model for application in populations with very different absolute risk of CHD are well known. The Third Task Force decided at the start of its work to adopt the results of SCORE for total CHD and CVD risk estimations [18]. The advantage of this is elaborated in the document.

Furthermore, the Third Joint Task Force has considered all new and published knowledge from the fields of preventive cardiology; a more systematic approach towards evidence based medicine has been applied. On the other hand we have tried to keep important steps such as risk estimation and risk factor management simple and user friendly. Finally, the need for an ongoing update was felt and initiatives are taken to answer that.

These guidelines represent the view of the Third Joint Task Force on CVD prevention in clinical practice. They were endorsed by the different societies. Health professionals are expected to take them fully into account when exercising their clinical judgement. These guidelines do not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with that patient, and when appropriate and necessary, the patient's guardian or carer.

2.2 Rationale for prevention of CVD

The overall objective of CVD prevention both in patients with clinically established CVD and in high risk subjects is the same:

- to reduce the risk of major cardiovascular events and thereby reduce premature disability and morbidity and prolong survival and quality of life.

There is a wealth of evidence that certain lifestyles related to diet, physical activity and tobacco smoking, have an important role as causes of the mass occurrence of cardiovascular diseases in populations and as con-

Table 4 Lifestyles and characteristics associated with the risk of cardiovascular events

Lifestyles	Biochemical or physiological characteristics	Personal characteristics
Diet	Arterial blood pressure	Age
Tobacco smoking	Total cholesterol	Sex
Physical activity	(LDL cholesterol)	Family history
	HDL cholesterol	of premature CVD
	Triglycerides	Personal history
	Glycaemia/diabetes	of CVD
	Overweight/obesity	Genetic markers
	Thrombogenic factors	
	Markers of chronic inflammation	

tributing factors to the risk of CVD in individuals within populations. These lifestyles lead in many subjects to adverse changes in biochemical and physiological characteristics that enhance the development of atherosclerosis and associated thrombotic complications (Table 4).

It becomes more and more apparent that all these factors interact with each other in a rather complex way. Intrauterine and early life influences may contribute to the development of an adverse cardiovascular risk factor profile in later life. Genetic susceptibility is important but appears to mediate largely through the interaction between genetic factors and the environment.

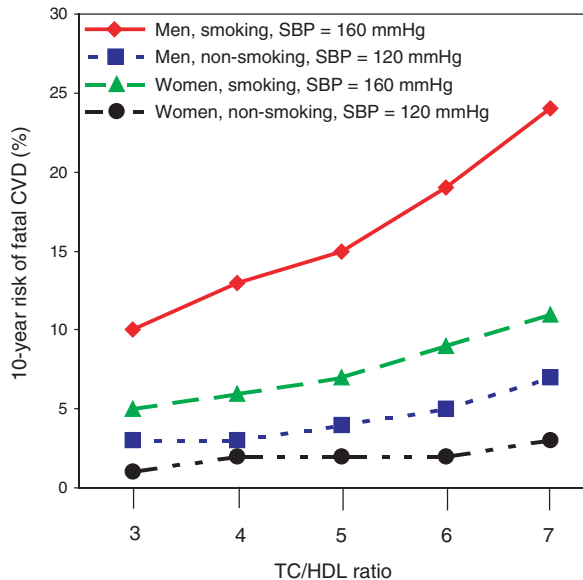
For a proper assessment of the total cardiovascular risk in an individual, the presence or absence and the degree of severity of each individual risk factor has to be considered, and in addition the potential impact of modifying existing risk factors has to be assessed against the background set by non-modifiable risk characteristics of each individual.

Figure 6, based on results from the SCORE project, illustrates the multiplicative effects of risk factors. In an asymptomatic man or woman, aged 60 years of age, with a moderate elevation of the total cholesterol/HDL cholesterol ratio but without other risk factors such as smoking and arterial hypertension, the risk of developing a fatal cardiovascular event over the next ten years may be lower than in a man or woman of the same age, but with the other risk factors even when the TC/HDL C ratio is lower. Therefore the concept of total CVD risk estimation has been proposed as an important principle in the development of preventive strategies aiming at a good match between the intensity of intervention versus magnitude of CVD risk. This principle has now been accepted and adopted by a great variety of expert groups.

2.3 Prevention strategies

The 1982 report of the World Health Organization Expert Committee on Prevention of Coronary Heart Disease considered that a comprehensive action for coronary heart disease prevention has to include three components: 1) **a population strategy** – for altering, in the entire population,

Fig. 6



The multiplicative effects of risk factors.

those lifestyle and environmental factors, and their social and economic determinants, that are the underlying causes of the mass occurrence of coronary heart disease, 2) **a high-risk strategy** – identification of high risk individuals, and action to reduce their risk factor levels and, 3) **secondary prevention** – prevention of recurrent coronary heart disease events and progression of the disease in patients with clinically established coronary heart disease.

The last two correspond to prevention activities targeted at individuals and should be an integral part of everyday clinical practice. They are the focus of this report. The population strategy targets entire communities and should be an integral part of food and nutrition, transport, employment, education, health and other policies at European, national, regional and local levels. This is in accordance with the notion that even small changes at population level, through the large number of individuals involved, will affect the health of many people [19]. It

also acknowledges the fact that an individual already suffering from atherosclerotic cardiovascular disease, or otherwise at high risk for a novel manifestation of a cardiovascular disease, will benefit from therapeutic and lifestyle interventions, as proven by the results of numerous primary and secondary intervention trials.

Table 5 summarises the most important distinctions between the population and the clinical prevention strategies.

2.3.1 The population strategy

The population and the clinical approaches are complementary, but the population strategy is fundamental to reduce the burden of cardiovascular diseases in Europe. Populations are not the mere sum of individuals but bear a higher level of complex social organizations. Thus, the population approach is not meant to reduce the incidence of cardiovascular diseases by medically treating all individuals of a population one by one, something unfeasible even for the richest of nations and unsafe for many individuals. On the contrary, it is meant to target the social and economic determinants of disease through political action.

A preventive population strategy can be successful, as demonstrated in Finland [21], but is critically dependent on the number of participating parties such as governments, insurance companies, the food industry, etc. The national cardiac and other professional societies, however, should not underestimate the impact that they as professionals can make in the public domain.

The population strategy must lead eventually to changes in lifestyle: a reduction in the number of people who smoke, an increased number of people eating a balanced diet, and an increased number of people who are physically active. These goals can be reached in many different ways, but political will and development of ad-hoc policies and investments at European, national, regional and local levels are a condition without which they could not be achieved.

The Task Force therefore endorses and recommends support for the implementation of the International Framework Convention for Tobacco Control, as initiated

Table 5 Main differences between the population and the clinical prevention strategies

Prevention in clinical practice	Population strategy: health promotion
The aim is the prevention of onset and progression of disease in an individual	The aim is the reduction of incidence of disease in the population
The targets are individuals	The target is the community
Quantitative methods	Use quantitative and qualitative methods
Instruments are medical interventions	Instruments are development and implementation of local, national and international policies
The standards are randomized controlled trials	Standards are both outcome and process evaluation
Less than therapeutic dose is unacceptable	Preventive dose rarely applied
Easier to treat an individual	Difficult to scale up health promotion programs that reach the whole population
Outcomes of interventions are to change individuals	Outcomes are to change the social norms, environments and behaviour of entire populations
Interventions can focus on most factors relevant to the outcome	Interventions take on social determinants external to the community

Modified from the OSAKA declaration [20]

Table 6 Proposed Tobacco Control Measures*

- 1) Related to the reduction of demand for tobacco
 - 1.1 Price and tax measures
 - 1.2 Non-price measures
 - 1.3 Protection from passive smoking by regulation
 - 1.4 Regulation of contents of tobacco products
 - 1.5 Regulation of tobacco products disclosures
 - 1.6 Packaging and labelling of tobacco products
 - 1.7 Education, communication, training and public awareness
 - 1.8 Advertising, promotion and sponsorship of tobacco products
 - 1.9 Demand reduction measures concerning tobacco dependence and cessation
- 2) Related to the reduction of the supply of tobacco
 - 2.1 Illicit trade (smuggling) in tobacco products
 - 2.2 Sales to minors
 - 2.3 Elimination of tobacco subsidies and provision of government support for other economically viable activities

*Based on: Intergovernmental negotiating body on the WHO framework convention on tobacco control, A/FCTC/INB 5/2, 25 June 2002, www.who.int/gb/fctc [22].

Table 7 Population dietary goals

- a) Goals* for which scientific evidence is strong and public health gain large
 1. Saturated fat and trans fats:
 - less than 10% of dietary energy from saturated fat, and
 - less than 2% of energy from trans fats
 2. Fruit and vegetables:
 - more than 400 g/day
 3. Salt:
 - less than 6 g/day
 4. Obesity and overweight:
 - BMI < 25 kg/m²
 - PAL[†] of more than 1.75 PAL
- b) Goals* for which scientific evidence is moderate and public health gain moderate
 5. Total fat
 - less than 30% of energy
 6. Polyunsaturated fat
 - n-6 polyunsaturated fat: 4–8% energy
 - n-3 polyunsaturated fat: 2 g/day of linolenic acid and 200 mg/day of very long chain fatty acids
- c) Goals* for which scientific evidence is weaker and public health gain smaller
 7. Dietary fibre: more than 25 g/day (or 3 MJ) of dietary fibre and more than 55% of energy from complex carbohydrates
 8. Folate from food: more than 400 µg/day
 9. Sugary foods: four or fewer occasions per day

*From: European Heart Network's Nutrition Expert Group – Food, Nutrition and Cardiovascular Disease Prevention in the European Region: Challenges for the New Millennium. European Heart Network, May 2002, www.ehnheart.org [23].

†Physical activity level (PAL) as the ratio of total energy expenditure to estimate basal metabolic rate. A PAL of 1.75 is equivalent to 60 min/day of moderate activity or 30 min/day of vigorous activity.

by the WHO (www.who.int), the European Commission Directive on Tobacco Control and the Warsaw Declaration for a Tobacco-free Europe (Table 6) [22], the Population Dietary and Physical Activity Goals, as formulated by the European Heart Network (Table 7) [23], and the WHO recommendations for the prevention of obesity. For a broader perspective, the Task Force refers to the Osaka Declaration, jointly endorsed by the 5th International Conference on Preventive Cardiology and the 4th International Heart Health Conference (www.med.mun.ca/chhdbc/pdf) (Table 8) [20].

Important social inequalities affect cardiovascular health. A population strategy should ensure specific actions to

Table 8 Health, Economics and Political Action*

- 1) Increase awareness of governments that the health agenda is not just an agenda of the 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, 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.

*Based on: Declaration of the fourth International Heart Health Conference, Osaka (Japan), May 2001, www.med.mun.ca/chhdbc/public.htm [20].

tackle the determinants of these inequalities. In addition, the population strategy has to ensure equity of access to everybody for preventive advice, diagnostic and therapeutic interventions, in order to reduce the social differences in health.

The goal of the Task Force is to make recommendations at the European level. However, the national societies are invited to actively contribute to develop national preventive population strategies, in partnership with their respective governments, other professional societies and the civil society, dependent on their own national needs and possibilities.

2.3.2 Prevention in clinical practice

The population strategy is aiming at a shift in the distributions of risk factors towards more favourable levels. Indeed, it has been shown that most cases of coronary heart disease and stroke occur among the large number of people in whom risk factors are only modestly elevated [24].

Within a favourable public health scenario, prevention work in clinical practice becomes much easier because changing lifestyle towards healthier directions is socially easier.

Patients with symptomatic coronary heart disease present to family physicians, cardiologists and other specialists and this offers a unique opportunity for preventive action. High risk persons could also be identified in clinical practice because of their lifestyle, e.g. smoking cigarettes or obesity, or through the detection of hypertension, hyperlipidemia, diabetes, or a combination of risk factors. A substantial number of such persons can be identified in daily clinical practice without having to resort to comprehensive cardiovascular screening of the population.

Preventive action directed at patients with established coronary heart disease, stroke or heart failure and at high risk persons should lead to contact with their families and other blood relatives for risk assessment and preventive advice among them, with preventive intervention if necessary. This type of action has, in addition, the advantage of contributing to the awareness and spread of preventive knowledge throughout the society as a whole.

Priorities in cardiovascular prevention in clinical practice

In European countries the number of patients with established cardiovascular diseases is large and the number of otherwise healthy individuals but at high risk of cardiovascular diseases is enormous. Understandably the medical community may feel the tasks of CVD prevention are too overwhelming and impossible to accomplish in their everyday work. On the other hand, the cost-benefit balance of interventions, especially the costs related to unwanted side effects of long-term treatments varies as the scale of cardiovascular risk goes down. Therefore, it is useful to define priorities for CVD prevention in clinical practice, and these are set out in Table 9. This list of priorities proposes the order in which preventive action should be directed to the different groups listed, because with limited resources a full-scale action directed to all groups potentially needing preventive advice is not possible within a short period of time. As soon as progress has been made in the top priority groups, action may be directed to groups with a lower rank order in the list. The highest priority is given to patients with clinically established CVD, and the next place to healthy individuals at high risk of CVD. Patients who present with CVD have already declared themselves to be at high-risk of a further major ischaemic event and therefore additional action is needed to reduce their modifiable risk factors. The next priority is given to the many healthy individuals at high CVD risk who have already been identified or will be detected in the context of daily clinical practice. Preventive action may then be extended to assessment of risk factor levels in the closest relatives of patients with early-onset CVD and those of high risk individuals, especially when familiar hyperlipidemia is suspected. Finally, physicians should also act as opinion leaders to inform and influence public health decisions which can facilitate healthy lifestyles at a population level in their society. They should try to avoid giving messages based on fear but adopt lucid messages instead, or even better establish alliances with communication experts.

2.4 How to evaluate the scientific evidence

Evidence Based Medicine (EBM) has been defined as the integration of individual clinical expertise with the

Table 9 Priorities of cardiovascular disease prevention in clinical practice

- | | |
|----|---|
| 1) | Patients with established coronary heart disease, peripheral artery disease and cerebrovascular atherosclerotic disease |
| 2) | Asymptomatic individuals who are at high risk of developing atherosclerotic cardiovascular disease because of: <ol style="list-style-type: none"> Multiple risk factors resulting in a 10 year risk of $\geq 5\%$ now (or if extrapolated to age 60) for developing a fatal cardiovascular event Markedly raised levels of single risk factors: cholesterol ≥ 8 mmol/l (320 mg/dl), LDL cholesterol ≥ 6 mmol/l (240 mg/dl), blood pressure $\geq 180/110$ mmHg Diabetes Type 2 and diabetes Type 1 with microalbuminuria |
| 3) | Close relatives (first degree relatives) of <ol style="list-style-type: none"> Patients with early-onset atherosclerotic cardiovascular disease Asymptomatic individuals at particularly high risk |
| 4. | Other individuals met in connection with ordinary clinical practice |

Table 10 Desirable attributes of clinical guidelines

Attribute of guideline	How to test the attribute
Validity	Are the health benefits/costs predicted achieved in practice?
Reproducibility	Does the same evidence and method result in the same recommendation?
Reliability	Do the guidelines result in the same interpretation in similar clinical circumstances?
Representative development	Were key groups affected by the guidelines involved in its development?
Clinical applicability	Can evidence be used to define the patients involved or does this require judgement?
Clinical flexibility	Are exceptions permitted and are patient preferences considered?
Clarity	Are the guidelines unambiguous and user friendly?
Meticulous documentation	Who does this, what assumptions are made, what evidence has been collected, and what methods have been used in compiling the guidelines?
Scheduled review	When and how will guidelines be reviewed and updated if necessary?

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 [25]. Despite a decade of educational effort, it is rare for clinicians to practice EBM as intended, with many considering that the major issue is finding the evidence [26].

This report aims to provide guidelines under the auspices of the Third Task Force of the European and other Societies on Cardiovascular Disease Prevention. We would wish 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 [27]. It has been shown that guidelines based on credible evidence are more likely to be adopted [28]. The desirable attributes of clinical guidelines have been discussed and are shown in Table 10 [29].

It is often apparent that despite using high quality evidence derived from systematic reviews of randomised controlled trials, predicted benefits are not achieved [30]. This is due to the diminishing impact of efficacious interventions when applied in the real world due to problems of poor coverage, professional compliance and patient adherence to the intervention [31]. In some circumstances, only those at high risk of poor outcomes will benefit owing to the trade off between hazards and benefits of treatment being adverse among low risk people [32]. There is evidence that the reproducibility and reliability of guidelines is influenced by the composition of the group producing the guidelines. Grimshaw and Russell comment that a surgical panel found more indications for surgery than a "balanced" panel [29]. Perhaps of greater concern are the findings of a study that compared five different guidelines on cholesterol testing and con-

cluded that “the more clinicians were involved in the development process, the less the guidelines reflected the research evidence.” [33]. Clinicians may well be more aware of the need for clinical applicability, flexibility and clarity in guidelines, that are necessary if they are to be implemented, and are well aware of the highly selected patients that enter clinical trials. These different goals may conflict resulting in guidelines that do not follow the research evidence. However, formal study of the ways in which the research evidence and clinical imperatives interact has not been conducted. In previous guidelines the link between evidence and recommendations has not always been apparent. In this new version we have aimed, where possible, to make the relationship between evidence and recommendation more transparent.

Adherence to the notion that the “hierarchy of evidence” flows in a downward quality direction from a Cochrane systematic review, other systematic reviews, randomised controlled trials, non-randomised comparative studies, prospective observational studies, retrospective observational studies, finishing at case studies is often misplaced. Quality implies being fit for purpose – the best evidence to identify rare hazards of treatment is not a systematic review or a randomised controlled trial. Case reports may provide the first hint that a treatment is hazardous but require confirmation in either large prospective surveillance studies.

We have attempted to ensure that the most appropriate evidence is used to underpin recommendations. For population prevention programmes observational epidemiological findings are clearly of great importance in determining causality and in the cases of smoking and physical activity, randomised controlled trials to determine the benefits of these behaviours would be inordinately difficult to conduct and might even be misleading. Clearly, systematic reviews of observational studies are preferable to citation of single observational studies. For example, individual studies of the relationship between homocysteine and cardiovascular disease have demonstrated variable associations [33]. Pooling data can provide greater understanding of sources of heterogeneity introduced either by study design (e.g. case control versus cohort) or by the nature of the participants and will provide a more precise estimate of effect. However, it is important to be aware that this increased precision may be spurious if the control for confounding and other biases is weak in the index studies [34].

A further and growing concern in observational 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 randomised controlled trials have shown that the interventions may even be harmful [34,35]. Similar concerns have now become apparent with hormone replacement therapy that was

thought to confer benefits, but an early systematic review [36] showing adverse cardiovascular effects was ignored until recent randomised controlled trials of hormone replacement therapy confirmed this adverse effect.

A further concern is the nature of available evidence. Much of the evidence concerns drug treatments rather than lifestyle interventions or health system improvements. Since robust evidence from systematic reviews of randomised controlled trials exists for benefits of statins on cardiovascular disease outcomes [37], it is tempting to prefer this evidence over the much weaker evidence from studies of dietary fat reduction for the same outcomes [38].

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 [39], particularly in preventive cardiology where baseline rates of cardiovascular disease 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.

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

We have critically reviewed the relevant literature to answer each question posed. 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 [9,15].

3) Total risk estimation

Total risk in the context of these recommendations means the likelihood of a person developing a fatal cardiovascular event over a defined period of time.

Table 11 illustrates how risk factor management decisions should not be based on consideration of a single risk factor such as cholesterol alone; a women with cholesterol of 8 mmol/l can be at nine times lower risk than a similarly aged man with a cholesterol of 5 mmol/l if the latter smokes and is hypertensive.

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 evidence based management decisions.

This realisation led to the development of the risk chart published in the 1994 and 1998 recommendations [8,10]. This chart, developed from a concept pioneered by Anderson [17], used age, sex, smoking status, total cholesterol and SBP to estimate the risk of any coronary heart disease event, fatal or non fatal over the next ten years. A ten year risk of 20% or more was used arbitrarily as a threshold for intensified risk factor intervention.

There were several problems with this risk chart. Firstly, it was derived from American data from the Framingham project and the applicability of the risk chart to European populations was uncertain. Secondly, the dataset used for the chart was fairly small. Thirdly, the definition of non fatal endpoints differed from that used in many other studies making it difficult to validate the chart.

The risk chart presented in the present recommendations was developed as part of an EU Concerted Action Project [18] and aims to address these concerns. It has become known as the SCORE system.

The SCORE risk prediction system is derived from 12 European Cohort Studies and comprises over 200 000 persons, 3 million person years of observations and over 7000 fatal cardiovascular events. It differs from the previous risk prediction system in several important ways:

- Mortality rather than total events has been used as a primary endpoint because this allows risk to be calculated for countries or regions for which only mortality data are available. In addition, non fatal endpoints have been defined in different ways by different investigators and this makes it difficult to merge the results of different cohort studies.
- All atherosclerotic deaths (not just coronary heart disease) have been included in the risk model by using a calculation method that allows stroke deaths to be considered separately from coronary heart disease deaths if required. Stroke deaths may be proportionately more important in low risk populations.

Table 11 Examples of how other risk factors may negate the advantages of having a desirable cholesterol level. Risk figures refer to the risk of dying of cardiovascular disease over the next 10 years (based on results from SCORE [18])

Sex	Age (years)	Cholesterol (mmol/l)	BP (mmHg)	Smoking	Risk (%)
Female	60	8	120	0	2
Female	60	7	140	+	5
Male	60	6	160	0	8
Male	60	5	180	+	19

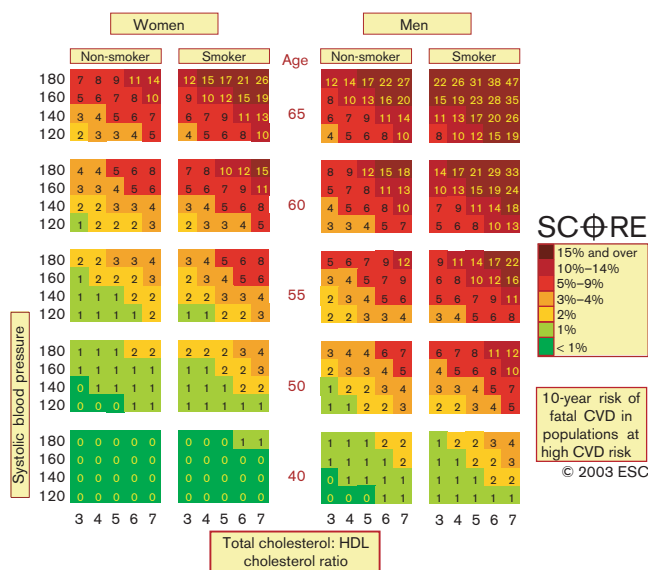
- The risk chart has been modified in several respects, notably in providing more detail in middle aged subjects where risk changes more rapidly with age.
- Separate charts have been prepared for higher and lower risk areas of Europe (see Figs 1 and 2). The low risk chart should be used in Belgium, France, Greece, Italy, Luxembourg, Spain, Switzerland and Portugal; the high risk chart should be used in all other countries of Europe. In the future it will be possible to produce individualised risk charts for individual countries, provided reliable mortality information is available.
- Separate charts have been prepared with the total cholesterol/HDL cholesterol ratio instead of total cholesterol (see Figs 7 and 8). There is almost no difference in the performance of these charts, and use of total cholesterol has the advantage that it is easier to relate to the results of therapeutic trials, most of which address cholesterol rather than the ratio. In Table 1 instructions are given on how to use these charts and in Table 2 qualifiers are highlighted that should be considered in estimating total CVD risk.

It should be stressed that the SCORE charts are specifically for use in subjects without known vascular disease. Subjects with clinical or investigational evidence of atherosclerotic vascular disease are already at high risk of vascular events and warrant intensive risk factor advice.

The SCORE chart has several functions:

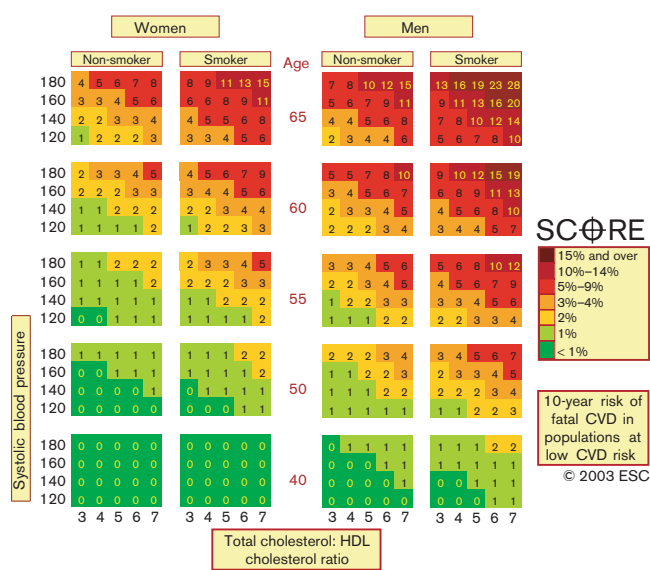
- An individual's risk of dying of cardiovascular disease over the next ten years can be read from the chart without any calculations.
- Although young people are generally at low risk, this will rise as age increases. The chart can be used by following the tables upward to illustrate the effects of lifetime risk by observing the increased risk with an increase in age. In general, risk will rise even further than indicated by the chart since risk factor levels will also tend to increase with age.
- Relative risk can readily be estimated by comparing the risk in one cell with that of a non smoking person of the same age and gender, systolic blood pressure < 140 mmHg and total cholesterol < 5 mmol/l (190 mg/dl).
- The chart can be used to give some indication of the effect of changes from one risk category to another, for example when the subject stops smoking or reduces other risk factors.

Fig. 7



Ten year risk of fatal CVD in **high risk** regions of Europe by gender, age, systolic blood pressure, total cholesterol/HDL cholesterol ratio and smoking status.

Fig. 8



Ten year risk of fatal CVD in **low risk** regions of Europe by gender, age, systolic blood pressure, total cholesterol/HDL cholesterol ratio and smoking status.

Even low risk individuals should be offered lifestyle advice to maintain their low risk status. In the chart, based on the Framingham study results, high risk was defined as a level of 20% or more. This would equate to a risk of approximately 5% or more in the present charts and anybody at or above this level would merit intensive risk factor advice.

4) Scientific evidence for risk estimation, risk factor modification and implementation programmes

4.1 Nutrition

4.1.1 Fatty acids and cholesterol

Food lipids are made up of 3 major classes of fatty acids (FA's): saturated (SFA's), monounsaturated (MUFA's) and polyunsaturated (PUFA's). This classification is based on the number of double bonds between carbon atoms. Fatty acids regulate cholesterol homeostasis and concentrations of blood lipoproteins. Besides, food FA's affect the levels of other cardiovascular risk factors, such as blood pressure, haemostasis and body weight through various mechanisms. In food, SFA's, MUFA's and PUFA's are mixed together [40], making the study of the effects of specific classes of FA's on cardiovascular outcomes considerably complex.

In the "Seven countries" study, the between cohorts comparison, showed that intake of total but mainly SFA's was associated with 10 and 25-year follow-up coronary mortality [41]. At the individual level in single cohort studies, only SFA's were related to coronary mortality. In

nutritional intervention studies, decrease of fat intake is associated with a relative or absolute increase in the intake of carbohydrates. In such circumstances, a decrease in LDL and HDL cholesterol levels and an increase in triglyceride concentrations is observed [42,43]. The effect on HDL cholesterol is attenuated when the subject loses weight [44] or when the carbohydrates are derived from food with high fibre content [45]. Finally, a diet with high fat content is dense in energy which may predispose to overweight and obesity. These in turn are two major causes for insulin resistance, diabetes and cardiovascular complications.

Saturated fatty acids

The sources of SFA's in human diet are mainly derived from animal products (i.e. meat and dairy products), oils used for cooking or ready-cooked meals from the food-processing industry (i.e. coconut and palm oils) and some home cooking fats (lard, hard margarines). In comparison with PUFA's, consumption of SFA's increases the concentration of LDL cholesterol.

The effect of reducing saturated fat intake on serum lipids depends on what the saturated fat is replaced with. Reducing saturated fat intake by a third and replacing with complex carbohydrate, polyunsaturated fat or monounsaturated fats results in mean changes in serum lipids in healthy volunteers as presented in Table 12 [46].

In randomised controlled trials of saturated fat reduction (either through replacement of saturated fat with other fats or with carbohydrates) only small effects on blood

Table 12 Effects of replacing dietary saturated fat with complex carbohydrates, polyunsaturated fats or monounsaturated fats

5% of total energy as saturated fat, replaced with:	Change in total serum cholesterol, mmol/l	Change in LDL cholesterol, mmol/l	Change in HDL cholesterol, mmol/l
Complex carbohydrate	-0.26	-0.18	-0.17
Polyunsaturated fats	-0.39	-0.29	-0.04
Monounsaturated fats	-0.24	-0.22	-0.04

lipids were observed, and little effect on mortality is seen. But in studies with at least 2 years follow-up, there was a significant reduction in cardiovascular events (rate ratio 0.76, 95% CI 0.65–0.90) [38]. It should be noted that most studies included in the review replaced saturated fat with mono- or polyunsaturated fats, rather than with carbohydrates.

SFA's make up a heterogeneous group of molecules with different metabolic properties [47]. In comparison with oleic acid (18 : 1), FA's with 12, 14 and 16 carbon atoms increase LDL cholesterol, whereas stearic acid (18 : 0) decreases HDL cholesterol [48–50]. International comparison studies [51] have found strong associations between the intake of SFA's and the risk of ischaemic heart disease [41]. Recently, the Nurses' Health Study showed only a weak relationship between the intake of SFA's and the risk of ischaemic heart diseases [40]. More precisely, a high intake of SFA's of 12 to 18 carbon chain increases the risk of ischaemic heart disease, whereas the intake of FA's with short or medium chains did not have such an impact [52]. Moreover, in comparison with fish and poultry, the intake of red meat, which is a significant source of SFA's is associated with a higher risk of ischaemic heart disease [52].

Monounsaturated fatty acids

MUFA's have a single double bond. Epidemiological data on MUFA's is scarce. Two prospective studies have shown a positive link between the intake of MUFA's and the risk of coronary disease [53,54]. However, these studies did not take into account possible confounding factors such as the concomitant ingestion of SFA's. This may arise as both meat fats are rich in MUFA's and SFA's. In a more detailed analysis, the substitution of SFA's by MUFA's is associated with a lower risk of coronary disease [40]. A systematic review of randomised controlled trials suggests that replacement of carbohydrates with MUFA's increases concentrations of HDL cholesterol without changing LDL cholesterol levels [55], and that replacement of saturated fats with either MUFA's or PUFA's fats raises the ratio of HDL to LDL, whilst replacement with carbohydrates leave this ratio unaltered. In the Nurses' Health study, a 5% increase in MUFA's intake was associated with a borderline protective association with CHD (RR: 0.81 [95% CI 0.65–1]) [40]. Beyond the effects on serum cholesterol, diets rich in MUFA's seem to have favourable biological effects on

lipoprotein oxidation, coagulation factors, endothelial function and blood pressure, although sound trial evidence is still lacking [56].

Polyunsaturated fatty acids

PUFA's belong to two major groups having different chemical compositions: n-6 and n-3. Linoleic acid is the main representative of the n-6 group. It is made up of 18 carbon atoms and two double bonds. The n-6 group FA's mainly originate from vegetable oils. Experimental clinical studies have shown that the intake of polyunsaturated FA's reduced plasma LDL cholesterol and, to a lesser extent, HDL cholesterol as compared to saturated FA's. In prospective epidemiological investigations, the consumption of polyunsaturated FA's instead of saturated FA's or trans FA's is inversely correlated to coronary artery disease risk [40]. Systematic review of randomised studies of high monounsaturated or high polyunsaturated diets (either in a crossover or parallel design) suggests no significant differences in total, LDL or HDL cholesterol with these two types of fat. Triglyceride levels were reduced by 0.14 (95% CI 0.00–0.29) mmol/l on the diets high in PUFA's especially by omega-3 FA's [57]. Unfortunately there is not enough data available to compare the effects of diets high on PUFA's or MUFA's on morbidity and mortality outcomes [38].

α -Linolenic acid is the precursor in the n-3 group. It is made up of 18 carbon atoms and 3 double bonds. The main food sources are certain vegetable oils: soybean, safflower and linseed oils. The α -linolenic acid is an essential fatty acid. In fact, there are physiologic needs for this FA, like vitamins and minerals. These needs are particularly important among new-born babies, young children and patients receiving parenteral nutrition. In prospective epidemiological studies, a high intake of α -linolenic acid is associated with a reduction in fatal cardiovascular events [58–60]. In the same way, in secondary prevention, a reduction of 65% and 56% in coronary and all-causes mortality was achieved after 46 months of follow-up among patients randomly assigned to a Mediterranean diet enriched with α -linolenic acid supplement [61] compared to a control diet. These benefits could be due, in part to heart-rate regulating properties of the α -linolenic acid [62,63] as have also been suggested by the results of a more recent trial [64].

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are two significant representatives of the n-3 group. These FA's are mainly derived from fish and special n-3 rich vegetal oils (i.e. canola and soybean oil). There is much evidence suggesting that consumption of EPA and DHA reduces concentrations of plasma triglycerides and, to a lesser extent, of HDL cholesterol [65]. In addition to their impact on lipid metabolism, n-3 FA's are beneficial to blood pressure, hemostatic balances and heart rhythm [66]. However, the effects on blood pres-

sure are seen at doses of 3–4 g/day, while the current average intake is around 1 g/day depending on the type of population. Prospective epidemiological population studies show lower rates of fatal coronary occurrences and sudden death among people who regularly consume fish than among non-consumers [67,68]. The DART study showed that the prescription to eat fish twice a week for patients having suffered myocardial infarctions resulted in a decrease in total mortality and coronary mortality, without any impact on non-fatal cardiovascular events [69]. In the GISSI study, the supplementation of the diet with 850 mg of EPA/DHA for subjects who have had heart attacks is associated with a reduced number of deaths during the 3.5-year follow-up period [70,71]. All these results suggest a significant protective effect of EPA and DHA on fatal cardiovascular events. These effects are partly due to a regulation of the heart rate. Systematic review of the effects of dietary and supplemental omega-3 FA's in people with coronary heart disease support a reduction in overall mortality (relative risk 0.8, 95% CI 0.7–0.9), as well as fatal myocardial infarction and sudden death, but not non-fatal myocardial infarction [72]. There were no significant differences between the effects of dietary or supplemental omega-3 fats.

Trans fatty acids

Trans FA's are MUFA's or PUFA's isomers whose conformation has been modified during the digestion of ruminants or by hydrogenation industrial processes. Trans-FA's are mainly derived from meat, dairy products, margarines and ready-cooked meals from the food-processing industry. Important efforts have been made to reduce the trans-FA's content in margarines in Europe. However, significant discrepancies within and between European countries still remain. Compared with oleic acid, trans-FA's increase LDL cholesterol concentrations and, to a lesser extent, they reduce plasma HDL cholesterol concentrations [73]. Generally, prospective epidemiological studies have found associations between the intake of trans FA's and cardiovascular morbidity and mortality in Northern America and in Europe [40,54,58,74,75]. On the other hand, the relationship between trans-FA's concentrations in the adipose tissue – which is a consumption marker of trans-FA's – with myocardial infarction occurrences, is not so clearly established in the EURAMIC study [76]. However, after the exclusion of an uninformative centre, the relative risk for developing a myocardial infarction increased while remaining non-statistically significant. Likewise, the connection between the trans-FA's intake and sudden death has been subject to contradictory reports [77,78]. In a study, no excess of sudden death was found across the distribution of trans-fatty acid in adipose tissue [77]. On the other hand, among subjects who had a cardiac arrest, concentrations of the trans isomers of FA's within the red cell membranes were significantly higher than in paired age- and sex-matched control subjects [78].

Dietary cholesterol intake

Dietary cholesterol intake appears to have relatively little effect on serum lipids. Reduction of 100 mg dietary cholesterol per day appears to reduce total serum cholesterol by only 0.06 or 0.07 mmol/l, roughly 1% [46,79], although this relationship may not be linear [80]. However, there is a tremendous heterogeneity among subjects and individual susceptibilities in the response to low cholesterol diet suggesting that some patients might benefit substantially from low cholesterol diet [81,82].

4.1.2 Sodium, potassium and other electrolytes and blood pressure

Sodium intake, especially in the form of sodium chloride influences arterial blood pressure and therefore the risk of arterial hypertension, stroke, CHD and heart failure. Blood pressure raises with age and it is an important risk factor in the age-related risk of CVD [83,84]. Newborn babies fed with low-sodium milk have lower blood pressure levels than babies fed with milk of normal sodium content during the first six months of life [85]. In societies with low salt intake there is no age-related increase in blood pressure [83], likewise in societies with low blood cholesterol, there is no massive CHD.

Revision of randomised controlled trials testing the effects of sodium restriction have shown on average, reductions of SBP of –4.8 mmHg and –1.9 mmHg in normotensive and hypertensive subjects respectively and of –1.9 and –1.1 mmHg in DBP [86]. Furthermore, recent results of the DASH-II trial of 30 days of intensive dietary advice have demonstrated, over this very short duration, not only that a reduction of sodium intake leads to a reduction of blood pressure both in hypertensive and normotensive subjects [87], but that the additional combined increase in the intake of potassium, magnesium and calcium, achieved through the combined approach of a diet rich in low SFA's dairy products and high in fruits and vegetables, was followed by greater reduction in blood pressure than the single effects of sodium restriction [88]. A recent systematic review [89] including only randomised controlled trials testing the effects of sodium restriction over at least 6 months have shown on average at between 24 and 36 months, reductions in SBP of only –1.1 mmHg (95% CI –1.9, –0.3) and –1.5 mmHg (95% CI –12.6, 9.6) in normotensive and hypertensive subjects respectively and of –0.5 (95% CI –1.1, 0) and –7.0 (95% CI –12.5, –1.5) mmHg in DBP. The few community intervention trials carried out showed that reduction of salt consumption levels are feasible and followed by a reduction of average blood pressure levels in the community [90,91].

4.1.3 Fruits and vegetables

Fruits and vegetables are significant sources of vitamins and fibre. Observational studies have shown favourable relationships between the consumption of the main antioxidant vitamins [92–94], or of the plasma levels of

such vitamins [95], and cardiovascular diseases. These results have been confirmed in cohort studies which have shown negative correlations between the consumption of fruits or vegetables and the occurrence of stroke [96–98] or coronary events [98–100]. In a meta-analysis, a 15% reduction in relative risk of ischaemic heart disease between the 10th and 90th centile of fruit and vegetable consumption (i.e. indicating a 4-fold difference in fruit and a 2-fold difference in vegetable consumption) was found, suggesting protection due to consumption of fruits and vegetables [101]. All these results suggest that eating fruits and vegetables on a regular basis has beneficial effects on the cardiovascular system. Recently, the DASH study has shown, in the short term, that having a regular diet with a higher fruit and vegetable content and a lower dairy product content reduces systolic and DBP [87,102] further supporting the properties of fruit and vegetable consumption. However, there is still no formal demonstration, by means of a randomised intervention trial, of a beneficial effects of a diet with a high content of fruits and vegetables on CHD events.

There is increasing evidence that phytonutrients (non-nutritive) compounds of many fruits and vegetables, such as flavonoids present in apples, onions, tea and red wine are associated with lower levels of CHD and stroke [103–106].

4.1.4 Vitamins: α -tocopherol (vitamin E), β -carotene (retinol) and folic acid

Vitamin E: α -tocopherol

Vitamin E is a powerful antioxidant. The incorporation of vitamin E to LDLs, through food supplementation, reduces the susceptibility of LDLs to oxidation *in vitro*. Cohort studies have demonstrated a reverse relationship between the intake of vitamin E and cardiac morbidity and mortality [92,93]. Intervention trials with vitamin supplements have shown contradictory results. In the CHAOS study, where 2000 patients with coronary disease were supplemented with 400 or 800 IU α -tocopherol, a reduced number of non-fatal myocardial infarctions was reported [107]. On the other hand, no beneficial effect was found for fatal heart attacks and total mortality. In the same way, no cardiovascular beneficial effect of vitamin E was observed among patients with high lung cancer risks in the ATBC study (treated with 50 mg/d of vitamin E) [108], among CHD patients in the GISSI study (300 mg/d) [70] and among high cardiovascular risk patients in the HOPE (400 IU/d) [109] and PPP (300 mg/d) [110] studies. Meta-analysis of these intervention studies found no effect of vitamin E on cardiovascular mortality (odds ratio 0.98, 95% CI 0.92–1.06) [111]. This has been further confirmed by the Heart Protection Study [112,113], a randomised trial of over 20 000 people at increased risk of heart disease. Participants were given antioxidant vitamins (600 mg vitamin E, 250 mg vitamin C and 20 mg beta-carotene daily) or placebo and followed up for 5 years. There were

no significant differences in total (Relative Risk 1.04, not statistically significant) or any specific cause mortalities or in any major vascular events (for all major vascular events the RR was 1.00) [113]. However, at the high doses given in these trials, which are higher than those present in usual diets, vitamin E becomes pro-oxidant rather than antioxidant, thus explaining the observed absence of effect in cardiovascular outcomes in these trials.

Vitamin A: β -carotene and retinol

Vitamin A is a general term combining a set of molecules: carotenoids (pro “vitamin A”) and retinoids. Many epidemiological observation, case/control and prospective studies have found an inverse relationship between vitamin A plasma levels, the intake of vitamin A in food and cardiac morbidity and mortality [114]. Intervention studies of vitamin supplements have failed to confirm these results. In ATBC, there was an increased risk of fatal coronary disease among cardiac patients who smoked and received a 20 mg/d β -carotene supplement or a combination of β -carotene and α -tocopherol [108,115]. In PHS, the 25 mg/d β -carotene treatment had no impact on the occurrence of cardiovascular deaths, myocardial infarctions and cerebral vascular accidents among physicians aged from 40 to 84 [116]. In CARET, the combination of 30 mg/d β -carotene and 25 000 IU retinol was associated with an increase in cardiovascular deaths [117] among subjects with high broncho-pulmonary cancer risks. All these results do not support the conclusion that β -carotene and retinol supplementation is beneficial for cardiovascular protection.

Folic acid and homocysteine

Folates are co-factors of significant biochemical reactions involving the transfer of carbon atoms. They contribute to the synthesis of DNA and to the metabolism of certain amino acids. Lack of nutritional folate intake is associated with defects in the DNA synthesis, inducing megaloblastic anaemia, anomalies in the closing of the foetus’ neural tube, cancers. More moderate chronic deficiencies have been inconsistently associated with a higher risk of cardiovascular disease. Most cross-sectional studies [118–122], though not all of them [123–125] have found a deficiency in the plasma concentrations of folate among coronary patients. These results have been confirmed in prospective studies which have shown a higher coronary [126–129], carotid stenosis [130] and stroke [130,131] risk among subjects lacking plasma folate. These results have not been repeated in other studies [132,133]. Finally, compared with subjects whose diet includes a “high” content of folate, subjects whose diet includes a “low” content of folate have a higher coronary risk [134–136]. The mechanisms through which leaf vegetable vitamins could have a beneficial impact are manifold – improved endothelial function, reduced homocysteine concentrations, antioxidant action, interaction with eNOS. Although the folic acid treatment reduces plasma homo-

cysteine concentrations [137], the final proof of the folate supplementation beneficial impact on coronary heart disease occurrence will be provided by the large-scale randomised trials being performed [135].

Homocysteine is an amino acid produced by the catabolism of methionine. Homocysteine plasmatic concentrations are determined by genetic and nutritional factors. They are increased by dietary deficiencies in leaf vegetable vitamin, vitamin B6 (pyridoxine) and vitamin B12 (cobalamin) and excessive methionine intake. Congenital hyperhomocysteinuria is associated with a significant risk of vascular pathology [138]. In a systematic analysis of case-control studies and prospective enquiries, a moderate increase in blood homocysteine is linked with a higher coronary risk [139]. This association is reported in case-control studies, but it is less obvious in prospective studies. Moreover, homocysteine increases the cardiovascular risk related to tobacco abuse, hypertension and dyslipemias [140]. The demonstration of a cardiovascular beneficial effect of reduced plasma homocysteine is being assessed through therapeutic trials.

4.1.5 Obesity and abdominal fat

Epidemiological studies in Western populations have highlighted a relationship between overweight, defined according to body mass index [weight (kg)/height (m)²] and total mortality [141]. Thin subjects have a slightly higher mortality rate than subjects having “normal” weights. Then, mortality rapidly increases with overweight [141–143]. The higher mortality rates are mainly due to cardiovascular complications, the impact of which is proportional to overweight [141,144] and weight gain since youth [145–147]. Obesity is also associated with an increased risk of stroke [148,149].

In addition to total adiposity, the distribution of fat in the organism and particularly in the abdominal cavity is a cardiovascular risk factor. Many abdominal adiposity markers have been suggested [150]. The waist measurement, and, to a lesser extent, the waist-to-hip ratio are simple, though incomplete appraisers of the abdominal adiposity. Epidemiological studies have shown that the waist-to-hip ratio is a coronary disease risk factor [146, 151–156]. The waist girth has also been associated with a higher risk of ischaemic heart diseases [146,155–157]. However, these relationships do not always remain significant after adjustment for body mass index and biological factors [146,156]. Abdominal obesity is also a risk factor for stroke [158].

Overweight and abdominal obesity are associated with many deleterious metabolic anomalies: low HDL cholesterol, high triglyceridemia, small and dense atherogenic LDLs, hypertension, glucose intolerance, insulin resistance and diabetes [159]. These metabolic anomalies tend to cluster among obese subjects to constitute a

metabolic syndrome [160]. In prospective epidemiological analyses, the relationship between the body mass index and cardiovascular morbidity and mortality is attenuated or disappears after an adjustment on these metabolic variables suggesting a significant role of such anomalies on obesity-related cardiovascular complications [144,156].

Because of adverse effects of obesity on many cardiovascular risk factors (for example, systematic review of weight reduction trials found that for every reduction of 1 kg in body weight, HDL cholesterol increased by 0.009 mmol/l and LDL cholesterol decreases [161]) and also because weight reduction is associated with improved clinical and biological metabolic disorders [162], obese subjects should lose weight.

4.1.6 Alcohol

Alcohol is not an essential nutriment. The pathophysiological consequences of its use depend on the quantities drunk, conditions of use (chronic or acute) as well as many individual factors (gender, age, genetic susceptibility). The relationship between alcohol consumption and total mortality has a U or J shape. Non-drinkers have a slightly higher risk than moderate drinkers. The excess of risk among non-drinkers could be related to pathologies which caused patients to stop drinking alcohol. Then, mortality increases in proportion to alcohol use. Death causes are manifold – violence, cirrhosis of the liver, pancreatitis, cancers, cardiomyopathies and neurological diseases, as well as pathological effects on the foetus [163–165]. Optimum consumption, associated with the lowest mortality rate, ranges between 10 and 30 g of alcohol per day, i.e. 1 to 3 units of alcohol (a standard ration means 150 ml of wine, 250 ml of beer, 30 to 50 ml of spirits). Optimum consumption is lower for women than for men because of enzymatic differences in alcohol metabolism in women [166,167]. Reduced mortality related to moderate alcohol use results from lower coronary mortality [165,168–175]. Presently, there is no reliable proof showing any higher cardiovascular benefit of any drink, compared with another [174–177]. Alcohol use is linked with an increase of haemorrhagic cerebrovascular accidents and, to a lesser extent, ischaemic stroke [176] which depends on the dose [178]. The pattern of alcohol use also has an effect on the cardiovascular risk: binge drinking is associated with a higher risk of sudden death [179] and stroke [176].

Alcohol has strong effects on cardiovascular risk factors. Alcohol increases systolic and DBP among men and women [178]. This increase is dependent on the dose. Alcohol increases HDL cholesterol, as well as triglyceride concentrations in certain subjects. Alcohol reduces concentrations of fibrinogen, antithrombin III and increases concentrations of plasminogen and of the tissue factor activator, thus modifying haemostatic balances favourably [180]. Finally, alcohol drinking is likely to

induce cardiac rhythm disturbances, a higher risk of sudden death as well as cardiomyopathy [179,181].

Finally, to date no randomised trial has yet proven that the voluntary intake of a moderate quantity of alcohol is beneficial in terms of cardiovascular morbidity and mortality. As a consequence, there is still a doubt in respect of the exact mechanisms of the reduction in cardiovascular mortality associated with alcohol use. In particular, regular moderate alcohol drinking may be the sign of a lifestyle or social condition associated with a low cardiovascular risk.

Because at the population level, adverse social, psychological and biological effects of alcohol tend to offset its possible beneficial effects on the coronary heart disease risk, it has been difficult to develop public health recommendations with regard to safe limits of alcohol use. However, at an individual level, where there are no contraindications to alcohol use, 10 to 30 g of ethanol per day for men and 10 to 20 g of ethanol per day for women may be considered safe [182], therefore people at high cardiovascular risk, enjoying moderate alcohol consumption, do not have to be discouraged.

4.2 Smoking

Smoking as a risk factor (Table 13)

There is overwhelming evidence for an adverse effect of smoking on health. In long term smokers, smoking is responsible for 50% of all avoidable deaths and one half of these are due to cardiovascular disease [183,184]. This adverse effect of smoking is related to the amount of tobacco smoked daily and to the duration of smoking [185,186]. The effect is present in both men and women, and may be even stronger in women, thus partly abolishing the relative protection of women from atherosclerotic disease [187]. The impact of smoking on atherosclerosis progression is greater for subjects with diabetes and hypertension [188]. The risk of future cardiovascular disease is particularly high if smoking starts before the age of 15 years [189]. Passive smoking has now been shown to increase the risk of coronary heart disease and other smoking related diseases [188,190–192]. The impact of smoking on cardiovascular disease risk is importantly modified in the presence of other risk factors. Within Europe, the impact of smoking on the absolute risk of coronary heart disease has been found to be smaller in Mediterranean populations than in Northern European populations [41]. Dietary factors probably explain this difference in the effect of smoking. Although the exact mechanisms by which tobacco smoking increases the risk of atherosclerotic disease are not yet fully understood, smoking enhances both the development of atherosclerosis and the occurrence of superimposed thrombotic phenomena. The latter effect may be even more important, because stopping smoking leads to a quicker reduction in the risk of subsequent

Table 13 Smoking of tobacco and CVD risk

- Smoking of tobacco is a strong and independent risk factor for CVD in asymptomatic subjects and in patients with CVD
- Passive smoking is also associated with an increase of CVD risk
- The effects of smoking on CVD interact synergistically in the presence of other CVD risk factors

coronary heart disease events in patients with established coronary heart disease than in asymptomatic individuals. In patients with established coronary heart disease the risk falls within 2–3 years to the level of those coronary heart disease patients who never smoked [186], whereas in asymptomatic individuals up to 10 years are needed to reach the risk level of those who never smoked [189,193].

In a meta-analysis of cohort studies on the effect of smoking cessation on mortality after a myocardial infarction all studies showed a mortality benefit with a combined odds ratio in those who quit of 0.54 (95% CI 0.46–0.62). The mortality benefit was consistent regardless of sex, duration of follow-up, study site and time period [194]. Therefore stopping smoking after a myocardial infarction is potentially the most effective of all preventive measures. Sufficient efforts should be devoted to this end.

Smoking-risk estimation

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

Smoking history should include the following questions: is the person a current smoker? If yes, number of cigarettes or grams of tobacco (cigars, pipes) smoked daily; duration of smoking; earlier attempts to stop. If the person has stopped smoking, for how many years has he/she stopped?

In addition, in some subjects it may be of interest to know their degree of addiction and their state of change. The Fagerström test for nicotine dependence can be used for the latter [195].

4.3 Physical activity

4.3.1 Physical inactivity as a risk factor

Physical inactivity is a growing public health problem. This will have a major impact on the prevalence of atherothrombotic cardiovascular diseases in the coming decades as a lack of physical activity is apparent in the young generation in several European countries.

Physical fitness has both a direct protective effect on the development of vascular lesions and an indirect effect through influencing other risk factors: lowering plasma LDL cholesterol and triglycerides, increasing plasma HDL cholesterol, reducing overweight and lowering blood pressure levels. A lack of physical fitness will have a reverse effect.

Thus, the promotion of regular physical activity at school, at the place of work, during leisure time and after old-age retirement is an important target for preventive cardiology as it may effectively ameliorate the future course of CVD in Europe.

Physical activity in children and adolescents

Atherosclerosis begins in childhood: the first stage, an often reversible fatty streak, is seen in most children. The more harmful later stage, the atheromatous plaque, does not appear until after puberty in boys and much later in girls. Traditional risk factors, such as hypertension, dyslipidemia and smoking are important in the early stages of the process [196]. Regular physical activity in young age protects against the early onset of atherosclerosis.

The epidemiology of CVD in young age is changing. Children have become less physically active in recent decades, with children today expending approximately 600 kcal/day less than their counterparts 50 years ago [197]. Outdoor games such as football and rope jumping have been replaced by long hours in front of a computer, often combined with the intake of unhealthy amounts of fast-food. Both the prevalence and severity of obesity are increasing [198], leading to the metabolic insulin resistance syndrome with rising blood pressure and the occurrence of type 2 diabetes mellitus in young individuals [199].

Physical education in school may form the starting point for an active lifestyle later in life. However, in only a few countries children have access to the recommended daily dose of physical work, school gymnastics and sports. More than half of the adolescents become physically inactive after leaving school.

Physical activity in adults without clinical signs of CVD

Over the past decades the physical demands at the place of work have decreased significantly. Only a minority of labourers will experience some degree of breathlessness in their daily work. Even in domestic work and during leisure time there is a trend to a lower energy demand.

Prospective epidemiological studies have shown that a sedentary lifestyle is associated with a doubling of the risk of premature death and with an increased risk of cardiovascular disease [200–211]. Both in healthy men and in individuals with diagnosed CVD exercise capacity is a more powerful predictor of mortality than other established risk factors for cardiovascular disease [212].

A high level of habitual physical activity helps to prevent overweight, ameliorates dyslipidemia and lowers blood pressure levels. Even moderate physical activity can have a beneficial effect on mortality as well as on the risk of non-fatal coronary heart disease events [201,202,205].

Maintaining regular physical fitness may also have a direct protective effect against CVD independent of other risk factors. Restitution of endothelial dysfunction has been proposed as an explanatory mechanism [213].

Regular exercise has been demonstrated to protect against the risks of strenuous exertion precipitating myocardial infarction: for the untrained individual sudden heavy work will increase the risk of an acute cardiac event considerably; a well-trained person will develop an adaptation to work stress, which will be protective against an acute cardiac event [214,215].

Physical activity in adults with clinical signs of CVD

Once CVD has been diagnosed patients tend to restrict their physical activity in fear of further deterioration of their heart condition or in order to prevent exercise induced attacks of chest pain. The protective attitude of the family may contribute to a sedentary lifestyle.

In Europe a minority of patients with CVD is routinely referred to comprehensive cardiac rehabilitation including exercise training programmes. Yet, meta-analyses of randomised trials of cardiac rehabilitation in patients surviving an acute myocardial infarction have shown that participation may lead to a 20–25% reduction in overall mortality [216,217]. In the latest meta-analysis, including 8440 patients, the pooled effect estimate for total mortality for the exercise only intervention showed a 27% reduction, whereas cardiac mortality was reduced with 31% and 26% in the exercise only and the comprehensive cardiac rehabilitation groups respectively [218].

In earlier studies it has been shown that exercise training contributes to an increase in cardio respiratory fitness with a lower heart rate and blood pressure at comparable workloads. It improves peripheral adaptation, HDL/LDL cholesterol balance and enhances the threshold for angina pectoris. Beneficial effects on fibrinolysis, carbohydrate metabolism, blood viscosity, weight reduction, mental health and the resumption of work have been reported.

Recent studies have brought new insight: leisure time physical activity may affect the natural history of the atherosclerotic lesions through an effect on endothelial dysfunction [219]. Exercise training affects the production of free radicals, protecting trained patients from the workload-induced oxidative stress [220]. It improves insulin sensitivity and metabolism and it reduces plasma homocysteine levels [221,222]. A physically active lifestyle may modify the sympathovagal balance towards a parasympathetic dominance resulting in protection against malignant arrhythmias and less myocardial wall stress. Heart rate variability (HRV) reflects this balance, which may be disturbed in patients with CVD. Exercise training, supervised or at home may restore this imbalance [223,224].

Physical inactivity is common in patients with congestive heart failure. Over the past decade several studies have shown the benefit of improving physical fitness in patients with mild to moderate CHF [225].

Physical activity in the elderly

Approximately one quarter of the population above 65 years suffers from CVD. This age group accounts for two thirds of all acute myocardial infarctions and half of all coronary interventions. Within the next 50 years it is expected that the number of individuals 65 years and older will double in Western society.

Several physiological changes that occur in the elderly may lead to physical inactivity. They include a decrease in maximum heart rate, stroke volume, cardiac output and down-grading of beta-adrenergic receptors, leading to a lower aerobic work capacity. Peripheral changes contribute: a decrease in muscular strength and coordination, peripheral oxygen-uptake, mineral skeletal content and lung function. Co-morbid conditions i.e. arthrosis, hypertension and diabetes mellitus may further deteriorate physical capacity. With increasing age larger parts of the activities of daily life demand a workload on sub-maximum or maximum level.

Regular physical activity will counteract or effectively slow down the age-related changes, thereby improving physical functioning and extending disease-free survival. Thus, preventive cardiology will have to play a major role in the elderly, promoting a healthy lifestyle with special focus on daily physical activity.

4.3.2 Estimating physical activity

Assessment in children and adolescents

The assessment of physical fitness in the general population of young age remains the responsibility of school health facilities and primary care physicians. Accurate assessment is necessary to identify current levels of activity and to demonstrate the effectiveness of programmes provided to increase physical activity. Recently, devices such as heart rate monitors, pedometers and accelerometers have become increasingly popular as measurement tools, although they may not be able to register all physical activity. These tools yield relatively high correlations using oxygen consumption or direct observation as criterion measures ($r = 0.62-0.93$, and $0.80-0.97$ respectively) [226]. Surveys and recall instruments must be used cautiously in a paediatric population that has difficulty recalling such information. Further investigation is needed to improve accuracy of the available methods.

In high-risk individuals, e.g. children with hereditary dyslipidemia or with a high CVD burden in the family and children suffering from diabetes mellitus, a formal assessment using standard exercise testing may be used in order to provide a starting point for life style counselling.

Assessment in non-CVD adults

A brief interview concerning the person's physical activity at work and leisure gives the basis for assessing his or her general level of fitness and the need to give advice for an increase in physical exercise. There are several self-reported recall questionnaires available. Even diaries for noting daily physical activity may be useful.

This may be completed with an exercise test using a bicycle ergometer or treadmill in order to obtain an objective estimate of the exercise capacity of the individual. Guidelines for exercise testing in healthy individuals and in patients with symptoms suggestive of CVD have been issued by the European Society of Cardiology Working Group on Exercise Physiology, Physiopathology and Electrocardiography [227] and more recently by the American Heart Association [228].

Assessment in adults with CVD

The medical and social history of CVD patients usually needs supplementary objective assessment, using exercise testing procedures in order to detect myocardial ischaemia, to stratify for risk of a further major ischaemic event, to select for coronary arteriography, to assess the impact of revascularisation or the response to anti-anginal medication.

Recently, guidelines for exercise testing in patients with congestive heart failure have been issued by a study group from the ESC Working Groups on Heart Failure and on Cardiac Rehabilitation & Exercise Physiology [229].

Assessment in the elderly

As in the younger age groups the patient interview remains the basis in assessing physical fitness. In the elderly the specific problems of deteriorating physical capacity, especially regarding the activities of daily living and the need of social support, should be addressed.

Exercise testing on a bicycle ergometer or treadmill may be needed in persons with symptoms of CVD. Less resource demanding methods as the 6-min Walk Test or the Shuttle Walk Test may also provide valuable information on the physical capacity of the elderly.

Conclusion

A lack of regular physical activity may contribute to the early onset and progression of cardiovascular disease. Assessment of physical activity on a population base is an important part of preventive public health efforts and assessment in coronary patients should be included in the service facilities of medical care.

4.4 Blood pressure

4.4.1 Blood pressure as a risk factor for CVD

The importance of elevated blood pressure as a risk factor for coronary heart disease, heart failure, cerebro-

vascular disease and renal failure in both men and women has been demonstrated in a large number of epidemiological studies [230–233]. Observational evidence is also available that blood pressure levels correlate negatively with cognitive function and that hypertension is associated with an increased incidence of dementia [234]. It has also been shown that, compared to normotensive individuals, those with an elevated blood pressure more commonly have other risk factors for cardiovascular disease (diabetes, insulin resistance, dyslipidemia) [232,235–237] and various types and degrees of target organ damage. Because risk factors may interact positively with each other, this makes the overall cardiovascular risk of hypertensive patients not infrequently high when the blood pressure elevation is only mild or moderate [17,238].

Blood pressure can be reduced either by lifestyle interventions or by drugs. Lifestyle interventions have been evaluated in randomised controlled trials in subjects with a mild blood pressure elevation who have been exposed to dietary sodium reduction, increased potassium intake [239], decreased alcohol consumption, body weight reduction, dietary regimens based on fish oils, increased physical activity and cessation of smoking [240]. Blood pressure was moderately reduced in most trials and the reduction was maintained for the overall study duration. This has recently been reported also in the DASH study in which a diet rich in fruits and vegetables, and low in saturated and total fat (low-fat dairy products) caused a substantial blood pressure reduction [102]. It should be emphasised that the size of the trials has been too small and their duration too short to provide evidence on the effect of lifestyle changes on cardiovascular morbidity and mortality. Furthermore, compliance to lifestyle changes out of the context of controlled trials has been shown to be poor, particularly with regard to weight loss whose maintenance in the long term represents a universal problem [241]. However, the TOHP study [242] has shown that even when body weight is regained, blood pressure may remain lower than in the control group. Also, in responsive and compliant individuals, lifestyle changes may 1) decrease the number and doses of antihypertensive drugs necessary to control blood pressure, 2) make it unnecessary to restart medication after effective drug treatment has been stopped and, 3) reduce the overall cardiovascular risk profile. This makes this approach mandatory under all circumstances.

Large-scale randomised controlled trials performed mostly in Caucasian populations have conclusively demonstrated that in hypertensive subjects a blood pressure reduction by antihypertensive drugs substantially reduces cardiovascular morbidity and mortality [243–247].

They have also provided evidence that the benefit:

1) occurs in both men and women;

- 2) extends at least to individuals up to 80 years of age [243,245,248]; and
- 3) includes all major conditions for which hypertension is a risk factor, e.g. stroke, coronary heart disease, congestive heart failure, progressive renal damage and insufficiency and, possibly, also cognitive dysfunction and dementia [200,249–252].

Evidence from placebo-controlled and comparative trials also makes it clear that cardiovascular protection can be obtained by treatments based on a variety of antihypertensive drug classes, i.e. diuretics, beta-blockers, ACE inhibitors, calcium antagonists and angiotensin II antagonists. This presumably means that the protection is due, to a substantial degree, to blood pressure lowering per se [13,253].

Following a myocardial infarction, blood pressure elevation is associated with an increased risk of reinfarction and death [254–256]. No randomised controlled trial evidence is available on the effect of blood pressure lowering per se in these circumstances. However, use of beta-blockers, ACE inhibitors and non-dihydropyridine calcium antagonists immediately after an acute myocardial infarction has resulted in a secondary cardioprotective effect together with a modest blood pressure reduction [257–259]. This has been seen in individuals with both elevated and normal blood pressure. Furthermore, antihypertensive treatment by several drug classes has been found to prevent cardiovascular disease in normotensive and hypertensive patients with a more distant history of myocardial infarction [260,261]. Finally, recent trials have demonstrated that clinically stable normotensive and hypertensive patients with a history of cerebrovascular disease show a marked decrease in their otherwise elevated incidence of stroke recurrence if blood pressure is reduced by ACE inhibitors alone or in combination with diuretics [262], with a decrease also in the incidence of myocardial infarction. This suggests use of antihypertensive drugs for secondary coronary and cerebrovascular prevention, even when blood pressure is not elevated. Treatment should be given according to guidelines for primary prevention but blood pressure should be lowered slowly and carefully because tissue necrosis, atherosclerotic plaques and cardiac hypertrophy may make coronary and cerebral blood pressure flow autoregulation less effective in preserving organ perfusion when perfusion pressure is reduced [263]. A similar approach should be considered also in patients with a high cardiovascular risk profile because of multiple cardiovascular risk factors, diabetes, or advanced renal damage.

Long-term observational data [264] provide evidence that in hypertensive patients in whom treatment effectively controls blood pressure, coronary, cerebro- and overall cardiovascular morbidity remains higher than that of normotensive controls. This may be accounted for by factors

such as irreversible organ damage at the time treatment is started, pointing to the need for earlier identification and correction of blood pressure elevation. Research efforts, however, currently also focus on the possibility that greater cardiovascular protection may be achieved by, 1) antihypertensive drugs with direct organ protective properties that might complement the protection due to the blood pressure reduction [260], 2) multiple drug treatments that more comprehensively address the overall cardiovascular risk profile and, 3) more aggressive blood pressure reductions below 140/90 mmHg. To date, trial evidence that for a given pressure reduction some antihypertensive agents are more protective than others is limited to the greater nephroprotective effects of drugs primarily acting on the renin-angiotensin system (ACE inhibitors and angiotensin II antagonists) [265–267] because, with few exceptions [268,269] comparisons between drugs have not shown differences in primary cardiovascular end-points and no substantial advantage of one class over another had emerged from their meta-analysis [270]. This has also been the case of a recent large-scale trial (involving more than 33 000 patients) comparing diuretic-, calcium antagonist-, and ACE inhibitor-based regimens [271]. The same trial has reported that, in patients with hyperlipidemia, the addition of pravastatin to antihypertensive treatment has no additional cardioprotective effect compared to the group in which a lipid-lowering treatment was left to the physician's discretion [272]. However, several large-scale studies have shown statins to be very effective in primary and secondary prevention and, also, in patients with hypertension and antihypertensive treatment [273,274]. Furthermore, in the ASCOT Study [275], the group of patients with baseline total cholesterol < 6.5 mmol/l treated with 10 mg atorvastatin in addition to antihypertensive treatment, has recently been stopped because of the evidence of a major reduction in cardiovascular disease (–30 to –40%) and stroke (–27%) compared to placebo. This suggests that, in treated hypertensive patients, lipid-lowering treatment may be of additional benefit. Evidence has been obtained, on the other hand, that in hypertensive patients in whom treatment provides an adequate blood pressure control, the addition of acetylsalicylic acid at a low daily dose (75 mg) further decreases (–35%) the incidence of myocardial infarction, [276] the benefit being particularly evident in the male gender [277] and in the subgroup with renal damage [278]. There is also evidence that in patients with type II diabetes mellitus or with diabetic nephropathy, aiming at blood pressure values well below the traditional ones is associated with a lower incidence of cardiovascular and renal events, respectively [279–281]. The latter is the case particularly in the presence of marked proteinuria. Thus antiplatelet treatment should be considered in hypertensives with blood pressure control. Furthermore, in diabetic and nephropathic [282,283] patients, on-treatment blood pressure values less than 130/80 mmHg or lower

(125/75 mmHg in patients with proteinuria > 1 g/24 h) should be achieved using all available drugs with evidence of antihypertensive efficacy and safety [284,285].

4.4.2 Blood pressure measurements

The large physiological variations in blood pressure [286] mean that, to diagnose hypertension, blood pressure should be measured in each individual several times on several separate occasions. If systolic and/or DBP is only slightly elevated, repeated measurements should be made over a period of several months to achieve an acceptable definition of the individual's "usual" blood pressure and to decide about initiating drug treatment. If systolic and/or DBP are more markedly elevated, repeated blood pressure measurements are required within a shorter period of time in order to make treatment decisions. This is also the case if the blood pressure elevation is accompanied by evidence of end-organ damage and/or by the concomitance of other cardiovascular risk factors that markedly increase overall cardiovascular risk. Repeated blood pressure measurements on several occasions are necessary to identify the relatively large number of persons in whom blood pressure elevation disappears following the first few visits. These individuals may need blood pressure measurements more frequently than the general population but drug treatment does not appear to be necessary because their cardiovascular risk is probably low [287].

Blood pressure measurement is carried out in the sitting position from the right or the left arm, after the patient has rested for 5 min. At the initial visit, blood pressure values from both arms should be obtained to detect patients in whom atherosclerotic plaques in subclavian or more central arteries may be responsible for substantial between-arm discrepancies. Under this circumstance the arm with the higher values should be selected. In elderly hypertensive individuals and in diabetic patients, it is also important to measure blood pressure in the standing position to detect possible orthostatic hypotension.

The use of a conventional sphygmomanometer with an appropriate bladder size is recommended. The reading of DBP should be taken at the disappearance of the sound (phase V) and blood pressure levels have to be read to the nearest 2 mmHg. At least two measurements have to be made on each visit. Because medical use of mercury is likely to be banned from some European countries in the near future, performance of non-mercury blood pressure measuring devices will become increasingly important. These devices should be properly tested and validated according to standardized protocols [288], as mentioned in the guidelines on blood pressure measurements of the European Society of Hypertension [289]. Currently available devices measuring blood pressure in the fingers or on the wrist should be avoided because of their limited relationship with central blood pressure waveform and/or possible inaccuracy [290].

Blood pressure measurements during exercise or laboratory stressors have been proposed as more sensitive indicators of blood pressure elevation and increased cardiovascular risk, but their clinical superiority over conventional blood pressure has never been conclusively proved and their use cannot be recommended. Semi-automatic and automatic devices are now available for home and for prolonged (24 h or more) ambulatory monitoring of blood pressure. Such recording procedures may provide useful additional information in a number of cases. Furthermore, home blood pressure can increase the patient's perception of the problem and compliance to treatment. However, insufficient information on their prognostic value makes both pressures still unsuitable as a routine substitute for clinic blood pressure in the diagnosis of hypertension, or to determine the need for treatment and assess treatment efficacy [291]. Ambulatory and home blood pressure measurements are currently used for the diagnosis of "white coat" or "isolated clinic" hypertension, [253,292,293] i.e. the condition in which blood pressure is persistently elevated in the physician's office while being normal at home (probably less than 135/85 mmHg) or over the 24 h (probably less than 125–130/80 mmHg) [294–297]. It is acknowledged that these individuals may represent a noticeable fraction of the overall hypertensive population [292]. It is also acknowledged that their cardiovascular risk is less than that of subjects with a blood pressure elevation in and out of the physician's office. Subjects with white coat or isolated office hypertension, however, have been not infrequently reported to have a greater prevalence of organ damage than controls [293,298] which makes its clinical innocence still controversial [299]. Physicians should thus be aware of this fact to address it carefully. That is, they should monitor these patients closely if drug treatment is not implemented and favour an active blood pressure reduction if there is organ damage or additional cardiovascular risk factors.

In patients with an acute myocardial infarction who have been treated for hypertension before their infarction, blood pressure may remain at much lower levels, or even return to normotensive values, for months or years without continuing antihypertensive treatment [300]. In such instances, the blood pressure level has to be measured properly to detect whether and when hypertensive values are regained and effective antihypertensive treatment should be restarted without delay.

4.5 Plasma lipids

4.5.1 Lipids and lipoproteins as risk factors

In blood plasma, lipids such as cholesterol and triglycerides are bound to various proteins to form lipoproteins. The degree to which lipoproteins cause atherosclerosis depends in part on their concentrations in plasma and in part on their size. The smallest lipoproteins, HDL (high density lipoproteins), enter the artery wall easily, but

they also leave it again easily, and they do not cause atherosclerosis. In contrast, LDL (low density lipoproteins), IDL (intermediate density lipoproteins), and small species of VLDL (very low density lipoproteins) are small enough to enter the artery wall. If they are chemically modified, for example by oxidation, they can be retained in the wall and gradually cause atherosclerosis. The largest lipoproteins, chylomicrons and large VLDL are too large to enter the artery wall and they are not atherogenic. Instead, high concentrations of these large triglyceride-rich lipoproteins can cause pancreatitis.

Cholesterol and LDL cholesterol

Most of cholesterol in blood plasma is normally carried in LDL, and, over a wide range of cholesterol concentrations, there is a strong and graded positive association between total as well as LDL cholesterol and the risk of cardiovascular disease [301,302]. The association applies to individuals without cardiovascular disease as well as to patients with established disease [303,304]. It applies to women as well as men, but the general level of risk is lower in women, and it applies to old as well as younger people [305].

The association is considerably modified by other risk factors [306]. At the concentrations of cholesterol given in the cardiovascular risk chart, overall risk depends critically on numerous other risk factors including the major factors that it is possible to capture in simple tabular form: age, sex, smoking, and blood pressure. Hypertriglyceridemia, low HDL (measured as HDL cholesterol) and diabetes aggravate the effect of LDL substantially, even though concentrations of LDL are only moderately elevated. Coronary artery disease is rare in populations with total cholesterol less than 3–4 mmol/l (115–155 mg/dl), even in the presence of other risk factors. Conversely, coronary artery disease is inevitable in untreated patients with the severest forms of familial hypercholesterolemia, even in the absence of other risk factors. In patients with the fairly common heterozygous form of familial hypercholesterolemia, LDL cholesterol can be quite elevated, 7–12 mmol/l (270–465 mg/dl), and LDL cholesterol is extremely elevated in the rare homozygous form, 12–20 mmol/l (465–770 mg/dl).

Like other classes of lipoprotein, LDL are heterogenous. Small, dense LDL appear in plasma when triglyceride concentrations exceed approximately 1.4 mmol/l, and they seem to be more atherogenic than larger forms of LDL [307]. They are associated with premature coronary artery disease, particularly in young and middle-aged people [308].

The results of epidemiological studies, as well as trials with angiographic or clinical end-points, confirm the importance of LDL as a cause of atherosclerosis. Reduction of LDL, measured as LDL cholesterol, must therefore be of prime concern in both primary and sec-

ondary prevention of atherosclerotic disease. This point of view has been strongly emphasised in previous recommendations developed in Europe [10] and the United States [11], and it is central to the recommendations in the present document, in which LDL cholesterol < 3 mmol/l (~115 mg/dl) is a goal of therapy for the majority of high-risk patients.

Triglycerides

Hypertriglyceridemia is also associated with risk of atherosclerotic disease, but the association is not as strong as it is for hypercholesterolemia, and the relationship of triglycerides to atherosclerosis continues to be a source of confusion to clinicians.

An early analysis of the literature indicated that the association of triglycerides to coronary heart disease might not be causal, since it was not statistically independent of other risk factors, HDL cholesterol in particular [309]. A later meta-analysis of 17 population-based studies, comprising more than 46 000 men and more than 10 000 women, showed that risk of cardiovascular disease in fact did increase with increasing degrees of hypertriglyceridemia [310]. Although these results were attenuated when adjustments were made for HDL cholesterol, they were significant in multivariate as well as univariate analysis. Risk is associated more strongly with moderate than with very severe hypertriglyceridemia, probably because the former often is due to accumulation in plasma of IDL and small VLDL, whereas the latter can be due to non-atherogenic large VLDL and chylomicrons [311].

The concept of statistical “independence” of the effects of triglycerides on risk makes limited sense, given the complex, multifactorial nature of the pathophysiology involved. As a result of a better understanding of this pathophysiology, a consensus on the clinical management of hypertriglyceridemia has begun to emerge. The association of hypertriglyceridemia to atherosclerosis can be explained in terms of at least 3 mechanisms.

The first is that, like LDL, some triglyceride-rich lipoproteins can enter the artery wall, where they can be retained to contribute to atherosclerosis. That seems to be the case for small VLDL and IDL.

The second is that the metabolism of triglyceride-rich lipoproteins is closely linked to that of LDL and HDL in ways that seem to promote atherosclerosis. Small dense LDL, which are especially atherogenic, appear in plasma when triglyceride concentrations rise above 1.4 mmol/l. By a variety of mechanisms, high concentrations of triglycerides are also commonly attended by low concentrations of HDL. As will be discussed later, the evidence is now strong that HDL can inhibit atherosclerosis, and the low HDL concentrations associated with hypertriglyceridemia are therefore probably also atherogenic.

By a variety of metabolic links, moderate elevation of triglycerides therefore signifies a generalised, atherogenic disturbance of lipoprotein metabolism.

The third is that hypertriglyceridemia can be associated with a large number of physiological and environmental phenomena that, by other mechanisms as well, promote the development of early-onset cardiovascular disease. They include the metabolic syndrome, type 2 diabetes, hypertension, low physical activity, obesity and low consumption of fruits and vegetables.

A triglyceride value > 1.7 mmol/l (~150 mg/dl) is considered a marker of increased risk, but concentrations < 1.7 mmol/l are not considered a goal of therapy. This recommendation is in broad agreement with the latest American guidelines [11].

HDL

Low concentrations of HDL can be clearly associated, not only with early development of atherosclerosis, but also with poor outcome in those who already have cardiovascular disease [302,303,312,313]. The association is not invariable, since it is not apparent in societies in which the risk of atherosclerotic cardiovascular disease is low [314,315]. The deleterious effects of low HDL therefore depend on larger contexts, and it is very strongly associated with risk in urbanised societies where people smoke, tend to be sedentary and eat large amounts of animal products.

HDL is associated with protection of the artery wall by several different mechanisms. One has already been discussed: low concentrations of HDL are metabolically linked to high concentrations of IDL and VLDL, which are atherogenic. Animal experiments show that HDL are also directly antiatherogenic [316,317]. There are numerous mechanisms to explain this more direct protective effect. They include stimulation of prostacyclin synthesis and inhibition of synthesis of platelet-activating factor in endothelial cells, antioxidant activity, and inhibition of adhesion of monocytes to endothelial cells, an early step in the atherosclerotic process [318].

The participation by HDL in transport of cholesterol to the liver from other organs is yet another mechanism by which HDL could protect the artery wall. This transport process has been termed reverse cholesterol transport, and low concentrations of HDL have mistakenly been taken to denote low rates of reverse cholesterol transport. Although a rare disease of humans, Tangier disease, in which cholesterol is accumulated in non-hepatic organs, probably including the arteries, in fact is characterised by extremely low or unmeasurable concentrations of HDL cholesterol and a severe failure of reverse cholesterol transport. Low concentrations of HDL do not in general signify that cholesterol is being transported to the liver at

lower rates than normal. By the same token, whether a bath tub is almost empty or almost full does not tell us how much water is entering and leaving it. Concentrations of HDL cholesterol are therefore not measurements of rates of reverse cholesterol transport [319], which cannot be gauged in any clinically useful way.

HDL cholesterol is not considered a goal of therapy in the present document. Instead, HDL cholesterol < 1 mmol/l (~40 mg/dl) in men and < 1.2 mmol/l (~46 mg/dl) in women is considered a marker of increased risk that should suggest to the physician that attention to lifestyle and management of high LDL cholesterol and high blood pressure is necessary.

High triglycerides, low HDL cholesterol

The combination of moderately elevated triglycerides and low concentrations of HDL is very common in patients with early-onset atherosclerotic disease. It is part of a pattern of deranged plasma lipoproteins characterised by a triad of increased concentrations of IDL and VLDL, the presence of small dense LDL, and low concentrations of HDL. This “lipid triad” has also been termed “atherogenic dyslipidemia” [11], and it may rival hypercholesterolemia, due to high concentrations of LDL, as a cause of atherosclerosis. Indeed, hypercholesterolemia and “atherogenic dyslipidemia” are the two major patterns of atherogenic disorders of lipoprotein metabolism. Both of them are, of course, atherogenic dyslipidemias, and it is therefore not entirely fortunate that the term is used to specify one of them. A more cumbersome but less ambiguous term is “high triglycerides, low HDL cholesterol”, which also reflects the limitation that one component of the triad, small dense LDL, cannot be measured in routine clinical practice. Whatever term is used, the combination of high triglycerides and low HDL cholesterol is characteristic, not only of patients with type 2 diabetes, but also of patients with abdominal obesity, insulin resistance and physical inactivity, all of whom are at greater risk of cardiovascular disease.

Other lipoproteins and lipoprotein components

Lp(a)

Lp(a) is pronounced “LP little a”. It is a low density lipoprotein to which is attached an additional protein called apolipoprotein(a). It has no known physiological role, and high concentrations of Lp(a) (arbitrarily > 30 mg/dl) are largely resistant to modification. They identify persons at increased risk of atherosclerotic diseases [320,321].

Apolipoprotein B

Apolipoprotein B (apoB) is the major protein component of LDL, IDL, VLDL and, in truncated form, chylomicrons. Since chylomicrons normally are not present in plasma in the fasting state, almost all apolipoprotein B is in atherogenic lipoproteins. Concentrations of apolipoprotein B are therefore a direct measure of the

concentration of atherogenic lipoproteins in plasma. The measurement is a useful indicator of risk of atherosclerosis, particularly in patients with hypertriglyceridemia [322] and in people with normal concentrations of LDL cholesterol [323]. Values > 150 mg/dl are clearly associated with increased risk. Since measurement of apolipoprotein B is not generally available to physicians in Europe, however, it is not included as an integral part of the present recommendations.

Apolipoprotein A1

Apolipoprotein A1 is the major protein component of HDL. Low concentrations of apolipoprotein A1 are, like HDL cholesterol, associated with higher risk of cardiovascular disease [322], but, as for apolipoprotein B, measurements of apolipoprotein A1 are not generally available, and they are not included in the present recommendations for assessing cardiovascular risk.

Calculated lipoprotein variables

LDL

LDL can be measured directly, but it is usually calculated by the Friedewald formula [323]:

- In mmol/l: LDL cholesterol = total cholesterol – HDL cholesterol – (0.45 × triglycerides)
- In mg/dl: LDL cholesterol = total cholesterol – HDL cholesterol – (0.2 × triglycerides)

The calculation is valid only when concentrations of triglycerides are less than approximately 4.5 mmol/l (400 mg/dl). That is because the ratio of triglyceride to cholesterol in triglyceride-carrying lipoproteins (VLDL and chylomicrons) progressively increases as hypertriglyceridemia becomes more severe.

Non-HDL

In the fasting state, non-HDL cholesterol is the cholesterol in LDL, IDL and VLDL. Calculated by simply subtracting HDL cholesterol from total cholesterol, non-HDL cholesterol, unlike LDL cholesterol, doesn't require triglycerides to be less than 5 mmol/l. It is, moreover, like apolipoprotein B, a measure of concentrations of atherogenic lipoproteins in plasma [324]. It is more readily available than measurements of apolipoprotein B, however, and the ATP-III has adopted non-HDL cholesterol as part of the routine lipoprotein variables on which to base assessments of risk [325]. Although not part of the general recommendations of the present document, which strongly emphasise simplicity, physicians who wish to exploit non-HDL cholesterol in the assessment of their patients should consider a value of < 4 mmol/l (~150 mg/dl) as a goal of therapy.

Total cholesterol/HDL cholesterol

Taking several plasma lipoprotein variables into account refines but also complicates the assessment of cardiovas-

cular risk. One way to do this has a long history in cardiovascular risk assessment. It is the ratio of either total cholesterol or LDL cholesterol to cholesterol in HDL. Total rather than LDL cholesterol is preferable in the numerator, because, as is apparent from the Friedewald formula, a mistake made in the measurement of HDL cholesterol will affect the calculation of LDL cholesterol and compound the mistake in the assessment of risk (an erroneously high HDL cholesterol reduces the amount of cholesterol calculated to be present in LDL and vice versa). It is therefore more prudent to use the ratio of total cholesterol to HDL cholesterol as an assessment of risk. A total cholesterol/HDL cholesterol ratio > 5 indicates increased risk and is particularly useful in the middle part of the cholesterol distribution (5–6.5 mmol/l ~190–250 mg/dl).

A caveat should be introduced here, however. The analysis of large European databases, on which the present recommendations for assessing cardiovascular risk are based, showed that the total cholesterol/HDL cholesterol ratio predicted cardiovascular events as well but not better than the simple measurement of total cholesterol. Indeed, for all cohorts, the mean difference in predictive power was less than 0.1%, and the concordance correlation coefficients were 0.97–0.98 [18].

The utility of the ratio of total cholesterol to HDL cholesterol as an indicator of risk of CHD is predicated on the idea of a close physiological relationship between LDL and HDL, especially the concept of a balance between two opposing processes: transport of cholesterol away from the liver and transport of cholesterol to the liver. As indicated above, however, the importance of HDL for cardiovascular risk may not be limited to its role in lipoprotein metabolism. It might also be due to properties such as antioxidant activity, effects on endothelial function, etc. If that is the case, use of the ratio of total cholesterol to HDL cholesterol makes no more sense than use of any other ratio of a positive to a negative risk factor, eg the ratio of SBP to HDL cholesterol (P. Barter, personal reflection).

Despite these considerations, the present document has included the total cholesterol/HDL cholesterol ratio in one version of the risk tables, because it is so well-established in European clinical practice.

4.5.2 Lipoproteins and risk of cardiovascular disease: the evidence for current recommendations for lipid management

Plasma cholesterol does not differentiate well between individuals destined and not destined to develop coronary artery disease [306]. That observation, of course, is one of the reasons for the multifactorial approach to risk estimation recommended in this document. On the population level, however, concentrations of plasma

cholesterol are powerful predictors of coronary artery disease. A meta-analysis of 10 cohort studies, including $\frac{1}{2}$ million men and 18 000 ischaemic heart disease events, indicated that a 10% increase in plasma cholesterol is associated with an increase in the incidence of coronary artery disease of 27% [326]. Observational data of this sort are good indicators of the magnitude of the public health problem associated with hyperlipidemia, but they do not establish the degree to which lowering of cholesterol is followed by reductions in risk. That information can only be obtained by randomised clinical trials.

Clinical trials of lowering cholesterol have used angiographic as well as clinical end-points. The number of such trials is very large, and numerous meta-analyses of published as well as unpublished data have been performed as the evidence gradually has accumulated during the past 40 years [37,326,328–334,336,348]. The analysis by Law *et al.* [326] considered 28 randomised clinical trials of cholesterol-lowering by diet, drugs or surgery, which in aggregate had included more than 46 000 men and more than 4000 events. It showed that a 10% reduction in plasma cholesterol was followed by a 25% reduction in incidence of coronary artery disease after five years, very close to the 27% estimate derived from the observational cohort data. The data for women were limited but indicated a similar effect.

These conclusions were confirmed and extended by the results of five large clinical trials of cholesterol-lowering with statins, which were published from 1994 to 1998. In all, they randomized more than 30 000 men and women, with and without coronary artery disease, to treatment with placebo or a statin drug [273,337–340]. They contributed large parts of the data that have been subjected to recent meta-analyses. But no meta-analysis has as yet included the results of the most recent large statin trials [274,275,347]. All in all, these three later trials randomised more than 40 000 patients to treatment with placebo or simvastatin, pravastatin or atorvastatin. With one exception, the last three statin trials confirmed the results of the first five trials, since they also showed that lowering LDL cholesterol with a statin reduced the risk of coronary artery disease events. The exception was the ALLHAT-LLT of pravastatin therapy, in which the differences in CHD events between the pravastatin and the placebo arms was not statistically significant. The authors explained their discrepant results by the exceptionally modest difference in cholesterol between the active and control groups of that study (9.6%) compared to that obtained in the earlier trials, including three earlier trials with pravastatin. Thus, clinical benefit does not occur if cholesterol is not adequately reduced.

Overall, several questions concerning subgroups, including diabetic patients, which had been left unanswered or

only partially answered by each of the earlier trials, and only tentatively answered by meta-analyses seem now to have been satisfactorily answered particularly by the Heart Protection Study (HPS) [274].

The main conclusions of the trials of lipid-lowering is that it is possible to inhibit progression of coronary atherosclerosis and to reduce risk of myocardial infarction. In several trials the resulting decrease in coronary death rates translated into a reduction of overall death rates. Moreover, the trials have consistently shown that treatment, with statins especially, reduces the need for coronary artery by-pass grafting and various forms of coronary angioplasty, and the HPS extended this evidence of benefit to carotid endarterectomy and other peripheral artery revascularisations as well.

In observational studies, plasma cholesterol is not associated to overall rates of stroke [341], and early meta-analyses indicated that lowering cholesterol does not lower risk of stroke [342]. It was therefore remarkable when several of the large statin trials reported reductions in stroke rates in patients with or at high risk of getting coronary artery disease [273,337,340,341]. Several meta-analyses indicated that cholesterol lowering with statins does reduce risk of ischaemic stroke [344–346] and the HPS has now also shown that statin therapy reduces rates of overall stroke due to a reduction in the rates of ischaemic stroke. There was no indication in the data from the statin trials that therapy increases the risk of hemorrhagic stroke, a concern that had been raised by observational data [349].

Four of the 5 large statin trials published until 1998 included women and patients over 65 years. Women constituted 14–19% of study subjects, and people older than 65 years at entry constituted 21–39%. In three of the trials, women and older patients were prespecified subgroups. The analyses indicated no differences in effects of lipid-lowering between men and women and between younger and older age groups [348]. Benefits in women and in the elderly are also supported by the HPS [274] and the PROSPER trial [347].

A result of early as well as later meta-analyses of the literature is that the benefits of cholesterol-lowering therapy depend on initial levels of risk: the higher the risk, the greater the benefit [37,332]. That concept has been central to the earlier versions of the Joint European Recommendations [8,338], and it is supported by the results of the statin trials. Since the relative reductions in risk as a consequence of lipid-lowering were approximately the same in patients at higher and lower risk, the absolute reductions in risk were highest in patients at highest baseline risk.

High-risk patients included, in particular, patients with established coronary artery disease [273,340,343], and the

earlier statin trials suggested that the absolute reductions in risk as a result of statin therapy are particularly marked in patients with diabetes [350]. The majority of patients in the HPS [274] had established coronary artery disease, but 35% did not. They were included because of hypertension, diabetes or atherosclerotic disease in the arteries to the brain and the legs. The finding that the incidence of new cardiovascular disease was significantly reduced also in these patients definitively expands the population of high-risk patients in whom lipid-lowering therapy is beneficial. Indeed, a major finding of the HPS [274] is that patients with cerebrovascular disease, peripheral artery disease and diabetes merit the same degree of attention to treatment of plasma lipids as patients with coronary artery disease.

The statin trials as well as several meta-analyses dispelled early concerns that lipid-lowering might cause non-cardiovascular mortality to increase. The concern was based, first, on the J-shaped curve relating cholesterol concentrations to mortality risk: at high concentrations, death rates are high due to an excess of cardiovascular deaths, but at the lower end of the distribution, there is also an excess of deaths including deaths due to cancers, depression, etc. [349]. The epidemiological evidence supports the interpretation that cancers and depression cause plasma cholesterol to fall rather than the other way around. The concern was also based on the results of a large trial of clofibrate [351], but meta-analyses support the interpretation that increased risk of non-cardiovascular death is associated with specific drugs, in this case clofibrate, rather than with lipid-lowering itself [332,334,336]. Indeed, rates of cancer and suicide seem to be unaffected by statin therapy [274,352].

4.6 Glucose

Epidemiological studies have shown that hyperglycaemia is associated with an increased risk of developing coronary heart disease as well as other atherosclerotic diseases [353–356]. This is true for diabetes as well as for individuals with impaired glucose tolerance (IGT) – the intermediate stage between normal and diabetic post load glucose levels. In diabetic individuals the relative risk of CVD is in the order of 2–4, while in individuals with IGT the relative risk is 1.5 compared to individuals with normal glucose tolerance [358].

More recently it has been demonstrated that there is a linear association between non-fasting glucose values and the risk of developing CVD continuing all the way down to the normal range. This has been demonstrated both using the 2-h value following an oral glucose tolerance test and using the integrated measure of glycated haemoglobin HbA_{1c} [359]. In the non-diabetic range, non-fasting plasma glucose values are more predictive than fasting values in relation to CVD, but these studies have compared fasting glucose values with the 2-h value following an oral glucose tolerance test. The clinically more

Table 14 Status of glucose regulation based on fasting and 2-h plasma glucose values.

	Fasting plasma glucose	2-h plasma glucose
Normal (NGT)	≤ 6.0 mmol/l (108 mg/dl)	< 7.8 mmol/l (140 mg/dl)
Impaired fasting glycaemia (IFG)	6.1 to 6.9 mmol/l (110 to 125 mg/dl)	< 7.8 mmol/l (140 mg/dl)
Impaired glucose tolerance (IGT)	< 7.0 mmol/l (125 mg/dl)	7.8 to 11.0 mmol/l (140 to <200 mg/dl)
Diabetes (DM)	≥ 7.0 mmol/l (125 mg/dl)	≥ 11.1 mmol/l (200 mg/dl)

relevant comparison would be between fasting and post-prandial glucose, but this study has not been performed.

4.6.1 Impaired glucose regulation and risk

The status of glucose regulation can be classified based on fasting and 2-h plasma glucose values (following a 75 g oral glucose load) into the categories normal glucose tolerance (NGT), impaired fasting glycaemia (IFG), impaired glucose tolerance (IGT) and diabetes (DM) as shown in Table 14 [360]:

Diabetes is classified into two major groups and a number of smaller specific disease entities. The major types of diabetes are type 1 diabetes and type 2 diabetes [360]. Type 1 diabetes is characterised by loss of beta cell function and endogenous insulin production to a level where the individual would die from ketoacidosis if not treated with insulin injection. The incidence is highest in children and young adults, but it can develop at any age.

Insulin resistance is one of the main characteristics of type 2 diabetes. Insulin may be necessary to obtain acceptable metabolic control [361]. The incidence and prevalence increases by age, but the condition is heavily associated with obesity and lack of physical activity, and for this reason the incidence is not only increasing world wide [362], the age at diabetes onset is also decreasing, and type 2 diabetes can be seen even in teenagers.

The primary underlying mechanism behind development of type 2 diabetes is insulin resistance. Insulin resistance is associated with a long list of cardiovascular risk factors including hypertension, dyslipidaemia, endothelial dysfunction and microalbuminuria [363], and these associations partly explains the association between diabetes/glucose intolerance and the increased risk of cardiovascular disease.

4.6.2 Risk of CVD, CHD and stroke in diabetes

The association between these macrovascular complications differs markedly between type 1 and type 2 diabetes. In type 1 diabetic patients there is a 2–3-fold increase in the risk of developing CVD, CHD and stroke, but this increased risk is almost entirely confined to the patients developing diabetic renal disease [364]. This is in contrast to patients with type 2 diabetes, where all patients are at increased risk, even in the absence of diabetic nephropathy. Finnish data indicates that the risk of developing a myocardial infarction in patients with type 2 diabetes is of the same order as for patients

without diabetes who have already suffered their first MI [365]. The results of a more recent Scottish study and the 18.8-year follow-up study of men screened for the Multiple Risk Factor Intervention Trial (MRFIT), based on a larger numbers of diabetic subjects, have, however, shown that the risk of diabetic subject without prior MI, although markedly higher than in non-diabetic subjects without prior MI, still remains lower than the risk of non-diabetic subjects with prior MI [366].

Although a substantial proportion of the excess risk of atherosclerotic disease in both type 1 and type 2 diabetes is caused by the diabetic state itself and related factors, from the point of prevention of atherosclerotic disease it is important to emphasise that the conventional, modifiable major cardiovascular risk factors, elevated blood pressure, elevated total cholesterol, and smoking show in both type 1 diabetic subjects [367] and type 2 diabetic subjects [368] similar relationship with the risk of cardiovascular disease as in non-diabetic subjects. Because diabetes itself increases the absolute risk of cardiovascular disease, the additional impact of conventional risk factors leads to a more dramatic increase in absolute risk than in non-diabetic subjects and thus the modification of these risk factors offers a great potential for prevention.

4.6.3 Glucose and diabetes: the evidence for current recommendations

With the exception of glucose management, prevention of CVD follows the same lines as for people without diabetes.

Glucose

The UK Prospective Diabetes Study (UKPDS) [369,370] was the first large scale randomised clinical trial to evaluate the effect of improved metabolic control on the risk of developing coronary heart disease or any other atherosclerotic disease. The study demonstrated a 16% borderline significant ($P = 0.052$) risk reduction for myocardial infarction associated with the 0.9% reduction in HbA_{1c} obtained in the study. The study used several different treatment modalities, and many patients changed treatment during the trial [361], and thus the authors have also estimated the overall risk reduction associated with a 1% decrease of HbA_{1c} independent of treatment modality. On the basis of their observational epidemiological analyses UKPDS investigators concluded that a significant 14% reduction in the risk of CVD would occur per 1% reduction in HbA_{1c} [371]. The risk-reduction for microvascular complications (retinopathy and nephropathy) was much larger [369], as also demonstrated in the Kumamoto study [372].

Blood pressure

The effect of blood pressure reduction on the risk of developing cardiovascular disease has predominantly been studied in studies including diabetic as well as non-diabetic patients, so most of the existing evidence is based on subgroup analysis from these combined trials.

The UKPDS-study randomised patients with hypertension to intensive or less intensive antihypertensive therapy [373]. In this substudy there was a marked and significant 44% risk reduction for stroke and a non-significant 21% risk reduction of myocardial infarction associated with a 10 mmHg reduction in systolic BP and 5 mmHg reduction in DBP.

Subgroup analyses restricted to the diabetic patients in the SHEP-study, Syst-Eur and the HDFP-study [374–376] consistently show a 40% risk reduction in cardiovascular morbidity and mortality, treatment effects as big as or bigger than those found in the non-diabetic groups. The Hypertension Optimal Study (HOT) comparing different DBP goals showed that the benefit from more aggressive treatment of blood pressure (goal: DBP of 80 mmHg) resulted in a larger reduction in cardiovascular events in diabetic individuals compared to non-diabetic individuals [276].

Dyslipidaemia

Before the publication of the Heart Protection Study (HPS) [274], several large lipid lowering trials had included subjects with diabetes (predominantly type 2 diabetes), and published subgroup analyses comparing the results in diabetic and non-diabetic subjects. Most of these studies were, however, underpowered for the diabetic group. Thus, although several studies demonstrated quite large treatment effects, confidence intervals were wide and in some studies results were non-significant.

The first trial used gemfibrozil as a lipid lowering agent in primary prevention [377], and this study demonstrated a non-significant 68% reduction in risk of MI or cardiovascular death. Several trials focused on secondary prevention in patients with already established coronary heart disease and used statins for lipid lowering. The first statin study was the Scandinavian Simvastatin Survival Study (4S) [350] that showed a significant 55% risk reduction in major CHD events, a significant 37% reduction in all cardiovascular events, and a borderline significant 43% reduction in all cause mortality. Subsequent secondary prevention studies with statins, including CARE and LIPID [338,340], demonstrated somewhat smaller magnitudes of effect, but similar reduction in the relative risk of coronary events in diabetic and non-diabetic patients. The Veterans Administration High-Density Lipoprotein Intervention Trial, a secondary prevention trial using a fibrate drug, gemfibrozil, included a relatively large group of diabetic patients with CHD and

demonstrated a similar, significant 24% reduction of major coronary and stroke events in diabetic and non-diabetic patients [378]. In this trial LDL cholesterol level remained almost unchanged in the gemfibrozil-treated group, but typically for fibrate effect, HDL cholesterol level increased and triglyceride level became reduced.

Recently the HPS [274] demonstrated in diabetic patients, and similarly also in non-diabetic patients a significant 30% risk reduction in CHD and stroke. This study included almost 6000 type 2 diabetic patients, and almost 4000 of them did not have prior myocardial infarction or angina pectoris. Thereby this study is larger than all previous studies on diabetic subjects combined, and in contrast to the previous studies, the study included all ranges of serum cholesterol down to 3.5 mmol/l. The relative treatment effect was independent of baseline cholesterol (although the absolute risk and thus also treatment effect increased with increasing cholesterol).

Antithrombotic therapy

Both type 1 and type 2 diabetes are associated with increased tendency to thrombotic phenomena. When the Anti-Platelet Trialists' Collaboration demonstrated in their meta-analyses the beneficial effect of the use of aspirin in patients with clinically established CHD, cerebrovascular disease and other forms of atherosclerotic disease [379], they also analysed data from about 4500 diabetic subjects included in the trials and concluded that treatment with antiplatelet drugs (mainly aspirin) resulted in a 25% reduction in the risk of cardiovascular events and that the effect would be similar in diabetic and non-diabetic subjects. The Antithrombotic Trialists' Collaboration have, however, now extended their meta-analyses to cover a larger number of trials on diabetic patients and have arrived to a much more modest benefit from antiplatelet therapy in diabetic patients – only a 7% reduction in the risk of cardiovascular events as compared to the overall reduction of 22% in the trials [380]. Importantly, Early Treatment Retinopathy Study demonstrated that in diabetic patients aspirin therapy did not increase the risk of vitreous or retinal haemorrhage [381]. A new trial examining the role of aspirin in the prevention of cardiovascular events in diabetic subjects is in progress in the UK.

Multifactorial intervention

The typical type 2 diabetic patient suffers from many components of the metabolic syndrome, and guidelines for treatment generally recommend intervention against all cardiovascular risk factors. Despite these recommendations, no studies have been targeted against all risk factors at the same time. The UKPDS [373] included intervention against glucose and hypertension, and demonstrated an effect of both, although the study was underpowered to evaluate the effect of the combined intervention. The STENO-type 2 study included 160 patients at very high

risk of CVD (type 2 diabetic patients with microalbuminuria), and the patients were randomised to standard treatment or intensive, polypharmacological treatment including insulin, statins, ACE-inhibitors, other antihypertensive agents, Acetylic Salicylic Acid, and lifestyle intervention (smoking, physical activity and diet). After 4 years a significant difference in incidence of microvascular complications was observed [382], and after 8 years a significant 53% risk reduction in macrovascular complications was observed [383]. Thus in patients with very high risk of cardiovascular disease, polypharmacological multitargeted intervention is needed to obtain the maximal risk reduction. Whether a similar intensive treatment regimen is necessary in the majority of patients with shorter diabetes duration, without microalbuminuria and with a less serious cardiovascular risk profile is still unknown, but this is currently being tested [384].

4.7 Metabolic syndrome

The metabolic syndrome, also known as the insulin resistance syndrome is characterised by a clustering of hyperinsulinemia and underlying insulin resistance with several other cardiovascular risk factors, including impaired glucose regulation, elevated triglycerides, decreased HDL cholesterol, raised blood pressure, and obesity and its central distribution. The pathogenesis of the syndrome is so far incompletely understood, but obesity, sedentary lifestyle, dietary factors and genetic factors are known to contribute and interact in its development [385–387]. The main importance of the metabolic syndrome is in its association with the risk of the development of type 2 diabetes mellitus and atherosclerotic cardiovascular disease.

Clinical and epidemiological research on the metabolic syndrome has suffered from the lack of agreement on the definition of the syndrome and from the diversity in the cut-offs used for its components.

The World Health Organization (WHO) consultation for diabetes and its complications [388] and the US National Cholesterol Education Program (NCEP) Expert Panel [325] have recently formulated definitions for the metabolic syndrome.

The NCEP definition of the metabolic syndrome was developed for clinical use [325]. It does not include any estimation of insulin resistance and is based on the presence of three or more of the following components:

- 1) central obesity (waist circumference > 102 cm in males, > 88 cm in females)
- 2) impaired glucose regulation [fasting plasma glucose ≥ 6.1 mmol/l (≥ 110 mg/dl)]
- 3) elevated triglycerides [≥ 1.7 mmol/l (≥ 150 mg/dl)]
- 4) low HDL cholesterol [< 1.0 mmol/l (< 40 mg/dl) in males, < 1.3 (< 50 mg/dl) in females]
- 5) raised blood pressure $\geq 130/85$ mmHg.

Findings from prospective cohort studies on the predictive value of the WHO and NCEP definitions of the metabolic syndrome with regard to the development of type 2 diabetes are so far limited. A 4-year follow-up study of Finnish middle-aged men showed that both definitions identified subjects at high risk of developing diabetes; the odds ratios were from 5.0 to 8.8, depending on the cut-offs used for the measures of central obesity [389]. In the 11.6-year follow-up of the same study cohort, men with the metabolic syndrome as defined by the WHO or NCEP were about 3 times more likely to die from coronary heart disease [390]. In the 11-year follow-up of the ARIC study population, the presence of the metabolic syndrome as defined by the NCEP was associated both in men and women with about 2-fold increase in the risk of incident coronary heart disease and stroke [388]. These results were obtained adjusting for the effect of smoking, LDL cholesterol and other risk characteristics which do not belong to the metabolic syndrome, suggesting that the high risk associated with the metabolic syndrome will not be well captured with risk prediction systems based on the conventional set of risk factors.

4.8 Other risk factors

4.8.1 Homocysteine

Raised plasma homocysteine is associated with increased risk of coronary heart disease although the risk estimates are greater in cross sectional and retrospective case-control than in prospective studies [139,391,392]. An elevated plasma total homocysteine substantially increases the risk associated with smoking, hypertension and hyperlipidaemia [140,393]. Dietary deficiency of B-vitamin cofactors is among the principal causes of raised plasma total homocysteine in the general population [394]. Lifestyle and biological risk factors of coronary heart disease are also associated with plasma total homocysteine [395–397]. Genetic factors also modulate total plasma homocysteine levels. Most frequent of these is the thermolabile variant of methylenetetrahydrofolate reductase [398]. This folate-sensitive variant is associated with raised plasma total homocysteine [399] and a higher risk of coronary heart disease particularly in folate-depleted individuals [400]. Folic acid reliably reduces plasma total homocysteine [392] but whether this reduces coronary heart disease risk is unknown. This question is being addressed in several ongoing randomised controlled trials. For the present, careful attention to conventional risk factors in individuals with raised plasma total homocysteine is warranted.

4.8.2 Markers of inflammation

Inflammatory processes may have a role in the pathogenesis of atherosclerosis and clinical manifestations of atherosclerotic disease. Elevations of plasma C-reactive protein (CRP), a marker of inflammation, using new sensitive assays, predict an increased risk of CHD events in

patients with unstable and stable angina pectoris. [401]. Prospective epidemiological studies of initially asymptomatic individuals have shown an association between elevated CRP levels and the risk of CHD events, stroke and peripheral vascular disease, independently of traditional risk factors. In a large cohort study of initially healthy women [402] it was suggested that CRP may be a better predictor of risk of a first vascular event than LDL cholesterol levels. Furthermore, in low cholesterol subjects, post-hoc trial analysis suggests that statin therapy may reduce both CRP and risk in subjects in whom CRP is raised [403]. However, it is not yet clear how clinicians should use screening results of C-reactive protein, and therefore widespread screening is not recommended. Future trials must address whether reducing CRP levels, with statins or by other means, actually reduce risk [404]. It has been suggested that cytokines, interleukin-6 and tumour necrosis factor alpha, which regulate CRP, could be mediators in the association between other laboratory markers for inflammation, such as increased leukocyte count and reduced plasma albumin, and CHD risk [405]. The association between elevated plasma fibrinogen and CHD risk may also in part reflect an on-going inflammatory process, because fibrinogen is an acute phase reactant. An association between elevated plasma levels of intercellular adhesion molecule ICAM-1 and CHD risk has also been demonstrated, suggesting that cellular mediators of inflammation have a role in atherogenesis. The possible role of markers of inflammation in the clinical assessment of cardiovascular risk remains to be determined.

There is also interest in the possible role of chronic infections caused by specific microorganisms, such as *Chlamydia pneumoniae*, *Helicobacter pylori*, and cytomegalovirus, mainly based on studies of antibodies to these microorganisms, in the pathogenesis of atherosclerosis and the precipitation of clinical manifestations of CHD and other atherosclerotic disease [406]. The evidence for the association between *C. Pneumoniae* and CHD is somewhat stronger than that found for *H. pylori* and cytomegalovirus. *C. Pneumoniae* particles have been found in coronary atherectomy specimens and not in normal coronary arteries, but the sequence of infection and the development of atherosclerotic lesions still remains uncertain.

4.8.3 Thrombogenic factors

Pathological evidence indicates that the majority of acute coronary events are caused by thrombosis in a coronary artery often following rupture of atheromatous plaque in the same vessel. [407,408]. Thrombolytic, anticoagulant and antiplatelet therapy are routinely used in clinical practice [409]. Many prospective studies have now examined which components of the complex, dynamic system of coagulation and fibrinolysis are important in predicting risk of subsequent cardiovascular events. Meta-analyses

of studies of fibrinogen, C-reactive protein, albumin and white cell count [405] and of haematocrit, viscosity and erythrocyte sedimentation rate [410], all of which are associated with coronary events, have been reported. Other studies and meta-analyses have shown von Willebrand factor [411,412] (a marker of endothelial dysfunction) and D-dimer antigen [413,414] (a marker of fibrin turnover) to be associated with risk. Two cohort studies [415,416] suggested that factor VII levels were independently related to risk of coronary events but other cohort studies have not confirmed this [133,417]. Two recent reports found plasminogen levels to be associated with increased risk of coronary events [417,418]. Observational studies of platelet aggregation [419,421] have failed to show useful prediction of disease although meta-analyses of antiplatelet treatments have clearly established a role for reduction of platelet aggregability in the prevention of cardiovascular events [379,380].

Studies which have compared the risk of subsequent coronary events in models in which thrombogenic factors replace conventional lipid factors have generally found that thrombogenic risk factors predict risk at least as well as lipids [421–423]. European [424] and International [425] Task Force reports acknowledge the relevance of thrombogenic risk factors, but the former notes that fibrinogen has been incorporated into some risk scores. A recent report from the PRIME Study in France and Northern Ireland notes that fibrinogen levels accounted for 30% of the difference in the excess risk in Northern Ireland whilst the combined effect of the classical risk factors accounted for only 25% of the excess [426]. Further international studies may be helpful in establishing the extent of the contribution of thrombogenic risk factors.

Several thrombogenic factors shown to predict risk of coronary disease are associated with lifestyle factors [427] which may be modifiable. Smoking habit has been shown to be closely associated with fibrinogen levels, plasma viscosity, white cell count, and D-dimer [427,428]. Smoking habit clearly has a major impact on the coagulation system and several mechanisms probably account for the increase in coagulability. Smoking also promotes an inflammatory or acute phase response which appears to persist for 10 years or more after quitting in middle aged men [429]. Not all thrombogenic risk factors are influenced by smoking habit however and clearly there is a need to further elucidate thrombogenic risk factors which could be modified by other lifestyle changes or by appropriate drug therapy. Finally there is a need to address the issue of the link between thrombogenic and inflammatory markers [430].

4.8.4 Genetic factors

Genetic information may be divided into three categories: information on family history, information on phenotypes, and information on genotypes. All three types of information may be useful to identify patients who are at

high risk of developing CHD, and who may therefore warrant earlier or more aggressive therapeutic intervention to reduce modifiable risk factors (e.g. plasma cholesterol or blood pressure). Information on phenotypes and genotypes may be additionally useful in guiding the particular therapeutic approach of choice.

Family history

The importance of a family history of CHD as a coronary risk factor has been established by a number of studies. A classical example is provided by a long-term follow-up of more than 20 000 twins in Sweden [431]. In this study, the relative risk (RR) of death from CHD in men, according to the age at which their twin died from CHD, decreased from ~8 in monozygotes and ~4 in dizygotes in the age range 36–55 years, to ~4 in monozygotes and ~2 in dizygotes in the age range 66–75 years. This suggests the influence of genetics weakens with age. However, as a consequence of the increasing frequency of coronary disease with age, at the population level, the risk of CHD attributable to genetics was maximal in the age range 55–75 years.

A detailed family history of CHD, or other atherosclerotic disease should be part of the assessment of all patients with CHD and in the identification of high-risk individuals. The risk of CHD increases (i) when an individual is closely related to a family member who has developed CHD. A history of CHD in a first degree relative (parents, brother or sister, or son or daughter) is more important than a similar history in a second degree relative (grandparent, aunt, uncle) or in a third degree relative (cousin); (ii) as the percentage of family members with CHD increases; and (iii) the younger the age at which family members develop CHD. Risk factor screening should be considered in the first degree relatives of any patient developing coronary disease before 55 years in men and 65 years in women. A family history of premature CHD should also be taken into account in assessing the risk of developing the disease in a healthy individual, including the taking of detailed history and drawing of a pedigree. Lifestyle advice and, where appropriate, therapeutic management of risk factors should be offered to members of families where coronary disease is highly prevalent.

Phenotypes

The pathophysiology of CHD is characterised by a mixture of acute events, such as plaque rupture, thrombosis and vasoconstriction, acting on a substrate of chronic processes, such as dyslipidaemia, hypertension, endothelial dysfunction, diabetes, cardiac and vascular hypertrophy, atherosclerosis. Each of these acute and chronic processes will have their own genetic and environmental determinants. Hundreds, if not thousands of molecules will thus be contributing to these complex disease processes and a wide spectrum of responses,

reflecting the variable expression or function of these molecules, can be expected. A better understanding of the genetic contribution to common cardiovascular diseases and strongly depends on a more precise assessment of the disease phenotypes. In other words, a purely clinical definition of a disease is largely irrelevant when discussing genotype-phenotype associations. To demonstrate their value genotypes will need to be aligned with appropriate phenotypes, corresponding to different clinical expressions of the disease.

For many measurable traits (phenotypes) there is good evidence for a relatively strongly genetic contribution to the determination of levels, which is usually estimated by “heritability”. For apoproteins and lipid traits heritability varies between 40–60% [432], meaning that genetic factors are determining around half of the between-individual differences and environmental factors the remainder. Similarly for CRP heritability appears high [433] although fibrinogen appears lower [434]. One exception to this is plasma Lp(a), a factor where levels are remarkably stable within an individual over time, and heritability is reported to be > 90% [435]. Interestingly, variability at the locus coding for the apo(a) gene itself accounts all most all of the variance of plasma Lp(a) in normal populations [436]. The relevance of this is that a recent meta-analysis reported that levels of Lp(a) in the top tertile was associated with a 1.6-fold greater risk of CHD [320], an effect which is of similar magnitude as smoking, and thus the (a) gene would appear to be a major genetic factor for CHD, as was confirmed recently by a genetic approach [437].

Genotypes

A gene may predispose to CHD if it exists functionally under different forms. Functional polymorphisms are relatively common and may affect regulatory or coding regions of genes. This may induce variability of biological mechanisms, which have neutral, beneficial or detrimental consequences. Genetic polymorphisms are defined as sequence variants that occur at a frequency greater than 1%. These include insertion/deletion variants and single nucleotide polymorphisms (SNPs). SNP analysis gained acceptability with the development of the Human Genome Project, and the publishing of the draft human genome sequence, which revealed that there were only 30–40 000 genes. SNPs have been used with increasing momentum [438] to study the genetic determinants of complex diseases such as CHD, in case-control analyses and association and linkage disequilibrium studies with intermediate traits [439]. The important issue is whether and under what circumstances will such genetic information be useful for diagnosis and patient management.

In general, the levels of CHD risk traits are influenced by both environmental and genetic factors, with, in most

subjects, gene variants of small or modest impact being involved. Thus an individual with, for example, high plasma cholesterol may have inherited several “raising” alleles acting in combination, or they may have few such alleles but are taking up a cholesterol-raising lifestyle (e.g. diet), but most likely they have a combination of both influences. In theory the identification of the complete list of the genetic variants that an individual has inherited may be of diagnostic or prognostic value, but since there will be many functional sites (SNPs) in each gene, some of which may increase risk and others decrease risk, and a very large number of genes involved in determining even each risk trait, it is unclear whether determining a few or even several hundred SNPs will be of great value (or practically possible). Some studies have suggested that particular genotypes may predispose to elevated CHD trait levels only in a certain environment, and understanding such interactions is likely to be of major research importance in future years, since these interactions shed light on pathophysiological processes. However the consequence of this is that in subjects in the general population, DNA-based tests do not, at the present time, add significantly to diagnostic utility or patient management, over-and-above the use of measures of established CHD risk factors.

A large number of “candidate” genes have already been investigated in relation to CHD traits and to risk of CHD itself, and a comprehensive list is beyond the scope of this report. Recently, meta-analyses have been used to obtain a statistically robust estimate of these effects, and several variants appear to be associated with statistically significant although rather modest effects on risk. These include ApoE, ACE and PAI-1 [440–444]. For the common ApoE protein variants (E2, E3 and E4), there is a strong and consistent impact on plasma lipid levels (E2 lowering and E4 raising), which translates into a modest E2 lower and E4 higher impact on CHD risk such that this genotype may explain 5–8% of the attributable risk of CHD in the population [441]. The ACE polymorphism has probably been the most extensively studied polymorphism so far, in relation to preclinical phenotypes and cardiovascular endpoints. One important feature of this polymorphism is that it appears to be a response modulator to a wide range of inducing factors. For example, it has been reported to modify the hypertrophic response of the heart to physical training [445], the restenotic process after stent angioplasty [446], the evolution of cardiac function after myocardial infarction [447] and the survival of patients with congestive heart failure [448], and with the development of diabetic nephropathy and retinopathy [449]. Interestingly, other candidate gene polymorphisms may also have the characteristic of being response modifiers to a number of stimuli. A fibrinogen promoter polymorphism may affect the plasma fibrinogen response to cigarette smoking, physical training or acute phase reaction [450–452], Cholesterol ester transfer protein (CETP) and alcohol dehydrogenase genotypes modify the relationship

between alcohol consumption and plasma HDL cholesterol [453,454], an amino acid variant that causes enzyme instability in the methylenetetrahydrofolate reductase (MTHFR) protein affects the relationship between folate intake and plasma homocysteine [399] and the α -adducin polymorphism between that of salt intake and blood pressure and risk of MI [455]. These interactions also need to be more widely replicated in larger studies but if confirmed they offer potential prospects for CHD prevention through the identification of responders to deleterious factors or beneficial ones (drugs for example) by genotyping appropriate candidate genes.

What the future contribution of molecular genetics will be to the management of common cardiovascular diseases is difficult to predict. In the longer term, understanding disease etiology in terms of genetic determinants may be useful in identifying high-risk individuals and adapting therapeutic management to the individuals genetic make-up.

Severe familial hyperlipidaemias and CHD

These confer a high risk of early CHD and a high blood lipid in an individual, and particularly if there is a family history of premature CHD, should lead to systematic screening of the close relatives. These include:

Familial hypercholesterolaemia (FH)

FH has an estimated prevalence of 1/500 [456], but may be much higher in some populations which recently increased in size (e.g. French Canadians, Afrikaners and Lebanese), as a consequence of the so-called founder effect. It is characterised by hypercholesterolaemia due to elevated plasma 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 [456], and those who smoke, are hypertensive or have other risk factors are at particularly high risk. FH is present in 5–10% of individuals who develop CHD under the age of 55 years [457]. Thus the early identification of FH individuals will allow changes in lifestyle, including dietary intervention and smoking cessation advice as well as for drug treatment, and these measures, particularly statin treatment, will lead to a longer healthier life [458]. Statin therapy is warranted even in young FH subjects who currently have no evidence of CHD because of their high lifetime risk. Cost-benefit modelling based on data in the UK has demonstrated the effectiveness of cascade testing in the relatives of FH patients [459], and an active programme in the Netherlands has been particularly successful in identifying FH relatives in this way [460].

FH is an autosomal dominant inherited disorder and is usually caused by a mutation in the low-density lipoprotein receptor gene (LDLR). To date over 700 different mutations have been identified world-wide (see

<http://www.ucl.ac.uk/fh>) although the spectrum within a single country is much smaller [461–463]. However, an LDLR mutation is not found in all patients with a clinical diagnosis of FH, and in approximately 3% of FH patients in the UK, North Europe and the USA a defect has been detected in the apolipoprotein B-100 gene (Apo B), the ligand for the LDL-receptor. This disorder has been designated familial defective apolipoprotein B-100 (FDB) [464]. FDB appears to be somewhat milder in its expression than LDLR but hypercholesterolaemia occurs in childhood, and early CHD is frequent. Recently two reports of a third distinct genetic cause of monogenic autosomal dominant familial hypercholesterolaemia have also been published [465,466] but no specific gene has yet been identified. Finally, a recessive form of hypercholesterolaemia has been reported, caused by defects in a chaperone protein [467]. The frequency of this is unknown but it appears to be rare.

Since cholesterol levels in FH and non-FH subjects overlap, molecular genetic testing can be useful in the correct diagnosis of relatives in such families, [468,469]. Using currently available routine clinical genetic diagnostic techniques [462], it is possible to demonstrate a mutation in the gene for the LDL receptor, or the gene for apolipoprotein-B, in many of these patients, but this is usually only available in a research setting. Such specialist services are available in several European countries including the Netherlands [461], UK [462] and Iceland [463], but each country should have its own programme for genetic testing for FH because the spectrum of mutations varies between countries.

Familial combined hyperlipidaemia (FCH)

This is the most common of the severe hyperlipidaemias, with a prevalence of perhaps 1/100 [470]. The genetic inheritance pattern is not so clear-cut as seen for FH, and a major gene determining this phenotype has so far been identified only by linkage in a few families from Finland [471]. FCH is likely to be more polygenic/multifactorial than FH, but the identification of the gene(s) involved will be of interest whether the disorder is caused by a “major gene” or the interplay of several.

Coagulation disorders

Although familial monogenic disorders have been identified they are mostly extremely rare. Mutations in the genes for clotting factor V (R506Q designated factor V Leiden) and for prothrombin (G20210A) have been identified, each with a carrier frequency of 2–3%, but these mutations primarily increase risk of venous thrombosis and have little effect on arterial thrombosis and risk of CHD [444].

4.8.5 Early life determinants of cardiovascular disease

The risk of cardiovascular diseases is modified by factors influencing foetal growth and development. This was first recognised by Forsdahl who showed that coronary

heart disease risk was correlated with prior infant mortality in the 20 counties of Norway, thus implicating some general aspect of infant health [472]. Barker has subsequently examined this hypothesis of early life determinants of adult disease [473]. This work has emphasised the importance of intrauterine nutrition as one of the major mechanisms by which the anatomy, physiology and metabolism of the body are programmed [474]. The consistent associations between birth weight, and other markers of intrauterine growth such as head circumference, placental weight and length, and later cardiovascular disease, independent of gestational age, maternal smoking and socio-economic position is of particular importance in highlighting the fact that increased risk is laid down very early in life [474].

Although the hypothesis that intrauterine nutrition is of importance in determining risk of various chronic diseases in adult is well-supported by evidence, it is apparent that markers, such as birth weight, are an incomplete explanation of the risk factor trajectories that children subsequently follow. For example, while it is clear that blood pressure is associated with birth weight [475,476] research has shown that weight in childhood is also an important determinant of blood pressure [477] and it appears that blood pressures are highest in those who were small at birth and become overweight as adults [474].

The realisation that neither “old-fashioned” risk factor epidemiology with its emphasis on smoking, hypertension and hyperlipidaemia nor the intrauterine nutrition hypothesis provided a comprehensive model has led epidemiologists to a lifecourse approach. In many scientific disciplines it has long been acknowledged that a deeper understanding of causal pathways is afforded by taking a life course approach. Life course epidemiology has recently developed as a means of structuring ideas about how various biological and social factors throughout life can influence adult health by independent, cumulative or interactive effects [478].

In women, evidence is accruing demonstrating that birth weight, age at menarche, number of pregnancies, and classical risk factors in adult life are all implicated in subsequent cardiovascular disease [479]. The implications of the early life and lifecourse determinants of cardiovascular disease are crucial for prevention. Traditionally orientated cardiovascular disease prevention programmes largely concerned with people in middle-age has been shown to be ineffective [480] and extending such investment would seem to be misplaced given our better understanding of the ways in which risk accumulates over the lifecourse. It would, of course, be simplistic to suggest that investing in better maternal and child health care alone would be sufficient to control cardiovascular disease. However, focusing on prevention across the life course should be rewarded by later benefits in adult health.

4.8.6 Microalbuminuria

Microalbuminuria, i.e. slightly elevated urinary albumin excretion, was initially demonstrated in patients with diabetes mellitus where it was shown to be associated with atherogenic changes in the cardiovascular risk profile [481,482] and to predict increased mortality and cardiovascular disease [483–485].

Subsequently several studies demonstrated an association between slightly elevated urinary albumin excretion and cardiovascular disease, even in the general population [486–489]. The level of urinary albumin excretion associated with a significant increase in the risk of CVD in the general population is approximately 7 µg/min or 10 mg/24 h [490–492] (corresponding to a urinary albumin/creatinine ratio of 1 mg/mmol), and this is substantially lower than what is found in the diabetic population.

The pathogenetic mechanisms explaining the association between microalbuminuria and cardiovascular disease are poorly understood, but microalbuminuria is associated with elevation of blood pressure and total cholesterol and with decreased HDL cholesterol [486–489]. Microalbuminuria is likely to be a marker of generalised endothelial dysfunction and hyperpermeability of macromolecules as indicated through the increased transvascular leakiness for albumin and increased fractional escape of LDL from plasma found in individuals with microalbuminuria [493–495].

The impact of microalbuminuria on the risk of ischaemic heart disease is of the same magnitude as that seen in smokers compared to non-smokers, males compared to females or an absolute increase in total cholesterol of 1.5 to 2.0 mmol/l, and the risk is independent of other well established risk factors as age, gender, smoking, blood pressure and lipid levels [496].

Intervention studies specifically targeted at answering whether lowering of the urinary albumin excretion rate reduces the risk of developing ischaemic heart disease have not been performed, but it is clear that antihypertensive therapy – particularly with ACE-inhibitors and angiotensin II antagonists – reduce the urinary albumin excretion. Intervention studies will, however, be difficult to perform, as the logical (and currently only possible) intervention would be antihypertensive therapy.

4.8.7 Left ventricular hypertrophy

Left ventricular hypertrophy, either detected electrocardiographically or by echocardiography, has repeatedly been shown to be an independent risk factor for cardiovascular morbidity and mortality in hypertensives [497,498].

Echocardiography is undoubtedly much more sensitive than electrocardiography in diagnosing LVH and predicting cardiovascular risk.

Classification into concentric and eccentric hypertrophy and concentric remodelling has been shown also to have risk-predicting value [499]. When treatment decisions are uncertain, an echocardiographic examination may help in more precisely classifying the overall risk of the patient [237].

4.9 Psychosocial factors

There is increasing scientific evidence that psychosocial factors contribute independently to the risk of coronary heart disease (CHD), even after statistical control for the effects of standard risk factors [500,501]. In addition to increasing the risk of a first event and worsening the prognosis in CHD, these factors may act as barriers to any effort to improve lifestyle and promote health and well being in patients and populations. Low socio-economic status, lack of social support and social isolation, stress at work and in family life, and negative emotions including depression and hostility, have been shown to influence both the risk of contracting CHD and the worsening of clinical course and prognosis in patients with CHD.

Evidence is also accumulating of therapeutic and preventive intervention methods that counteract psychosocial stress and promote healthy behaviours and lifestyle [502,503] such that they may prevent the progression of clinical CHD.

Low socio-economic status

Men and women with low socio-economic status (SES), defined as low education, holding a low status job or living in a poor residential area, have an increased all-cause as well as CHD mortality risk. Several attempts have been made to “explain” the SES gradients in CHD.

Several population based studies have examined this question in a similar and conclusive manner. For instance in British civil servants [504], in Finnish men from the North Karelia region [505] and in Swedish women from Stockholm [506,509], CHD morbidity and mortality were inversely related to SES in a graded fashion, with a four-fold difference between the highest and lowest occupational categories.

Controlling for standard risk factors reduced the size of the gradient, but a relevant proportion of the variance according to SES was explained by distinct psychosocial factors which either mediate or modify the effect of SES on CHD. They originated from lack of control at work, social isolation and lack of social support, poor capacity to cope with stressors, hopelessness and a depressed mood.

Low SES as such is not amenable to change. However, the mechanisms mediating the effects of low social class on CHD risk can be modified, as they are concerned with both the standard physiological risk factors, the lifestyle behavioural risk factors and the psychosocial stressors.

Therefore, preventive efforts need to focus especially on individuals and patients with low education, low job positions and in poor residence areas.

Social isolation

People who are isolated or disconnected from others are at increased risk of dying prematurely from ischaemic heart disease [508–513]. Similarly lack of social support leads to decreased survival and poorer prognosis among people with clinical manifestations of CVD [514–519]. Most studies report that social networks are related more strongly to mortality than to the incidence of acute myocardial infarction [509,512,513].

Several aspects of low social support have been associated with poor outcomes in patients with heart disease even after adjustment for other risk factors. These include living alone [515], living without a confidant [519], low emotional support [514], social isolation coupled with life stress [518], low instrumental support [520], low social integration [510], low availability of social support [521], and low perceived social support [522]. Distinctions are made between the structural component of the social networks, which refer to the people, with whom one is connected, and the functional component, referring to the support that they provide.

Three dimensions of social support have been distinguished: emotional support, provided by family and other close persons to increase self esteem and strengthen the sense of identity of the subject, appraisal support, providing information, advice and guidance in difficult situations and tangible or practical support. The latter two are mostly provided by friends, neighbours, co-workers along with family members.

Psychophysiological pathways of social support include beneficial effects on lifestyle and behaviour change. Evidence of sympathetic nervous system activation with direct effects of social isolation on blood pressure and heart rates, as well as pathways involving the hypothalamic–pituitary–adrenocortical (HPA) axis, have been described. In summary, the harmful effects of lack of social support on the cardiovascular system as shown in epidemiologic studies, are consistent, whereas mechanisms are only partly explored [523].

Psychosocial stress at work and outside work

Stress at work, as measured by the high demand/low control model [524] and the high effort/low reward model [529] predict CHD risk separately and together [526]. These effects are seen in both women and men [527,528]. Possible pathogenic pathways include progression of intima–media thickening of the carotid arteries [529] and elevated ambulatory blood pressure [530], particularly in combination with excessive alcohol use [531].

Prolonged exposure to work at irregular hours, including work at night, increases CHD risk, with a higher risk as the number of years in shift work increases [532–534]. A direct and causal effect of shift work on CHD is suggested in women [535] and in men [536]. The shift work schedule may violate endogenous circadian rhythms which regulate the biological sleep – wakefulness cycle and disturb the balance between cardiac sympathetic and vagal modulation. A manifestation of autonomic imbalance of the sinoatrial node activity, decreased heart rate variability, has been related to shift work exposure [537]. In the Helsinki Heart Study, shift workers, who had a 50% excess risk of CHD over day workers, exhibited large increases in perceived job stress suggesting a direct stress-related mechanism explaining part of the CHD risk [538].

In addition to perceived stress at work, conflicts, crises and long term stressful conditions in family life have also been shown to increase CHD risk. In Stockholm women, marital discord was found to worsen prognosis in acute coronary syndrome and reduce event-free survival over and above the effects of standard clinical prognostic factors [539]. Although all women were employed outside the home, the hazards of marital stress were stronger than those of stress at work in these women.

Hostility

The scientific evidence supporting Type A behaviour as a risk factor for CVD, is confined to the hostility component of the global Type A construct [540]. Early findings linking higher scores on the Cook and Medley Hostility scale to coronary atherosclerosis severity [541] and to CHD incidence and all-cause mortality [542,543] have been coupled with more recent findings in a comprehensive review by Miller *et al.* [544] The psychological characteristic of hostility, as measured with a wide array of instruments, was confirmed as a risk factor, not only for CHD but also for virtually any physical illness.

Hostility is associated with alterations in autonomic balance and HPA axis function that could account for at least some of their health-damaging effects. When anger is induced in laboratory studies [545–547], hostile persons exhibit larger sympathetic nervous system (SNS)-mediated cardiovascular responses than non-hostile persons. Hostile persons also show increased SNS activation during everyday life, as documented by down regulation of beta-adrenergic receptors in lymphocytes [548]. Laboratory research [549] has shown decreased parasympathetic antagonism of SNS effects is reduced in hostile persons. Hostility [550] is further associated with decreased parasympathetic function during ambulatory ECG monitoring.

Depression

Clinical depression, depressive symptoms and other negative emotions have been shown to predict incident CHD, and worsen its prognosis, independently of standard risk

factors. For example, clinical depression is associated with a threefold risk for major cardiac events in established CHD. Further evidence suggests that both prevalence of depressive symptoms as well as association with somatic outcome are higher/stronger in women compared to men. Besides the adverse behavioural consequences of negative affect, depression may also increase platelet activation, inflammation and ischaemia, while decreasing heart rate variability [500]. Increased risk may also be mediated by side effects of tricyclic antidepressants.

In patients with manifest coronary disease, depression has well-documented effects on cardiac symptoms, overall quality of life and illness behaviour (including increased health care utilisation, low adherence with behaviour change recommendations or cardiac medications, and low rates of work resumption). After an acute coronary syndrome, patients with depressive symptoms also show worse cardiac outcomes [551]. Perceived social support seems to counteract the adverse effect of depression [522], whereas lack of support was found to reinforce the effects [552]. Prognostic risk is highest in persons with a combination of chronic negative affectivity and social inhibition [553,554].

Clustering of psychosocial risk factors and biobehavioural mechanisms (Table 15)

As was noted in the introduction, CVD's multifactorial aetiology and the multiplicative effect of coronary risk factors mean that in attempting to reduce risk we must deal with the whole person and not with isolated risk factors. This principle is no less true when it comes to psychosocial risk factors and the biobehavioural mechanisms which mediate effects on pathogenesis and prognosis.

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. Women who report high job strain, for example, are also more hostile, depressed, and socially isolated [555]. Both women and men of lower SES are more likely to be depressed, hostile, socially isolated, and to engage in risky health behaviours, all characteristics that contribute to the SES gradient of CHD risk [505,506,556]. In addition to risky health behaviours like smoking, high alcohol consump-

tion, and unhealthy nutrition, persons with psychosocial risk factors are also more likely to express biological characteristics – e.g. alterations in autonomic function and disturbances of the HPA axis, which affect haemostatic and inflammatory processes – that are undoubtedly involved in mediating the links between psychosocial factors and cardiovascular disease. Dysregulated CNS serotonergic function is one such neurobiological mechanism, that could account for the clustering of psychosocial and biobehavioural risk characteristics [556].

The tendency of psychosocial risk factors and biobehavioural mechanisms to cluster in the same individuals and groups has important implications not only for understanding who is at risk of developing CHD, but also for strategies to modify risk and improve quality of life. Because persons with high levels of negative affect are more likely to smoke, attempts to help them quit smoking might be more successful if they include elements designed to reduce hostility and depression. Similarly, attempts to reduce the CVD risk in the socially disadvantaged, might be more effective by incorporating training in skills that will reduce negative feelings and increase access to positive, supportive social ties. In other words, behavioural interventions that reduce levels of psychosocial risk factors are likely to have broad benefits in terms of enabling people to be more successful in modifying unhealthy lifestyles and reducing biological consequences of stress – e.g. altered haemostatic and inflammatory functions – that are directly involved in pathogenesis.

Evidence for risk factor modification

Methods to improve psychosocial factors are available and a number of psychosocial intervention strategies have been demonstrated to have positive effects on both risk factors and CVD outcomes – but, the modes and contents of these interventions are variable. Even if they intend to target only single psychosocial risk factors, group-based behavioural interventions often contain elements, which affect multiple risk factors [557,558]. Nevertheless, recent meta-analyses suggest that interventions adding psychosocial and psycho-educational components to standard cardiologic care, can significantly improve quality of life and diminish cardiovascular risk. Furthermore, they seem to have the potential of substantially reducing cardiac

Table 15 Behavioural and pathogenic pathways for psychosocial risk factors in CVD

Psychosocial risk factors	Behavioural consequences	Pathogenic mechanisms
<ul style="list-style-type: none"> • Low socio-economic status • Social isolation and low social support • Psychosocial stress at work, work at irregular hours, family stress • Negative emotions of anger, hostility and depression 	<ul style="list-style-type: none"> • Unhealthy lifestyle, e.g. food choice, smoking, sedentary lifestyle • Barriers to the adoption of healthy lifestyle change and poor maintenance once change has been made • Inadequate utilisation of medical resources, e.g. delay in seeking help for serious symptoms, poor attendance to cardiac rehabilitation programmes • Disturbed sleep and negative social interactions 	<ul style="list-style-type: none"> • Autonomic dysfunction e.g. decreased heart rate variability • Sympato-adreno-medullary activation, e.g. increased heart rate and blood pressure reactivity, increased platelet adhesiveness • Hypothalamic pituitary-adrenocortical-activation e.g. disturbed cortisol and serotonergic diurnal patterns • Inflammatory and haemostatic processes, e.g. fibrinogen, CRP, PAI-1, TNF-alpha, cytokines • Metabolic dysfunction, central adiposity, insulin resistance, hypertension, dyslipidemia

morbidity as well as cardiac mortality [502,503]. The major psychosocial intervention study in post-MI patients, for example, was the Recurrent Coronary Prevention Project, which employed group-based cognitive behaviour therapy and decreased hostility and depressed affect [559] as well as the combined medical endpoint of cardiac death and non-fatal MI [557].

Two recent randomised controlled trials have targeted depression. Coronary patients with clinically significant depression can safely and effectively be treated with psychotherapy [560,561] or selective serotonin reuptake inhibitors [562]. The marked improvement in quality of life achieved by these treatments justifies their routine use in depressed patients with coronary artery disease. Although a definite beneficial effect on cardiac endpoints still needs to be documented, a recent multicenter clinical trial to decrease depressive feelings and improve social support, found beneficial cardiovascular effects in men but not in women [561].

There are, however, several other approaches to psychosocial intervention, which have proved to be useful. Thus it has been shown, in hostile CHD patients [563,564] that a group based hostility-control intervention may lead, not only to decreases in behaviourally assessed hostility levels, but also decreased depression, resting heart rate and cardiovascular reactivity to mental stress, as well as increased social support and satisfaction with life.

Likewise, in group based, psychosocial interventions, an element of increased social support is often the natural consequence. For example, work-reorganisations aimed at improving autonomy and increasing control at work may result in improved social support and reduction in physiological stress responses [565]. Work stress reduction in managers and supervisors may have beneficial health effects on the target individuals but also improve perceived social support in their subordinates [566]. Such effects are likely to contribute to decreased risk and improved prognosis in CHD through their stress reducing components.

Interventions that focus on improving both coping skills and social supports are particularly promising. Such interventions suggest that it is possible to diminish the harmful effects of family related stress and reduce anxiety and depressive feelings in women with coronary disease in group based intervention programmes [567].

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

Unfortunately, sudden cardiac death is for many individuals the first manifestation of cardiovascular disease. In others a large myocardial infarction, or a severe stroke may result in serious disability for the rest of their life. Therefore, one could think of a CVD detection programme as having the following objective: 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 medical technology to detect atherosclerotic arterial disease is already available but its role in population screening has yet to be evaluated.

Different criteria should be met, including:

- 1) The non-invasive technique for detecting arterial disease is valid, precise, easy and acceptable.
- 2) The relationship between arterial disease detected non-invasively and the development of symptomatic CVD has been quantified.
- 3) There is a defined screening strategy and a defined intervention and follow-up policy.
- 4) Screening and intervention results in reduction of CVD events.
- 5) Screening has no adverse effects.

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 radionuclide 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.

These new tests are based on the principle that atherosclerosis is a systemic disease of the arterial tree, with preferential involvement of the aorta and its large branches, coronary arteries, cerebral arteries, and lower-extremity arteries. Pathology studies have documented that levels of traditional risk factors are associated with the extent and severity of atherosclerosis. However, at every level of risk factor exposure, there is substantial variation in the amount of atherosclerosis. This variation in disease is probably due to genetic susceptibility combinations of different risk factors and interactions between genetic and environmental factors. Thus, measurements of subclinical disease, representing the current effect of risk exposures, may be useful for improving CHD risk prediction. Non-invasive tests such as carotid artery duplex scanning, EB-CT, MS-CT, ankle/brachial blood pressure ratios, and MRI techniques offer the potential for directly or indirectly measuring and monitoring atherosclerosis in asymptomatic persons.

4.10.1 Early detection of CVD in asymptomatic subjects with MRI

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 [568–572]. Currently, the sensitivity, specificity and robustness of this technique is 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 [573–575]. Moreover, it has become possible to noninvasively depict coronary plaques by MRI [576–580]. Using optimised 3D imaging sequences to improve contrast between lumen and vessel wall, a spatial resolution of $0.66 \times 0.66 \times 2 \text{ mm}^3$ can be obtained [579]. Regression of the lipid component of atherosclerotic plaques induced in animal models can now be demonstrated by serial *in vivo* MR examinations [581]. The current fast technical improvement has led to three-dimensional black-blood vessel wall imaging which permits *in vivo* distinction between “normal” and diseased vessel walls [582,583]. Carotid aortic and even coronary plaque assessment with MRI may soon lead to its use as a screening tool for quantifying subclinical disease, predicting future cardiovascular events and evaluating therapeutic interventions. 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 CAD. The Prevention Conference V participants [584] have recommended that more studies of MRI in CHD risk prediction should be encouraged. Additional technical development in this area is expected and should be of considerable value in the application of this emerging technology.

4.10.2 Quantitative assessment of coronary calcifications for the detection of asymptomatic high risk individuals

Background

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 [585–588]. 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 [586,587,589]. Coronary calcification is neither an indicator for stability nor instability of an atherosclerotic plaque [590–593]. In patients with acute coronary syndrome, there is almost always proof of coronary calcium. In these patients, the extent of coronary calcification is more pronounced than in control groups without known coronary artery disease [594–596]. Recently, the inflammatory component has been emphasised for patients with acute coronary syndrome [597], underlining the concept of evaluation of the total coronary plaque burden by quantification of coronary calcium burden [593,598].

Methods

Proof of coronary calcium with sensitive X-ray methods for the first time offers the possibility to detect and quantify coronary atherosclerosis non-invasively at an early stage. There are no other widely developed and clinically useful tools for the non-invasive detection and quantification of total coronary plaque burden [599].

The visualization of coronary calcium by means of fluoroscopy is not sensitive enough to detect clinically relevant information at early stages [600]. The sensitive detection of calcified coronary atherosclerosis was in the last years performed via EB-CT. With this method, no moving X-ray tube is used; therefore, there are no mechanical limitations (acquisition time = 100 ms/image). The vast majority of scientific data for the evaluation of presence and extent of coronary calcified atherosclerosis (“Agatston score”) result from EB-CT experience. EB-CT, however, is predominantly limited by its high cost and thus limited availability. Therefore, recent developments in technology of the classic CT resulted in multislice CT-devices, which are still limited by the mechanical rotation of the X-ray tubes, but have “ultra fast” rotation times of 250 ms/180° (e.g. 250 ms acquisition time per 4 simultaneously acquired slices) [601]. MS-CT, like EB-CT, for coronary calcification can be performed in a single breath hold without need of contrast medium. The major advantage of MS-CT is its considerably lower cost and therefore widespread utilisation. In contrast to EB-CT, MS-CT is not yet standardised, especially with much more variability in acquisition parameters compared with EB-CT. The minimal requirement for MS-CT is ECG-triggering [602,603]. If ECG-triggering is performed prospectively, radiation exposure is reduced and its results agree closely with EB-CT findings [608,609]. Radiation exposure of calcium scanning with the properly selected techniques is approx. 1mSv.

For over ten years, the amount of coronary artery calcification has been expressed by the “Agatston score,” which is a simple parameter containing the area as well as the density of calcified plaques, detecting calcium masses of $\geq 1 \text{ mg}$ [606]. Recently it has been suggested that the Agatston score be replaced with volumetric parameters, like total calcium volume (mm^3), calcium mass (mg), or calcium density (mg/mm^3). For clinical purposes, however, it is not yet known if these new parameters are superior to the Agatston score [607]. Since this will take another ten years to evaluate, the use of the Agatston score for routine purposes is recommended.

The value of the Agatston score can be further increased if not only the absolute score but also the age and gender distribution within percentiles are taken into account [595,608]. For example, an Agatston score of 10 in a 30-year-old woman reflects the 99th percentile, whereas the same score for a 72-year-old man reflects the 25th percentile.

Value of coronary calcification for proving or ruling out relevant coronary stenoses

The proof of coronary calcium is not in the least identical with the presence of relevant coronary stenosis, because its specificity regarding the presence of $\geq 50\%$ stenosis is only 50% (like flipping a coin) [600,609–612]. The misunderstandings in recent years regarding coronary calcium and extrapolation to coronary artery disease are due to a mix-up of definitions: while the presence of coronary calcium proves a “coronary disease” (coronary atherosclerosis) – it does not necessarily reflect “coronary artery disease” defined as $\geq 50\%$ narrowing. If coronary calcium scanning is applied inappropriately, the proof of coronary calcium may lead to an unnecessary increase of diagnostic cardiac catheterisations or even coronary interventions in asymptomatic persons. Therefore, even in the presence of coronary calcium, the decision for coronary angiography remains unchanged and depends on the presence of angina pectoris and/or objective myocardial ischaemia.

In contrast, coronary calcium scanning shows a very high negative predictive value: the Agatston score of 0 (ruling out coronary calcium) has a negative predictive value of nearly 100% for ruling out a significant coronary narrowing [609,613,614]. Therefore, in patients with atypical chest pain and an Agatston score of 0, coronary angiography can be easily dismissed. Furthermore, the Agatston score is suitable for differentiating between false positive and true positive exercise ECGs [615]. In very few cases, even no or only little coronary calcium has been observed in myocardial infarction [616,617].

Prognostic value of coronary calcium

In patients with heart attacks, a previously “non-significant” or better “hemodynamically non-significant” coronary narrowing has been observed with a frequency between 31% and 72% in 1091 patients [618–627]. In asymptomatic patients with risk factors but without known coronary artery disease, coronary calcium can show whether the exposure to the risk factors over time has already led to a development of atherosclerotic plaques over time in the coronary arteries of an individual person. Many prospective studies have shown the prognostic relevance of the amount of coronary calcium [595,628–632]. Even in patients undergoing coronary angiography, the measurement of the extent of coronary calcification adds valuable prognostic information [633].

If age and gender distribution of the percentiles are additionally taken into consideration, even patients with a “CAD equivalent” can be identified [634]: this “CAD equivalent” (defined as an annual risk of a fatal cardiac event $> 2\%$ /year) has been documented in a study with 1173 patients with 1.8% [629], another with 1196 patients with 2.3% [630] and another with 962 patients with 4.5%

[595]. Especially this group of patients may possibly benefit from focused statin therapy – even at “normal” lipid levels [635,636]. Besides this, the images of coronary calcium are an impressive motivation for the patients to modify their lifestyle [641].

Although today the prognostic impact of the Agatston score has been proven and accepted, one has to ask the key question whether the Agatston score is independent of the classical risk factors, meaning that the Agatston score provides additional clinically relevant information [598,638–641]. Recent publications supply an answer to this question: the Agatston score is an independent risk factor regarding the extent of coronary artery disease [638, 642–647] and regarding prognostic impact [629,631,646, 648]; for example, two men of the same age and identical classical risk profile may show an 8-fold different risk of a coronary event [648]. Aside from one study in older, high-risk patients [630], all studies showed that the prognostic value of coronary calcium offers information beyond the conventional risk factors [595,628,629,649]. The Rotterdam calcification study showed that the upper percentile range reflects a 12-fold increased risk of myocardial infarction – independent of the classical risk factors – even in elderly people [650]. The calcium score also adds important prognostic information to the measurement of C-reactive protein [651]. Furthermore, the extent of coronary calcium seems to reflect genetic components [652]. Even psychosocial factors seem to play a role in the presence and extent of coronary calcification [653,654].

Clinical indications

Although calcium scanning is widely applied today, it should not be uncritically used as a screening method. The clinical application of calcium scanning should only be applied in carefully selected individuals. Prospective studies proving the value of coronary scanning and unequivocally resulting in a class I indication with evidence class A for some indications, however, do not exist. With today’s knowledge, these studies may be even considered unethical. According to ACC/AHA guidelines, coronary calcium scanning can be performed in selected asymptomatic individuals, if a comparison with classic risk factors leads to expected additional analysis information for therapeutic strategies [612]. Coronary calcium scanning is thus especially suited for patients at medium risk [612,641,649, 655–658]. Today, an age of ≥ 45 years in men and ≥ 55 years in women is regarded as a risk factor [325]. The US Society of Atherosclerosis Imaging recommends coronary calcium scanning as the initial diagnostic test in individuals 65 years of age with symptoms atypical for angina and unknown CAD [659]. If coronary calcium is not present, the decisions regarding necessity and extent of primary prevention are made based on the analysis of the classical risk factors.

The indication for coronary calcium scanning must be assessed by well-trained physicians and interpreted

taking the total clinical presentation and the laboratory results into account.

4.10.3 Carotid ultrasound

Population based studies have shown a correlation between the severity of atherosclerosis in one arterial territory and involvement of other arteries [660]. The detection of atherosclerotic lesions in legs or carotid arteries is more accessible for non-invasive examinations than 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.

Sonography of superficial arteries is a relatively inexpensive means of non-invasively visualising the lumen and walls of arteries which are involved in the ubiquitous process of atherosclerosis. Risk assessment using carotid ultrasound focuses on measurement of the intima-media thickness (IMT) and plaque characteristics.

Intima-media thickness (IMT)

IMT is an integrated measurement of the involvement of both the intima and the media in the atherosclerotic process. Current ultrasound instrumentation with transducers ≥ 8 MHz is capable of identifying the borders between the vessel lumen and the intima as well as between the media and the adventitia. The two arterial interfaces are measured in both carotid arteries on the distal straight 1 cm of the common carotid arteries, the carotid bifurcations, and the proximal 1 cm of the internal carotid arteries. The carotid intima-media thickness is determined as the average of 12 measurements (both sides 6 measurements each from the near and far wall of each of the three segments). B-mode ultrasound is a valid and reliable technique for measuring IMT [661]. Reproducibility of measurements is best for the carotid arteries of normal persons.

Although there is a graded increase of cardiovascular risk with increasing IMT, a value > 1.3 mm for IMT is considered abnormal. Persons without known cardiovascular disease with increased IMT are at increased risk for cardiac events and stroke [662]. Although the relative risk for events is slightly lower after statistical correction for the presence of traditional risk factors, the risk remains elevated at higher IMT [660,662].

When IMT is used to predict the incidence of subsequent stroke, the risk is graded but non-linear with hazards increasing more rapidly at lower IMTs than at higher IMTs [660]. Therefore, precision of measurements is of greatest importance in the submillimeter range which poses high requirements on instruments and physicians. The risk of cardiac events over 4–7 years of follow-up in patients free of clinical coronary artery disease at baseline is also non-linearly related to IMT [663]. In the ARIC-study [664] the

hazard rate ratio comparing mean IMT of ≥ 1 mm to < 1 mm was 5.07 for women (95% confidence interval 3.08–8.36) and 1.85 for men (95% confidence interval 1.28–2.69). The strength of the association was reduced by including major CHD risk factors, but remained elevated at higher IMT. The low hazard rate ratio in men indicates that the predictive power of IMT measurements is limited. However, it may be useful not to use IMT measurements to make decisions about normal and abnormal but include them in a risk assessment model.

Plaque characteristics

Recently, plaque characteristics as assessed by carotid ultrasound were found to be predictive of subsequent cerebral ischaemic events [664]. Patients with echo lucent stenotic plaques had a much higher risk of stroke and cerebrovascular events than subjects with other plaque types. On B-mode ultrasound assessments, lipids, thrombi, and haemorrhage all will appear as echo lucent structures. As haemorrhage seldom occupies $> 2\%$ of total plaque size, lipids and thrombi which are plaque component known to be associated with unstable coronary disease most likely are the major components of dangerous plaques in the carotid system.

Thus, ultrasound imaging of the carotids is a non-invasive means of assessing subclinical atherosclerosis. The extent of carotid IMT is an independent predictor of cerebral and coronary events but seems to be more predictive in women than in men. Consequently, carotid ultrasound can add information beyond assessment of traditional risk factors which may help to make decisions about the necessity to institute medical treatment for primary prevention. One limitation of using carotid ultrasound for global risk assessment is the absence of reliable data relating IMT numbers to 10 year event rates. Therefore, it is currently not clear how IMT measurements can be formally incorporated into existing risk algorithms used in asymptomatic persons.

4.10.4 Ankle-brachial index (ABI)

Technical background

The measurement of the ankle-brachial blood pressure index (ABI) is an easy-to-perform, inexpensive and reproducible non-invasive test to detect asymptomatic atherosclerotic disease. Technical requirements are a regular blood pressure cuff and a doppler ultrasound device to measure the SBPs in left and right brachial arteries as well as both posterior tibial and dorsalis pedis arteries [584].

ABI as a measurement of peripheral artery disease (PAD)

An ABI < 0.9 reflects a $\geq 50\%$ stenosis between the aorta and the distal leg arteries. Because of its high sensitivity and specificity ($> 90\%$ respectively), an ABI < 0.90 is considered a reliable sign of peripheral arterial disease [665–667]. Its high specificity is partially explained by the

fact that the ABI may paradoxically be elevated with age-dependent increased arterial stiffness, including arterial calcification. Therefore, an ABI > 1.5 may be difficult to interpret [639]. ABI reflecting significant PAD adds additional value to medical history, because 50% to 89% of patients with an ABI < 0.9 do not have typical claudication [667–669]. The history of claudication alone “dramatically underestimates” the presence of large vessel PAD [674].

ABI as a prognostic tool

The presence of PAD is strongly related to a high incidence of coronary events and stroke [667]. Therefore, ABI also strongly relates to further development of angina, myocardial infarction, congestive heart failure, coronary artery bypass graft surgery, stroke or carotid surgery [667,671–675]. Even in patients with known multivessel coronary disease, a reduced ABI confers additional risk [676]. However, ABI should not be considered as a continuous measure of generalised atherosclerosis [639]. In asymptomatic individuals over 55 years of age, an ABI < 0.9 may be found in 12% to 27% [667,670]. Even in an elderly population (71–93 years), a low ABI further identifies a higher risk CHD subgroup [677].

5) Management of risk in clinical practice

5.1 Behaviour change and management of behavioural risk factors

Strategies for promoting behavioural change

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 to attend special programmes elsewhere [678].

Prochaska and DiClemente [679] have proposed a “stages of change model” which argues that everyone is not equally ready to change one’s behaviour at a given point in time. It is therefore important to assess the individual’s thoughts, attitudes and beliefs concerning the perceived ability to change behaviour, as well as the environmental context in which attempts to change are made, and subsequently to maintain the lifestyle change. Five stages are identified: pre-contemplation, contemplation, preparation, action and maintenance.

In the pre-contemplation stage, individuals do not intend to change their behaviour, and the pros of the risky behaviour are considered as greater than the cons. Contemplation is the stage where people intend to change their behaviour, but keep putting it off. The pros and cons are evaluated as

about equal; hence there is considerable ambivalence about changing. In these two stages, further pros regarding behavioural change should be provided, such as the demonstration of associations between lifestyle and symptoms, illness in other family members, social pressures and so on.

In the preparation stage, individuals intend to take action and have usually made some modest behavioural change, such as reducing the number of cigarettes smoked per day or slightly modifying their diet. In this stage, further cues to action should be provided, such as dietary counselling and smoking cessation programmes. In the action stage, individuals have already made behavioural changes, but there is a great risk for relapse. During this period many processes interact including intrapersonal (e.g. perceived self-efficacy), interpersonal (e.g. social support) and environmental (e.g. unavoidable exposure to unhealthy environments). An intervention strategy must focus on these topics actively, determining whether, for example, the newly quit smoker proceeds to the next stage (maintenance) or regresses to the earlier stage.

This model of the Stages of Change Framework has been demonstrated to work well in the primary care setting (US Preventive Services Task Force, 1996) [680]. Furthermore, the Report of the US Preventive Services Task Force has identified ten strategies to enhance the effectiveness of counselling on behavioural change (see Table 16).

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

The physician-patient interaction is a powerful tool to enhance patients’ coping with stress and illness and adherence to recommended lifestyle change. Social support is known to exert positive influences on illness behaviour, on coping and on adherence; conversely, a non-supportive environment may lead to attention shifts, to motivational problems and may cause patients to ignore the threats of chronic illness and the needs to change lifestyle.

Social support provided by caregivers, including physicians, may be of primary importance to help patients maintain healthy habits and follow medical advice.

Table 16 Ten strategic steps to enhance the effectiveness of behavioural counselling

-
- Develop a therapeutic alliance
 - Counsel all patients
 - Ensure that patients understand the relationship between behaviour and health
 - Help patients to assess the barriers to behaviour change
 - Gain commitments from patients to behaviour change
 - Involve patients in identifying and selecting the risk factors to change
 - Use a combination of strategies including reinforcement of patient’s own capacity for change
 - Design a lifestyle modification plan
 - Monitor progress through follow-up contact
 - Involve other health care staff wherever possible
-

In this context it should be recognised that the physician is not the only professional person involved. The expertise of psychiatry, psychology, nutrition and behavioural sciences in a broader sense is highly needed. In particular therapeutic and preventive interdisciplinary team work should be attempted, combining the appropriate knowledge and skills to optimise the preventive efforts.

It is further necessary for the physician/caregiver to recognise the social, emotional and cognitive problems associated with illness and lifestyle change and to develop strategies to solve them. A friendly and positive physician-patient interaction is crucial, since a patient is more likely to accept and follow physicians advice, if he/she feels understood and accepted. Conversely, inappropriate interaction patterns can lead to a cycle of misunderstandings and destructive emotions (e.g. rage and anger), which in turn exert a negative influence on the adherence to medical regimen, on illness behaviour and on compliance in general. The physician's use of some principles of effective communication will facilitate successful treatment and prevention of CVD (Table 17).

Multimodal interventions

Multimodal, behavioural interventions integrate educational efforts with practical training sessions, combining learning with practical implementation and skills training. They are especially recommended for patients with clinically manifest CHD and for individuals at very high risk. Interventions should be performed on a multimodal basis, integrating education on healthy lifestyle and medical resources, exercise training, relaxation training, and smoking cessation programmes for resistant smokers. Whenever needed, additional individual or group counselling should be performed, in order to enhance coping with illness, to improve compliance with prescribed medication, and to facilitate adequate utilisation of medical resources, in particular to minimise delay in seeking help in case of central chest pain or other serious symptoms. Psychosocial risk factors (stress, social isolation and negative emotions) that may act as barriers against behaviour change will also be addressed in individual or group counselling sessions, according to specific needs of the participants (see Table 18).

Multimodal interventions need team work and special education of the staff. There is evidence that more extensive/longer interventions may lead to better long term results with respect to behaviour change and somatic outcome. Patients of low socio-economic status, of older age, or female gender may need tailored programmes, in order to meet their specific needs regarding information and emotional support.

Management of psychosocial risk factors (Table 19)

Recognising the psychosocial risk associated with depression, hostility, low socio-economic status (SES),

Table 17 Recommendations for good and effective physician/caregiver-patient interactions

- Spend enough time with the patient, even two minutes more can make a difference
- Listen carefully to the patient and recognise strengths and weaknesses in the patient's attitude to illness and lifestyle change
- Accept the patient's personal view of his/her disease and allow expressions of worries and anxieties
- Speak to the patient in his/her own language and be supportive of every improvement in lifestyle
- Make sure that the patient has understood your advice and has the means to follow it

Table 18 Components of multimodal, behavioural interventions

- Education on healthy lifestyle and medical resources
- Exercise training
- Relaxation training
- Smoking cessation programmes for resistant smokers
- Individual or group counselling on psychosocial risk factors and means to improve coping with stress and illness

Table 19 Recommendations for management of psychosocial risk factors in clinical practice

- Assess psychosocial risk factors, e.g. depression and hostility, low SES, social isolation, and chronic life stress by clinical interview or standardised questionnaires
- Discuss relevance with patient in respect to quality of life and medical outcome
- Prescribe multimodal, behavioural intervention, integrating individual or group counselling for psychosocial risk factors and coping with stress and illness
- Refer to a specialist in case of clinically significant emotional distress

Table 20 Core questions for the assessment of psychosocial risk factors in clinical practice

- Depression: Do you feel down, depressed and hopeless? Have you lost interest and pleasure in life?
- 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?
- 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?
- Low SES: Do you have no more than mandatory education? Are you a manual worker?

lack of social support or chronic psychosocial stress in patients and situations may be crucial as a means to reduce risk. Standardised measurements for depression, hostility, SES, social support or psychosocial stress are available in many languages and countries.

Alternatively, a preliminary assessment of psychosocial factors can be made within the physicians' clinical interview (Table 20).

A "yes" to any of these questions indicates a potential problem area. For patients with low SES, lack of social support or chronic psychosocial stress, further interventions need to focus on these areas in order to improve both their quality of life and medical outcome. If available, patients should be recommended to join a multimodal, behavioural intervention that includes stress

management and social reintegration. Whenever possible these interventions should occur on a group basis to enhance social interaction and improve social support.

Depression and other negative effects tend to persist or even increase as cardiac disease progresses. While awaiting conclusive results that treating depression will alter CVD prognosis, a prudent approach at present, is to treat patients with clinically significant depression according to established guidelines, with psychotherapy and anti-depressive medication.

5.2 Dietary changes

Nutrition in the prevention of cardiovascular disease

Dietary interventions are highly effective in the prevention of recurrent events in patients with established CHD [61,64], dietary changes are an integral part of prevention and management strategies.

Cost effectiveness appears very good relative to other common interventions [681]. This diet should be encouraged in all those at increased risk of cardiovascular disease, not just in those referred with established coronary heart disease, stroke or other clinical manifestation of atherosclerosis. Such persons should be given advice and specific recommendations, by a specialist, on the food and dietary options which will help them in reducing cardiovascular risk. Participation of the family, most notably of the person in charge of buying and cooking food, is particularly important. However, in an era when a substantial part of meals are taken outside home, the collaboration of the food industry and commerce and hostel services is essential in order to ensure that healthy food choices are feasible.

General recommendations

The following recommendations are given as a general guideline that must be adapted according to local and cultural particularities.

- A varied and well energy-balanced regimen together with regular exercise are critical to the preservation of a good cardiovascular health. Eating food from each major food group will ensure dietary balance.
- The intake of some types of food will be more particularly encouraged: fruits and vegetables, cereals and grain products, skimmed dairy products, fish and lean meat.
- Eating omega-3 FA's – from seafood and some vegetable oils – seems to be particularly appropriate as it provides great protection against fatal cardiovascular accidents. It is the most important dietary advice for those with cardiovascular disease as fish or fish oil supplements is dramatically protective, and rapidly so.
- Other important elements of the diet include replacement of some saturated and trans-FA's with MUFA's or PUFA's of vegetable and seafood origins. The intake of lipids in food will have to represent approximately 30% of energetic intake. The intake of satu-

rated fats must not exceed 30% of total lipids. The intake of cholesterol must be less than 300 mg/d.

- Energetic intake will be adjusted to maintain ideal weight.

Cardio protective dietary advice should always be set in the context of an adequately balanced and healthy diet overall. Micronutrient intake is sometimes compromised by dietary changes. Particular mention should be made of calcium and iron which may be severely restricted in the battle to reduce saturated fats, and should therefore be assessed or discussed following initial dietary advice. For frail or elderly people (in danger of nutritional compromise, especially lack of appetite leading to low food intake, and resulting in excess weight loss) oily fish, fruit and vegetables are encouraged, but dietary fats only altered if this can be achieved with no loss of enjoyment.

Specific recommendations

Treatment of dyslipidemia

- The reduction in LDL cholesterol is the main objective of the nutritional treatment of subjects with a high cardiovascular risk. This reduction is obtained by lowering the intake of saturated FA's and trans-FA's and, to a lesser extent, by reducing the intake of cholesterol in food. Conversely, the intake of polyunsaturated FA's, soluble fibres and phytosterols reduces the plasma concentrations of LDL cholesterol.
- Although the evidence of a beneficial impact of the increase in HDL cholesterol on cardiovascular morbidity and mortality is still lacking, dietetic interventions aiming at increasing the concentrations of plasma HDL cholesterol are also recommended. More exercise by sedentary subjects, loss of weight among obese subjects and glycaemia control among diabetic subjects coincide with concomitant increases of HDL cholesterol. Moderate use of alcohol is not contra-indicated for subjects having low HDL cholesterol concentrations. Eating refined sugars is associated with a reduction in HDL cholesterol concentrations among certain susceptible subjects. These sugars will be replaced with complex sugars.
- Because high triglycerides levels are associated with numerous metabolic anomalies, which are deleterious for the cardiovascular system, it may be relevant to treat hypertriglyceridemia with dietetic means. More exercise by sedentary subjects, loss of weight for obese subjects and glycaemia control for diabetic patients coincide with concomitant reductions in plasma triglycerides. The intake of refined sugars and alcohol will have to be controlled as it is associated with increases in plasma triglycerides, among certain susceptible subjects. The intake of omega-3 FA's present in fat fishes and some vegetable oils strongly contribute to a decrease in plasma triglyceride concentrations. Finally, certain major hypertriglyceridemia due to increased chylomicron levels require specialist treatment.

Arterial blood pressure

- Dietetics plays a critical part in the arterial pressure control. The main objectives are controlling the intake of salt and alcohol, weight loss for obese subjects and increasing the intake of potassium. In addition to that, the DASH study has demonstrated that a varied diet with a high content of fruits and vegetables and low content of dairy products coincided with a significant reduction in DBP and SBP [102].
- The aim should be not to exceed 6 g of sodium chloride per day. Although the trial evidence demonstrates that these measures are of modest benefit, they may help patients to reduce their medication. Mmol per mmol potassium is more effective in lowering blood pressure than sodium in increasing blood pressure [682]. An increase in potassium intake at the population level is thus also highly desirable. The most important sources of potassium are fruits and vegetables and calcium is also present in many of them and not only in dairy products. Some non-steroidal anti-inflammatory agents are also important carriers of sodium. This should be borne in mind when treating co-morbidities requiring these drugs in cardiovascular patients, especially hypertensives. As the most important sources of sodium intake come from non-discretionary sources, i.e. commercially prepared foods and specially bread and cheese, it is of great public health impact to tackle these sources of dietary sodium. Therefore cooperation with food manufacturers and retailers in reducing the sodium content should be part of the population strategy.

Body weight and abdominal fat management

- Weight reduction is strongly recommended for obese subjects having a body mass index ≥ 30 kg/m² and for those with increased abdominal fat assessed by waist circumference > 102 cm in men and > 88 cm in women. To do so, the caloric intake must be reduced and more exercise needs to be taken.
- Reduced caloric intake is achieved at the expense of high energetic density foods – food fats (9 kcal/g) and alcohol (7 kcal/g) will be reduced in priority. The reduction in saturated fats is the preferred target due to its effects on the lipoprotein profile. All through the weight-lowering diet, the lipid intake should be less than 30% of the energetic intake. Exercise must be adapted to the physical condition of the patient. It plays a critical part in weight loss, preservation of a stable weight and the prevention of weight gain. Systematic review of the effectiveness of weight reduction interventions suggests that behavioural, diet, exercise and drug treatments have all been shown to be effective to some extent in reducing obesity in adults, especially when used in combination, however most people begin to regain weight a few months after treatment [682,683].

- Therefore, successful weight reduction requires good motivation by the person and encouragement and long term support by the physician, as well as appropriate counselling in practical aspects of weight reduction. A weight loss of 0.5 to 1 kg per week is a realistic objective until the weight target is attained. Reduction of body weight is associated with a concomitant reduction of waist girth. When weight loss is achieved, the objective becomes preserving a stable weight and blocking any new weight gain. For this, foods with a high lipid content will have to be replaced with vegetables, fruits and cereal products.

Motivation

The cardioprotective diet should always be discussed in the context of a healthy lifestyle and reference should be made to activity and exercise levels, smoking cessation and continued use of relevant prescribed medication. Patients are often apprehensive about the perceived restrictions of a cardioprotective diet and may be visibly relieved when the positive changes are described and encouraged. The cardioprotective diet, like exercise and non-smoking, is protective as long as it is continued. To have eaten well or been fit last year is not helpful now. To help people maintain their healthier habits regular review is advisable. This may involve regular dietetic review in a central location or the community, or be delegated to other community staff (who must be trained, updated and provided with appropriate support materials).

Motivation can also be boosted by involving the whole family [683]. Where this occurs the sense of isolation is reduced and the whole family group (who may also be at increased genetic or lifestyle risk of CHD) reaps the benefits in risk reduction.

5.3 Prevention and management of smoking (Tables 21–22)

Physician's firm advice that a patient with coronary heart disease or other atherosclerotic disease should stop smoking 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 cardiovascular disease and in connection with an invasive treatment, such as coronary artery bypass grafting, percutaneous transluminal coronary angioplasty or vascular surgery. Physician's advice is equally important in helping healthy high-risk individuals to attempt quitting smoking. Quitting smoking is a complex and difficult process, because this habit is strongly addictive both pharmacologically and psychologically. Despite this, many people who succeed in quitting, manage to do this without any special programmes or treatment. Physician's explicit advice to quit smoking completely and ascertainment that the person is willing to try to do it are the decisive first steps. Brief reiteration of the cardiovascular and other health hazards

Table 21 Smoking and CVD prevention

- Smoking cessation can deliver immediate benefits, especially for patients with CVD
- Smoking cessation has been shown to be a highly cost-effective intervention
- Smoking cessation can be difficult in cases of severe tobacco dependence; a professional approach, supplemented by the application of nicotine replacement therapy, other pharmacological interventions and behavioural counselling, should be used

Table 22 Strategies to help smoking cessation: the 5 "A's"

Ask:	systematically identify all smokers at every opportunity
Assess:	determine the patient's degree of addiction and his/her readiness to cease smoking
Advise:	urge strongly all smokers to quit
Assist:	agree on a smoking cessation strategy including behavioural counselling, NRT and/or pharmacological intervention
Arrange:	schedule follow-up visits

of smoking, providing appropriate literature, and agreeing on a specific plan with a follow-up arrangement are the essential features of the brief advice version of smoking cessation in clinical practice. This may involve the assessment of the degree of addiction and their state of change (see sections 4.2 and 5.1). Pooled data from 16 trials of brief advice versus no advice revealed a small but significant increase in the odds of quitting (odds ratio 1.69, 95% CI 1.45–1.98). This equates to an absolute difference in the cessation rate of 2.5%; more intensive interventions were marginally more effective than minimal interventions [684].

Readers are referred to specific recommendations describing the principles of brief advice and other interventions for smoking cessation in clinical practice [195]. At hospital-based clinics and primary health care practices nurses are an important resource in individual counselling on smoking cessation. Physicians and nurses need to set an example for their patients by not smoking themselves. Primary pipe or cigar smokers may be at somewhat smaller cardiovascular risk than cigarette smokers, mainly because many of them tend to be non-inhalers. It is advisable to try to get patients with atherosclerotic disease and high-risk individuals to also stop these forms of smoking. If cigarette smokers shift to pipe or cigar smoking, they usually continue to inhale and therefore this shift should be discouraged.

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. A Cochrane review on the effectiveness of different forms of nicotine replacement therapy (NRT) revealed that the quit rates increase approximately 1.5 to 2-fold with the use of nicotine replacement [685]. Initial success is often followed by a relapse, but cessation rates of 10% or more for one year or longer have been achieved following nicotine replacement therapy. The use of nicotine patches has been successfully tested in patients who have coronary heart disease without any adverse effects [195].

The effectiveness of antidepressant medication in aiding long term smoking cessation has been reviewed [686]. From this it seems that bupropion and nortriptyline can aid smoking cessation. In one trial the combination of bupropion and nicotine patch produced slightly higher quit rates than patch alone. Support by the spouse 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. In many European countries a favourable development has occurred with the creation of 'smoke-free' environments, including restrictions of smoking at work sites, in public transport vehicles, restaurants etc. These changes provide an improved atmosphere for smoking cessation attempts by individuals.

5.4 Management of physical activity (Table 23)

How to improve physical activity in children and adolescents

One of the main aims of preventive cardiology is to lessen the burden of CVD throughout Europe, thus creating a strong argument for physical fitness in young age. Physical activity in young age is a major predictor of maintained fitness throughout life.

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, which should be translated into tangible action. Each child in Europe should have access to a moment of physical activity each day, be it in school or during leisure time. Physical education should be upgraded in the curriculum of the schools. Special efforts should be made to ascertain that adolescents maintain a physically active lifestyle, using the available resources in society such as sport clubs etc.

Table 23 Recommendations for physical activity

Aim	In all age groups: 30–45 min of physical activity at least five days a week
Rationale	<ul style="list-style-type: none"> • To prevent or delay the onset of cardiovascular disease • To limit the progress of existing cardiovascular disease
Method	<ul style="list-style-type: none"> • Promote daily physical exercise at school • Provide options for regular physical activity at the work site, encourage an active leisure time, e.g. brisk walking, cycling, swimming, gardening or other in/outdoor sports and hobbies. • For coronary patients: participation in supervised or home-based programmes of physical training • For elderly: stimulate the maintenance of a physically active lifestyle, even in higher age groups
Result	<ul style="list-style-type: none"> • Lower risk of cardiac mortality and morbidity • Adequate level of physical fitness, increase of VO₂-max and endurance capacity • Lowering of heart rate and blood pressure • Improvement of coronary blood flow • Effect on symptoms of angina pectoris • Adaptation of the peripheral resistance • Protective effect on the sympathetic-vagal balance • Reduction of overweight • Cardio-protective effect on lipid metabolism and on insulin-resistance • Effect on platelets and fibrinolysis

In predisposed individuals the simple and effective measures for prevention include regular physical exercise, maintenance of ideal body weight, avoidance of smoking, eating a balanced diet and early periodic monitoring of blood pressure and metabolic status. The family doctor may play a supportive role in the advice and follow-up of the young patient at high risk for future CVD.

Not only should physical activity be promoted; even research will have to be intensified, especially in finding instruments for measuring physical fitness and activity and in validating programmes dedicated to improve physical activity in the younger age groups.

How to promote physical activity in healthy adults

Interventions promoting physical activity amongst the general public are more likely to be effective if they involve activities which can fit into an individual's daily routine than if they require attendance at exercise facilities [687]. The choice of lifestyle, including maintained physical fitness, remains the sole responsibility of the individual person. This choice may be supported by family and friends, her or his work environment, access to attractive and affordable leisure time activities and by health promoting campaigns. The employer will benefit from physically fit workers as this will diminish the loss of labour due to sick leave. Thus, it should be recommended to support regular physical exercise within the resources of the work place, as is being provided in several European countries. The ultimate goal should be at least half an hour of physical activity on most days of the week.

In general, persons have to be advised about the intensity, duration and frequency of exercise. The intensity may be defined in terms of target heart rate during peak exercise, 60–75% of the average maximum heart rate being the preferred target heart rate. Alternatively, as not all persons are used to monitor heart rates, the Borg scale [688] of perceived exertion may be applied, using the level of “moderate exertion” as a guide level. This level is easily achieved by exercises involving the large muscle groups, e.g. brisk walking or jogging, cycling, swimming, aerobic dancing, tennis, golf or even cross-country skiing.

The duration of physical activity should preferably be 30–45 min, including a 5–10 min warm-up phase, an aerobic phase of 20–30 min and a 5–10 min cool-down phase at its end. A frequency of 4–5 times weekly is recommended. At present there is no scientific evidence indicating that considerably higher doses of exercise would result in further significant preventive gains.

The use of exercise training in adults with CVD

Recommendations for patients with clinically established CVD have to be based on a comprehensive clinical judgement including the results of exercise testing. Patients with unstable angina pectoris should be

attended to with conventional non-invasive or invasive methods before they may be included in physical training. Patients with stable angina pectoris often obtain marked subjective benefit from gradually increased and regular exercise, but their anti-anginal and other medical treatment should be optimal before starting such a programme. The intensity and duration should initially be set low and increased step-wise according to the limits imposed by exercise-induced symptoms. Here, the result of pre-training exercise testing will be valuable.

Patients recovering from an acute myocardial infarction or other ischaemic event and, similarly, patients following angioplasty or recovering from coronary artery bypass grafting should be recommended to start a suitable, increasing physical activity programme. Many patients will benefit from an organized rehabilitation programme provided by a multidisciplinary team. Such a programme may be available on an ambulatory basis or as an in-patient facility in specialised centres, as is the tradition in some central European countries. The rehabilitation programmes, in addition to supervised physical exercise, give a good opportunity for a comprehensive evaluation of the patient's risk factor status and for further advice and measures aimed at risk reduction.

If patients prefer to perform the physical training programme at home, they will need clear prescriptions, encouragement and regular follow-up by their physician. Written material, audiocassettes, videos or CD-ROM disks are useful supplements to verbal advice. Devices such as heart rate monitors or pedometers maybe helpful in the follow-up of a home-based programme for physical training.

Detailed recommendations on exercise prescription and rehabilitation for cardiac patients, as well as on counselling for recreational and vocational activities have been published by the European Society of Cardiology Working Group on Rehabilitation [689], the American Association of Cardiovascular and Pulmonary Rehabilitation [690] and other experts in this field [691–693].

For patients with mild to moderate heart failure guidelines are available, issued by the ESC Working Groups on Heart Failure and on Cardiac Rehabilitation and Exercise Physiology [229]. Different forms of aerobic training have shown beneficial effects on exercise capacity, the need for rehospitalisation and on quality of life but there are as yet no data on mortality. Although there is no consensus on the optimal training regimen in CHF both dynamic interval training with moderate intensity and resistance training may be advantageous.

Promoting physical fitness in the elderly

General public health measures for the promotion of physical fitness apply to the elderly population as they do to

younger generations. With the growing number of senior citizens these measures will have a major impact on health care resources. In several European countries gymnastic classes for elderly are being organized. Sports clubs, patient organisations and other commercial and non-commercial institutions provide a growing diversity of physical exercise facilities. Yet, further initiatives are recommended, especially for the large group of sedentary elderly women.

When counselling elderly persons the family doctor is recommended to assess activity regularly and advise to maintain daily physical activity on a moderate to sub-maximum level. Brisk walking at a pace at which a conversation still can be held ("walk-and-talk model") is a good example of advice for healthy elderly.

Older patients with signs of CVD, will benefit from comprehensive rehabilitation programmes: exercise training is safe and improves strength, aerobic fitness, endurance and physical function. It will improve conventional risk factors, mental state and quality of life [694]. There are no gender differences in the outcome of training for elderly CVD patients. Resistance training may be an attractive alternative; it can be used in home-training, if transport is a limiting factor for participation in ambulatory group training.

However, as in the healthy population of all ages and among patients with established CVD the ultimate goal of all physical training programmes should be the acceptance and maintenance of a lifestyle in which efforts of regular physical exercise are rewarded by the cardiovascular as well as other benefits of general physical fitness.

Conclusion

Regular physical activity and the maintenance of physical fitness is beneficial in all age groups and should be promoted as an integral part of preventive cardiology.

5.5 Control of arterial hypertension

Guidelines on the management of hypertension vary slightly in their definitions of hypertension and its subdivision into borderline, mild, moderate, or more severe stages [13,253,695]. As stated in the 1996 World Health Organization Expert Committee report on hypertension control [697] and in the 2003 ESH/ESC guidelines for the management of arterial hypertension [696] all definitions of hypertension are by necessity arbitrary because the risk of cardiovascular disease increases continuously with rising blood pressure, starting from levels that are considered to be within the normal range. The dividing line between "normotensive" and "hypertensive" individuals can only be determined operationally by intervention trials demonstrating at which blood pressure levels treatment is beneficial. In epidemiologic studies there is no evident lower threshold below which a reduction in blood pressure is no longer associated with a reduction in risk [230].

The decision to start pharmacological treatment, however, depends not only on the blood pressure level but, also, on the overall cardiovascular risk, which calls for a proper history, physical examination and laboratory examination to identify 1) the presence of clinically established cardiovascular disease, 2) the coexistence of other cardiovascular risk factors, and 3) the presence of subclinical cardiovascular disease or end-organ damage. The presence of clinically established cardiovascular disease (myocardial infarction, angina pectoris, heart failure, coronary revascularisation, transient ischaemic attacks, stroke, renal insufficiency, etc.) dramatically increases the risk of subsequent cardiovascular events regardless of the blood pressure level. This is particularly the case also for the association of hypertension and other cardiovascular risk factors such as diabetes.

The coexistence of other cardiovascular risk factors (smoking, increased plasma cholesterol, family history of premature cardiovascular disease) also greatly adds to the risk associated with a mild blood pressure elevation (see SCORE risk chart) [18].

Markers of end-organ damage such as electrocardiographic left ventricular hypertrophy, carotid or femoral artery wall thickening, an even moderate increase in serum creatinine [278], proteinuria, and retinal haemorrhages and/or exudates with or without papilloedema are also associated with a marked increase in risk at any given blood pressure level. Thus, in hypertensive patients, an electrocardiogram, a serum creatinine value, a urinalysis, a lipid profile, and an eye fundus examination should always be obtained, together with examinations able to determine whether the patient has diabetes according to current guidelines [388]. Echocardiography has been shown to be a more sensitive marker of left ventricular hypertrophy than electrocardiography, and "echocardiographic" left ventricular hypertrophy has been conclusively associated with a marked increase in cardiovascular morbidity and mortality [498,698,699]. This has also been the case for microalbuminuria in diabetic [700] patients and in non-diabetic patients [490,701].

Ultrasonographic evidence of the prognostic importance of an increase in carotid and femoral artery intima/media thickness has recently also been obtained [660,702]. An echocardiogram, an ultrasonographic assessment of the carotid wall thickness, and a semiquantitative assessment of the presence or absence of proteinuria and microalbuminuria should thus be undertaken whenever possible to detect target organ damage in hypertensive patients and thus identify high-risk individuals. Implementation of these more sophisticated procedures helps to diagnose organ damage more frequently than previously used routine procedures [239,703]. Preliminary evidence has also been obtained of the prognostic importance of additional markers of organ damage such as endothelial dys-

function and large artery wall stiffening [704,705]. This information, however, needs complex, expensive and time-consuming measurements which at present prevent their use for assessment of organ damage in clinical practice. Pulse pressure is an indirect marker of arterial distensibility and its value has been shown in observational studies to predict the cardiovascular risk [706]. However, discrepancies between central and peripheral pulse pressure, inaccuracies related to its nature as a derived value and lack of a universally accepted threshold for risk and treatment have to date limited its use.

Whom to treat?

Although most randomised therapeutic trials in hypertension have defined and treated patients on the basis of DBP values only, there is now a consensus that SBP values should also be taken into account in defining and managing hypertension because first of all in a large number of epidemiological studies, SBP has a greater predictive value than DBP [707]. This is particularly true for patients aged over 50 years because, with increasing age, there is a gradual shift from DBP to SBP as predictors of cardiovascular disease [708] and secondly some of the intervention studies in hypertension indicate that cardiovascular events correlate more closely with the achieved SBP than with DBP [245]. Favourable results of recent trials in isolated systolic hypertension have also added to the evidence about the importance of SBP not only in risk assessment but, also, in patients' protection by treatment [252,709]. Therefore, SBP deserves at least the same attention as DBP both before and during treatment, although most recently completed or ongoing trials demonstrate that the goal SBP is more difficult to achieve than DBP [252,268,709–712].

In patients presenting with severe hypertension, hypertension of a recent origin and hypertension developing at young age (particularly if without any family history), causes of secondary hypertension should be ruled out and attention should be directed to blood pressure-lowering interventions. As shown in Fig. 3, advice on lifestyle changes (see below) should be immediately given to all patients. The decision on whether and how fast drug treatment should be started, however, will depend on the risk stratification charts, the blood pressure level and the presence or absence of subclinical organ damage with a proven effect on patients' prognosis. With a SBP ≥ 180 mmHg and/or a DBP ≥ 110 mmHg, drug treatment should be instituted immediately and independently of the absolute risk. This should also be the case with SBP values of ≥ 140 mmHg and/or DBP ≥ 90 mmHg if the 10-year absolute risk of fatal cardiovascular disease is $\geq 5\%$ (which corresponds to formerly used 20% risk of a composite of coronary heart disease events or exceeds 5% if projected to the age of 60 years), regardless of the presence or absence of organ damage. Drug treatment should also be quickly implemented if

the 10-year absolute risk of fatal cardiovascular disease is $< 5\%$, provided that there is subclinical organ damage. Individuals with a history of cerebrovascular or coronary heart disease, with target organ damage, or accumulation of known risk factors, should also be considered candidates for drug treatment if their blood pressure is in the "high normal" range, i.e. 130–139 mmHg systolic and/or 85–89 mmHg diastolic.

If, on the other hand, blood pressure is within the range of 140–179/90–99 mmHg, and there is no subclinical or end-organ damage, blood pressure should be repeatedly measured over a period long enough (several months) to minimise the problem of spontaneous blood pressure variability, taking into account its possible spontaneous normalisation, and enabling a more precise evaluation of the patient's "usual" blood pressure. If, after this period (usually up to 6 months), DBP remains ≥ 95 mmHg and/or SBP ≥ 150 mmHg, drug treatment should be instituted. If DBP falls to between 90–94 mmHg or SBP to between 140–149 mmHg, lifestyle counselling should be reinforced together with frequent blood pressure measurements (e.g. twice a year). Drug treatment should be considered after asking the patient for his/her preference. If values fall to < 90 mmHg diastolic and < 140 mmHg systolic, it is desirable to continue lifestyle counselling and measure blood pressure at yearly intervals.

Individuals with a SBP < 140 mmHg and a DBP < 90 mmHg do not normally need antihypertensive treatment. Observational studies, however, have demonstrated that the linear relationship between cardiovascular disease and systolic or DBP continues below 140/90 mmHg [230]. Furthermore, a recent analysis of the Framingham data [238] has shown that individuals with high-normal blood pressure (i.e. 130–139 mmHg and/or 85–89 mmHg) have much higher absolute rates of cardiovascular events than those with optimal blood pressure (defined as SBP < 120 mmHg and DBP < 80 mmHg). In addition, individuals with high-normal blood pressure develop hypertension more frequently. These findings support recommendations for measuring blood pressure in individuals with high-normal blood pressure once a year, and monitoring those with normal blood pressure every two years [713].

Finally, in two studies on patients with diabetes, multiple additional cardiovascular risk factors or a history of myocardial infarction or stroke, substantial cardiovascular protection was obtained by administering antihypertensive drug such as ACE inhibitors and/or diuretics even when blood pressure was reduced by several mmHg from an initial value less than 140 mmHg systolic and 85–80 mmHg diastolic because of either a normotensive or a hypertensive condition under control by treatment [109,262,701,714]. Thus in patients with a high or very high cardiovascular risk profile blood pressure lowering

interventions may be beneficial even when the initial blood pressure is below the traditional cut-off value dividing hypertensive from normotensive individuals. Isolated systolic hypertension may be found in adolescents and young people, but it is particularly common in the elderly [252,709]. Isolated systolic hypertension in elderly people not only carries an additional cardiovascular risk, but trial evidence is now available indicating that pharmacological reduction of raised SBP results in considerable benefit in terms of reduced cardiovascular morbidity and mortality from cerebrovascular and cardiac complications. Isolated systolic hypertension of the elderly therefore represents a condition that needs treatment both with lifestyle and drug therapies. Drug treatment should be started whenever SBP is persistently ≥ 140 mmHg regardless of the DBP value.

How to treat?

Several lifestyle interventions are known to have a blood pressure-lowering effect. Treatment based on these interventions alone may be sufficient for patients with mildly elevated blood pressure and, as emphasised before, it should always be advised for patients who are receiving antihypertensive drugs, because the dosage of antihypertensives needed for good blood pressure control can be reduced by lifestyle measures. Because long-term compliance in lifestyle changes may be poor, frequent reinforcement of these recommendations in connection with blood pressure measurements is needed.

Lifestyle interventions include: weight reduction in overweight individuals; reduction in the use of sodium chloride to less than 6 g/day; restriction of alcohol consumption to no more than 10–30 g/day ethanol 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/day ethanol in women (1–2 of these drinks/day); and regular physical activity in sedentary individuals.

Since tobacco smoking has a particularly adverse effect on the cardiovascular risk of hypertensive patients, intensive efforts should be made to help hypertensive smokers to stop smoking. Because the acute pressure effect of smoking may raise daytime blood pressure [715] this may also directly favour blood pressure control, at least in heavy smokers.

Hypertension is often associated with plasma lipid abnormalities. Even in the absence of marked dyslipidaemia, it is prudent to advise hypertensive patients to change their diet with regard to fat content and composition to that described in the diet section.

Steroid hormone contraceptives may raise blood pressure and therefore contraceptive alternatives may have to be considered for hypertensive women of child-bearing age.

Hormone replacement therapy in postmenopausal females usually does not affect blood pressure levels, but frequent monitoring of blood pressure is needed if such therapy is initiated in hypertensive women.

Antihypertensive drugs

Drugs to be used for the treatment of hypertension should be capable of, 1) effectively lowering systolic and DBP, 2) having a favourable tolerability and safety profile and, 3) reducing, in the context of controlled trials, cardiovascular morbidity and mortality. There are currently five classes of drugs which meet these requirements: diuretics, beta-blockers, ACE inhibitors [717], calcium-channel blockers [261,717] and angiotensin II antagonists [268]. In a meta-analysis of several comparative trials involving a total of more than 160 000 patients [270], these classes have shown comparable effects on the incidence of cardiovascular disease. This has been confirmed in a recent trial of about 33 000 hypertensive patients which has shown diuretic-, calcium antagonist-, and ACE inhibitor-based treatment to be associated with a similar incidence of coronary heart disease (the primary end-point) and total mortality [271]. These classes can therefore be recommended as first-line choice for antihypertensive treatment. Alpha-blockers were also previously considered first-choice drugs [253]. However, in a large-scale trial in high-risk patients [718], the group treated with an alpha-1 blocker such as doxazosin was stopped because of a greater incidence of congestive heart failure and, to a lesser extent, cardiovascular morbidity than in the group treated with a thiazide diuretic. Because, 1) the trial had a number of limitations (e.g. limited information on previous diuretic administration, which might have concealed the symptoms of heart failure, use of central agents that might have reduced the antihypertensive efficacy of the alpha-1-blockers, lack of Event Committee, and full validation of events) and, 2) coronary heart disease and overall mortality did not differ between the two groups, the results are open to criticism. This is also the case of the more recent finding of a greater incidence of heart failure in the group treated with an ACE inhibitor (lisinopril) [272]. However, several other trials with ACE inhibitors showed a marked positive effect in heart failure patients. Yet, in the absence of additional data, it is appropriate to consider alpha-1-blockers for combination treatment, particularly in elderly men, with benign prostatic hypertrophy to whom they offer symptomatic relief.

In all trials, blood pressure control has frequently been achieved by the combination of two or even three drugs [719]. This has been particularly the case when lower blood pressure targets have been pursued or high-risk patients have been studied [276]. This (and the relationship between on-treatment blood pressure levels and cardiovascular morbidity) makes drug combination a fundamental part of the antihypertensive treatment strat-

egy. All antihypertensive drugs can be used for this purpose although preference should be given to combinations of drugs having different mechanisms of action as well as a greater antihypertensive efficacy and/or a better tolerability profile than the combination components. Combinations with proven efficacy and a favourable tolerability profile are, 1) a diuretic with a beta-blocker, an ACE inhibitor, an angiotensin II antagonist, 2) a beta-blocker with a long-acting dihydropyridine calcium antagonist or an alpha-blocker and, 3) an ACE inhibitor with a calcium-channel blocker. Patients should be moved to combination treatment when the drug initially administered is only partly effective. Increasing the dose of the initial drug should not normally be adopted because, in several instances, this has little additional effect on blood pressure while increasing side effects. Switching from one drug class to another should be the adopted strategy only in the presence of major side effects or in the absence of any blood pressure reduction.

The ALLHAT [272] study has reported that, compared to diuretics, calcium antagonist and ACE inhibitor treatment was associated with a higher incidence of heart failure, and ACE inhibitor treatment with a higher incidence of stroke. However, in addition to the previous limitations, the study failed to achieve similar blood pressure reductions in the three groups, i.e. the ACE inhibitor group showed 2–3 mmHg greater values (4 or more in blacks), which could have accounted for the results. Based on the benefit shown in most studies on hypertension as well as in patients with myocardial infarction and heart failure, diuretics, ACE inhibitors [720] or beta-blockers [721] should be preferred in patients with overt heart failure, the latter two classes being the preferred ones in patients with asymptomatic left ventricular dysfunction. However, beta-blockers should only be used after the patient's condition has stabilised under careful supervision. Beta-blockers or calcium-channel blockers should be preferentially used in patients with stable angina pectoris; beta-blockers and ACE inhibitors in patients with a recent myocardial infarction; ACE inhibitors but also calcium-channel blockers in diabetic individuals as well as in patients with a high cardiovascular risk profile; angiotensin II antagonists in patients with type-2 diabetic nephropathy [265] and ACE inhibitors in non-diabetic [722] nephropathy; ACE inhibitors and diuretics in patients with a history of cerebrovascular disease; diuretics and calcium antagonists in black patients (with low priority for ACE inhibitors and angiotensin II antagonists). Alpha-blockers might be considered in men with benign prostatic hypertrophy as well as for combination treatment. Regression of cardiac (left ventricular hypertrophy) and vascular (increased arterial wall thickness and atherosclerosis) damage might be better achieved by ACE inhibitors, calcium-channel blockers and, also, by angiotensin II antagonists. The most important goal should in any case be effective blood

pressure reduction using all drugs and drug combinations needed for this purpose.

Blood pressure goals

A major problem in the treatment of hypertension is that the optimal blood pressure to be achieved by treatment has not been identified by the trials undertaken so far. There is no question, however, that DBP should be reduced to less than 90 mmHg based on observational and interventional studies. Lower values (down to < 80 mmHg) are desirable in patients with diabetic nephropathy in whom renal protection may be maximized at values less than 80 mmHg, particularly in the presence of sizeable proteinuria. The blood pressure to be achieved should also be low in diabetic hypertensive patients without evidence of nephropathy because, in the HOT [276] and the UKPDS [373] studies, diabetic hypertensive patients randomised to a more aggressive DBP control (diastolic values close to 80 mmHg) showed much lower cardiovascular morbidity and mortality than patients randomised to more traditional DBP targets. The optimal SBP goal is less certain, but a reduction to values, 1) < 140 mmHg, in the general hypertensive population and, 2) < 130 mmHg in diabetic patients with or without nephropathy also seems, if well tolerated, appropriate. The possibility that an excessive blood pressure fall may lead to increased morbidity and mortality, i.e. the so called J shape phenomenon [723,254] is currently regarded as unlikely (at least between values 140–120 mmHg systolic and 90–70 mmHg diastolic) because of, 1) the epidemiological evidence that, in the general and elderly population, cerebrovascular and coronary morbidity are linearly related to systolic and DBP down to about 110 and 70 mmHg respectively, 2) the evidence from a randomised controlled trial in isolated systolic hypertension in the elderly, that cardiovascular morbidity is reduced when the DBP is reduced to less than 70 mmHg and, 3) the data provided by trials in individuals with a high-risk profile or overt cerebral or cardiac disease (i.e. in whom vital organ auto regulation is more likely to be impaired) that blood pressure reduction from initially normal blood pressure values is accompanied by cardiovascular protection rather than harm [260,262,276,373,724]. In the PROGRESS trial, patients with cerebrovascular disease and initial blood pressure less than 140/85 mmHg showed much less stroke recurrence and myocardial infarction if on-treatment values were about 125 mmHg systolic and 75 mmHg diastolic. In conclusion, treatment should aim at lowering blood pressure to less than 140/90 mmHg in the general hypertensive population with lower targets in diabetic and high-risk patients as well as in nephropathic patients. The optimal BP levels to be achieved cannot be precisely defined, but values lower than 130/80 mmHg might be desirable. It should be emphasised, however, that SBP values below 140 mmHg may be difficult to achieve in many patients [726], even when available combination treatments are employed. It should also be

emphasised that, in these patients, blood pressure reductions from levels below traditional thresholds or beyond the traditional targets lower the cardiovascular risk (a substantial benefit being achieved with a small blood pressure reduction of 2–3 mmHg in diastolic pressure).

In all patients, however, the blood pressure reduction should be obtained gradually. This is particularly necessary in elderly patients, in patients with isolated systolic hypertension, in patients with severe atherosclerotic disease, and in diabetic patients. In these patients, an excessive orthostatic blood pressure fall should be avoided and the optimal blood pressure value, which can be achieved, should be established by monitoring patients' symptoms, vital organ function, and well-being.

Duration of treatment

Generally, antihypertensive therapy should be maintained indefinitely. Cessation of therapy in patients who had been correctly diagnosed as hypertensives is, in most instances, followed sooner or later by the return of blood pressure to pre-treatment levels [727]. Nevertheless, after prolonged good blood pressure control, it may be possible to attempt a careful progressive reduction in the dosage, or number of drugs used, particularly in patients strictly following lifestyle recommendations. However, attempts to step down treatment should be accompanied by careful, continued monitoring of blood pressure, particularly in high-risk patients and in patients with target organ damage. Careful consideration should be given to the fact that, in general clinical practice, hypertension is not well treated and that the number of patients in whom blood pressure is reduced to below 140/90 mmHg is a minority of the hypertensive population [727]. Increasing compliance to antihypertensive treatment and achieving a wide blood pressure control in the population thus represents a major goal for clinical practice in the future.

5.6 Management of dyslipidemia

Exclusion of secondary dyslipidemia

Hyperlipidemias secondary to other conditions are common, and for obvious reasons they must be excluded before beginning diet and especially drug therapies. They include abuse of alcohol, diabetes, hypothyroidism, diseases of the liver and kidneys and several drugs. Exclusion requires clinical assessment and a small battery of clinical chemical tests such as thyroid-stimulating hormone, alanine aminotransferase, γ -glutamyltransferase, albumin, glucose, glycosylated hemoglobin and creatinine in plasma; a measurement of erythrocyte volume; and glucose and protein in urine. Patients who could have genetic diseases such as familial hypercholesterolemia should, if possible, be referred to specialist evaluation, which might include molecular genetic diagnosis.

A guide to Lipid Management in asymptomatic subjects is given in Fig. 4.

Diet

All patients with atherosclerotic disease, and persons at high risk of developing atherosclerotic disease, should follow the dietary recommendations given in this document (section 5.2). Some patients with severe hypertriglyceridemia require a diet that is severely restricted in long-chain fatty acids from vegetable as well as animal sources. The purpose of this diet is to prevent pancreatitis. It differs substantially from the general dietary recommendations, and most patients will need the assistance of a well-trained dietician.

Drugs

A result of most [37,326,334,336] but not all meta-analyses [728] is that the benefits of lowering cholesterol depend on the manner by which it is lowered.

In most European countries, the current armamentarium of lipid-lowering drugs includes inhibitors of HMG CoA reductase (statins), fibrates, bile acid sequestrants (anion exchange resins), and nicotinic acid and its derivatives. To various extents, they have all been used in angiographic trials demonstrating inhibition of the progression of atherosclerosis. All four classes of drugs, but not all drugs within each class, have also been shown in trials to reduce myocardial infarction and coronary death.

The most convincing evidence from angiographic as well as clinical end-point trials has nevertheless been obtained with the most potent of the lipid-lowering drugs, namely the statins. This class of drugs also has a good safety record, and it is the easiest to use. At present, the statins are therefore first line drugs for lowering LDL cholesterol. They vary in the degree to which they reduce LDL, but, as indicated earlier, the question of the benefits of reducing LDL cholesterol well below current goals of therapy is being tested in large clinical trials in progress. Other differences are in ancillary properties such as antithrombotic and anti-inflammatory effects. It should be appreciated, however, that the experimental basis for these pleiotropic effects of statins is very small compared to the data emerging from the major trials with clinical end-points, on which clinical practice should be based. The statins used in these trials were pravastatin [337,340,343], simvastatin [273,274] lovastatin [339] and atorvastatin [275]. A more recent, relatively small trial suggests that treatment with fluvastatin also reduces rates of cardiovascular disease [729]. Although long-term trials have indicated that statins are quite safe [352], post-marketing surveillance has shown that cerivastatin, especially, when given in conjunction with other drugs such as mibefradil, fibrates, cyclosporine, macrolide antibiotics, warfarin, digoxin, and azole antifungals can cause fatal rhabdomyolysis [730]. It is therefore part of the current recommendations that statins and other powerful drugs should remain prescription drugs.

Fibrates are also easy to use, and they lower triglycerides and increase HDL quite effectively. The evidence from clinical trials to support the wide-spread use of fibrates is not as good as that supporting statins, however. Indeed, a conclusion of several meta-analyses has been that there is no good indication for the use of the fibrate group of drugs [37,334,336]. This verdict is not entirely justified, however, because closer analysis of the results of the fibrate trials, one of which is very encouraging [378], suggests that there is clinically significant benefit, but that it may be restricted to subgroups of dyslipidemic patients, in particular patients with low HDL, high triglycerides, and other characteristics of the insulin resistance syndrome and type 2 diabetes. The proper indications for use of the fibrates must therefore be defined by ongoing clinical trials such as the Field study (Fenofibrate Intervention and Event Lowering in Diabetes).

Valuable and safe drugs also include the anion-exchange resins and niacin (nicotinic acid). They can be difficult to use, however, and annoying side-effects such as constipation and flushing, respectively, now usually limit the use of these drugs to lipid specialists.

An inhibitor of cholesterol absorption from the small intestine (ezetimibe) has been marketed in some European countries. Studies to demonstrate the efficacy of ezetimibe in the prevention of complications of atherosclerosis have not yet been completed.

Triglyceride measurements to guide drug choice

Bile acid sequestrants (anion-exchange resins) tend to increase triglycerides, and they should only be used when triglycerides are less than 2 mmol/l (~180 mg/dl) or if given in conjunction with triglyceride-lowering agents. Statins are usually used for patients with triglycerides up to 5 mmol/l (~450 mg/dl). When triglycerides are between 5 and 10 mmol/l (~450–900 mg/dl), either fibrates or statins may be used as first choice drugs, and niacin is a good drug in selected patients. When triglycerides exceed 10 mmol/l (~900 mg/dl), drugs are generally not useful. Instead, to prevent pancreatitis, triglycerides must be reduced by restriction of alcohol, treatment of diabetes with insulin, withdrawal of estrogen therapy, etc. In the rare patients with severe primary hypertriglyceridemia, it is necessary to severely restrict long-chain fat of both animal and vegetable origin.

Drug combinations

Lipid-lowering drugs can be used in combination. In familial hypercholesterolemia, for example, the combination of a bile-acid sequestrant and a statin is very useful, and even a triple regimen of a bile-acid sequestrant, a statin and niacin can be necessary in some patients. Statins can also be combined with fibrates, but this combination has been associated with myopathy, even fatal rhabdomyolysis, and patients must be carefully selected

and carefully instructed about warning symptoms (myalgia). The combination of a statin with a cholesterol absorption inhibitor could turn out to be valuable.

When to begin lipid-lowering therapy after myocardial infarction

The MIRACL trial in patients with acute coronary syndromes showed that treatment with atorvastatin, initiated within 4 days, can reduce the recurrence of myocardial ischemia during the following 4 months [731]. These findings should be replicated, however, before it is considered mandatory to begin treatment in the acute phase of the disease or immediately thereafter. In principle, therefore, drug treatment can be postponed for 3 months. The advantage of this approach is that estimation of untreated plasma lipids, and the evaluation of response to drug therapy, are more reliable, because the acute phase response of plasma lipids to myocardial infarction has passed. Moreover, it gives cardiologists and general practitioners the time and opportunity to consider whether the patient has a genetically determined dyslipidemia requiring family investigation.

The disadvantage of postponing initiation of therapy is that many patients will no longer be under the care of a cardiologist when drug therapy should be started. In some cases, this means that drug treatment will never be considered. Many cardiologists are therefore prescribing drug treatment in hospital on the basis of the initial cholesterol measurement. Such early drug treatment should nevertheless be combined with effective dietary intervention. The strategy to ensure that goal concentrations are reached must obviously depend on the organisation of medical care in each European country.

LDL apheresis

Rare patients with severe hypercholesterolemia, especially homozygous familial hypercholesterolemia, require specialist evaluation of the need for LDL apheresis. By this expensive but effective technique, LDL is removed from plasma during extracorporeal circulation weekly or every other week.

Goals of therapy

Physiological concentrations of LDL cholesterol are probably around 1–2 mmol/l (40–80 mg/dl), but whether clinical benefit results from reducing LDL cholesterol to such low levels has been the subject of some controversy. Post-hoc analyses of the results of the CARE [732] and the WOSCOPS [733] suggested that lowering LDL cholesterol below 3 mmol/l (115 mg/dl) confers no benefit, whereas similar analyses of the 4S [303] and LIPID trials [304] indicated that there is no level of LDL cholesterol below which further reduction is futile. The results of the Heart Protection Study [274] demonstrated the same degree of benefit, given in relative terms, of lowering LDL cholesterol from 3 to 2 mmol/l as from 4 to

3 mmol/l, suggesting again that, at least down to about 2 mmol/l, there is no threshold value for benefit. This conclusion is also supported by the result of the ASCOT-LLA trial, which demonstrated clinical benefit from reducing LDL cholesterol by about 1.2 mmol/l from a baseline level of only 3.4 mmol/l [275]. It is also consistent with observational epidemiology [734].

In 1998, the Joint European Societies recommended that reduction of total cholesterol below 5 mmol/l (~190 mg/dl) and LDL cholesterol below 3 mmol/l (~115 mg/dl) could be goals of therapy consistent with the evidence available at that time [10]. As the main body of evidence accrued since then, the results of the Heart Protection Study and the ASCOT-LLA require consideration of whether the goals for total cholesterol and LDL cholesterol should be lowered.

The current recommendation is that in general the goals should not be changed. Lower goals would require higher doses of statins and other lipid-lowering drugs for the majority of patients. It is therefore important to emphasise that the Heart Protection Study (HPS) [274] did not test whether a statin given in higher doses produces greater clinical benefit than when it is given in moderate doses. In the HPS, all patients received moderate doses of simvastatin (40 mg/day), but lowering of LDL cholesterol by approximately 1 mmol/l resulted in the same degree of benefit irrespective of whether LDL cholesterol was 3, 4 or 5 mmol/l at the beginning of the study. Similar data emerged from closer analyses of the results of the 4S and LIPID [303,304], which showed that there was no significant variation in the relative treatment effects according to baseline lipid levels. The difference between the earlier studies and the HPS is that baseline lipids were higher in the early studies. The question of whether high dose therapy is superior to moderate dose therapy is currently being addressed by three large clinical trials with clinical endpoints (IDEAL, SEARCH and TNT), the results of which should be published before goals of therapy are changed.

This recommendation for unchanged total cholesterol and LDL cholesterol goals in general requires three qualifications however.

First in patients with established cardiovascular disease and patients with diabetes the treatment goals should be lower: total cholesterol < 4.5 mmol/l (175 mg/dl) and LDL cholesterol < 2.5 mmol/l (100 mg/dl).

Secondly, asymptomatic people at high risk of developing CVD, whose untreated values of total and LDL cholesterol already are 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 from further reduc-

tion of LDL cholesterol to < 2.5 mmol/l (100 mg/dl) with moderate doses of lipid lowering drugs.

Thirdly, goals cannot be reached with the same ease by all patients. Patients with concentrations of plasma lipids that are only slightly abnormal can reach goals of therapy fairly easily with diet and moderate doses of drugs. When goals have not been reached, doses should be higher and certainly no lower than those employed in trials demonstrating clinical benefit.

A minority of patients have familial hypercholesterolemia or other severe, genetically determined disturbances of lipid metabolism. Even with dual or triple drug regimens, reducing LDL cholesterol below 3 mmol/l (115 mg/dl) can sometimes be difficult, and the physician must prepare the patient for that situation. The statin trials indicated that a reduction of total cholesterol by at least 20% and of LDL cholesterol by at least 30% are accompanied by substantial clinical benefit, and the physician can elect to advise the patient that these degrees of lipid-lowering are satisfactory. However, with moderate to high-dose statin therapy, or with various forms of combination therapy, much greater percentage reductions of LDL cholesterol and total cholesterol are often possible, and it is now quite feasible to halve the concentration of LDL cholesterol (50% reduction) whatever the baseline level.

As indicated in section 4.5, the current recommendations are that triglycerides > 1.7 mmol/l (~150 mg/dl) and HDL cholesterol < 1 mmol/l (~40 mg/dl) in men and < 1.2 mmol/l (~46 mg/dl) in women continue to be regarded as markers of increased risk, but that triglycerides and HDL continue not to be regarded as goals of therapy. The main reason for this recommendation is that, in contrast to the evidence underpinning reduction of LDL, there is still no evidence from clinical trials defining to which levels triglycerides should be reduced, or HDL cholesterol should be increased, to reduce risk of cardiovascular disease. Apart from being powerful indicators of risk, measurements of triglycerides and HDL cholesterol should also be used to guide the choice of drug therapy.

5.7 Prevention of risk of CVD in diabetes

The optimal way to prevent the increased risk of CVD associated with diabetes would be through prevention of diabetes itself. Studies from China, Finland, USA and Canada have consistently shown that type 2 diabetes can at least be postponed through lifestyle intervention [735–738]. None of these studies, however, were designed and powered to look at the impact of preventing diabetes on the incidence of CVD. Population based intervention studies have apparently been successful in preventing CVD, but none of these studies compared the incidence of type 2 diabetes in the intervention and control region [739,740].

Glucose

There is convincing evidence from randomised controlled clinical trials that good glycaemic control prevents microvascular complications in both type 1 and type 2 diabetic patients [369,370,373,724]. The evidence with respect to prevention of macrovascular complications is less convincing, although the UKPDS-study strongly indicates that this may be the case [369].

In patients with type 1 diabetes without nephropathy good glucose control helps maintain normal plasma lipid levels. Diabetic nephropathy, however, is accompanied with multiple plasma lipid abnormalities which are not fully normalised by good glucose control. Plasma lipid abnormalities associated with type 2 diabetes, elevated triglycerides and low HDL cholesterol, are to some extent but in most instances not corrected by good glucose control. Thus there are good reasons to aim for good glucose control as can practically be achieved in patients with type 1 and type 2 diabetes, and this may be beneficial for the prevention of coronary artery disease and other atherosclerotic disease. 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 treatments aiming at good glucose control. If these measures do not lead to a sufficient reduction of hyperglycaemia, treatment with oral hypoglycaemic drugs (sulphonylurea or biguanide or their combination) or insulin has to be added to the treatment regimen. In overweight and obese patients metformin has proved to be the optimal treatment associated with minimal weight gain in combination with the lowest risk of late diabetic complications [370], but apart from this, no specific oral hypoglycaemic agent has proved to be superior in relation to outcome. In patients with very strict glycaemic control hypoglycaemia becomes an important issue, and here very short acting sulphonylurea compounds would be preferential [741]. Insulin-treatment (alone or in combination with oral hypoglycaemic agents) may be necessary in as many as 50% of the patients [361], and it is essential that barriers to insulin treatment are identified and overcome. Self-monitoring of blood glucose is essential in the treatment of type 1 diabetes to improve the safety and quality of treatment, and is a vital safeguard against serious hypoglycaemia. Self-monitoring is also recommended for patients with type 2 diabetes treated with sulphonylureas or insulin.

Recommended treatment targets for patients with type 1 diabetes and type 2 diabetes have been defined by the International Diabetes Federation Europe [742,743] (Table 24 and 25). Treatment targets should however always be individualised, particularly in patients with other competing life-threatening diseases, very severe late diabetic complications and in the elderly patient.

Table 24 Glucose control assessment levels for type 1 diabetes [742]

		Non-diabetic	Adequate	Inadequate
HbA _{1c} (DCCT-standardized)	HbA _{1c} (%)	< 6.1	6.2–7.5	> 7.5
Self-monitored blood glucose	Fasting/preprandial mmol/l	4.0–5.0	5.1–6.5	> 6.5
		70–90	91–120	> 120
	Postprandial (peak) mmol/l	4.0–7.5	7.6–9.0	> 9.0
		70–135	136–160	> 160
	Prebed mmol/l	4.0–5.0	6.0–7.5	> 7.5
		70–90	110–135	> 135

Table 25 Glucose control assessment levels for type 2 diabetes [743]

		Non-diabetic	Adequate	Inadequate
HbA _{1c} (DCCT-standardized)	HbA _{1c} (%)	≤ 6.1	6.2–7.5	> 7.5
Venous plasma glucose	Fasting/preprandial mmol/l	≤ 6.0	6.1–7.0	≥ 7.0
		< 110	110–125	> 125
Self-monitored blood glucose	Fasting/preprandial mmol/l	4.0–5.0	5.1–6.5	> 6.5
		70–90	91–120	> 120
	Postprandial mmol/l	4.0–7.5	7.6–9.0	> 9.0
		70–135	136–160	> 160
	mg/dl	70–90	91–120	> 120
		70–135	136–160	> 160

Blood pressure

Targets for blood pressure are generally more ambitious in patients with diabetes. This is first of all due to the fact that very strict control of blood pressure is the most important single factor preventing development of diabetic nephropathy and end stage renal failure [265–267,701,744]. Furthermore, subgroup analysis of the diabetic patients in trials focused on prevention of CVD in patients with hypertension have demonstrated more beneficial treatment effects in the diabetic group in the non-diabetic group, and suggests that stricter treatment targets are indicated [276,375,745]. The HOPE study showed that in patients with initial blood pressure of 130/79 mmHg a further, small reduction of BP (3/1 mmHg) was associated with a further reduction in cardiovascular risk [701]. The optimal BP levels to be achieved cannot be precisely defined, but values below 130/80 may be desirable in diabetic patients. In diabetic patients with diabetic nephropathy and proteinuria > 1 g/24 h, values as low as 125/75 or lower are recommended if achievable without unacceptable side effects.

The type of antihypertensive medication also seems to be important. ACE inhibitors and angiotensin II receptor inhibitors have proven to be particularly effective in preventing progression from microalbuminuria to overt nephropathy in type 1 as well as in type 2 diabetic patients [265–267,701,744]. Thus in these groups of patients, ACE inhibitors and angiotensin II receptor blockers would be preferred as initial therapy; however most patients will require a combination of two or more drugs [373].

In diabetic patients with hypertension and established coronary heart disease, particularly those who have survived a myocardial infarction and in those with angina pectoris, the use of beta-blockers is indicated.

Lipid lowering therapy

Although important new information is available on the results of trials of lipid-lowering drug therapy with statins in diabetic subjects, a worldwide consensus about the indications and goals of lipid-lowering therapy has not yet been reached. In the United States, even before the publication of the Heart Protection Study [274] results, the Cholesterol Education Program Adult Treatment Panel III (ATP-III) in their recommendations published in 2001 [325] took the position that diabetes should be considered to be a CHD risk equivalent, which means that individuals with diabetes would have a similar risk of future CHD events as patients with clinically established CHD. Therefore, in ATP-III recommendations, and similarly in the recommendations of the American Diabetes Association the LDL cholesterol goals and LDL cholesterol levels for the initiation of therapy were defined to be for diabetic subjects similar to those for patients with CHD or other atherosclerotic disease: LDL cholesterol goal < 2.6 mmol/l (100 mg/dl), and LDL cholesterol level for the initiation of therapeutic lifestyle changes was defined to be ≥ 2.6 mmol/l (100 mg/dl) irrespective of the presence or absence of CHD or other atherosclerotic disease. LDL cholesterol levels for the initiation of drug therapy were defined to be in diabetic patients with CHD or other atherosclerotic disease ≥ 2.6 mmol/l (100 mg/dl) and in those without atherosclerotic disease ≥ 3.35 mmol/l (130 mg/dl). These American recommendations have, however, not defined at what age aggressive lipid management should be initiated in people with type 1 diabetes and in people who develop type 2 diabetes at relatively young age. The Heart Protection Study gave simvastatin 40 mg to all diabetic individuals (type 1 and type 2 diabetic patients) if total cholesterol was > 3.5 mmol/l. A continuous risk reduction was observed in all ranges of baseline cholesterol, indication that treatment with simvastatin is beneficial, at least in all type 2 diabetic patients. The Heart Protection Study [274] can, however, not identify the clinically relevant treatment targets for total cholesterol and LDL cholesterol, and thus treatment targets should be as indicated above.

In people with type 1 diabetes plasma lipid levels do not differ much from those in non-diabetic people, if their glycaemic control is good and if they do not have nephropathy, but when nephropathy even its mildest form ensues, plasma triglyceride levels tend to increase and HDL levels which are often somewhat increased in type 1 diabetes tend to decrease. In people with type 2 diabetes LDL cholesterol levels are similar to those in non-diabetic subjects and the most common form of dys-

lipidaemia in type 2 diabetes is characterised by elevated triglycerides and low HDL cholesterol. Although fibrates would seem to be the most suitable drug for the dyslipidaemia of type 2 diabetes, the trial experience of their use in the management of dyslipidaemia in diabetic patients is still rather limited. A large trial (FIELD) testing the efficacy of fenofibrate is currently in progress in Australia and Finland. Because trial experience on efficacy and safety of statins is extensive and now, with the results of the Heart Protection Study, even compelling, statins are currently recommended as first choice for lipid-lowering drug for people with type 1 and type 2 diabetes.

The debate around the aggressive approach for lipid management in diabetic people recommended by Americans still continues in Europe and not all national or other expert groups are ready to underwrite the American recommendations. The main argument for a more individualistic approach is based on the observation that according to epidemiological observations the variation in the multifactorial risk of diabetic individuals is wide, although its distribution is shifted to a higher level than in non-diabetic individuals. The influence of age and gender and the presence or absence of diabetic complications on the benefits of lipid-lowering treatment need to be addressed in more detail on the basis of data from already completed trials and the results of trials which are still going on.

Antiplatelet therapy

As indicated above, recent results reported by the Antithrombotic Trialists' Collaboration [380] have cast some doubts about the efficacy of antiplatelet therapy in the prevention of cardiovascular disease events in diabetic patients. The use of aspirin or some other antiplatelet drug, if aspirin is contraindicated, may still be considered in the preventive management in diabetic patients who already have clinically established cardiovascular disease.

Precursors of diabetes

Impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG) are both conditions associated with an increased risk of developing type 2 diabetes, and IGT is associated with a deterioration of the cardiovascular risk profile [746] and increased risk of death from all causes as well as from CVD, CHD and stroke [747]. In patients with IGT, several studies have demonstrated that progression to diabetes can be prevented or delayed by lifestyle intervention, and thus these patients should be identified where possible and provided with necessary support.

Increasing levels of metabolic risk factors are seen across the spectrum of non-diabetic glucose values [748], and hyperinsulinaemia is associated with all the components of the metabolic syndrome. Individuals with the metabolic syndrome are at high risk of developing cardiovascular disease, and in these individuals a total risk

assessment based on the existing risk engines should be performed to assess risk, and to identify the most important risk factors available for intervention.

5.8 Prevention in subjects with the metabolic syndrome

Cardiovascular risk prediction systems, such as the SCORE and other multifactorial risk prediction systems based on conventional risk factors, do not completely capture the increased risk associated with the metabolic syndrome, because the excess risk arises from a particular clustering of risk factors. The definition of the metabolic syndrome given by the NCEP [325] (see section 4.7) was developed for the clinical practice and can be used in the identification of people with this risk factor constellation. Because the metabolic syndrome increases the risk of developing type 2 diabetes and cardiovascular disease, identification of this syndrome is of particular importance in non-diabetic people.

Since lifestyles have a strong influence on all the components of the metabolic syndrome, the main emphasis in the management of the risk in people with this syndrome should be in professionally supervised lifestyle change, including efforts directed to the reduction of overweight and increased physical activity. Although the dyslipidaemia of the metabolic syndrome is characterised by elevated triglycerides and/or low HDL cholesterol, lipid management should, however, be steered with LDL cholesterol goals in mind. Experience from clinical trials has shown that in this type of dyslipidaemia both statins and fibrates are very effective in reducing the risk of coronary heart disease events [749,750].

5.9 Prophylactic drug therapy

Since 1998 new systematic reviews, meta-analyses and individual clinical trial results have been published on the use of prophylactic drug therapies for both patients with established CVD and individuals at high risk of developing symptomatic atherosclerotic disease. This new trial evidence, particularly for statins and ACE inhibitors, strongly reinforces the concept of total risk management in these atherosclerotic disease patients and high risk individuals.

In addition to drugs which may be needed to control symptoms, keep blood pressure, lipids and glucose levels to recommended goal, the use of prophylactic drugs shown in clinical trials to reduce CVD morbidity and mortality must be considered. While some of these drugs are appropriate for all individuals at high total risk, whether from established CVD or at high risk of developing CVD, others are specifically indicated for selected patients.

Anti-platelet therapies

Aspirin or other platelet modifying drugs are recommended in virtually all patients at high risk of occlusive

arterial disease. The most recent meta-analysis of anti-platelet trials by the Antithrombotic Trialist's Collaboration provides convincing evidence of a significant reduction in all causes mortality, vascular mortality, non-fatal re-infarction of the myocardium and non-fatal stroke in patients with unstable angina, acute myocardial infarction, stroke, transient ischaemic attacks or other clinical evidence of vascular disease [380]. In the trials which used aspirin, the most widely tested doses varied between 75–325 mg/day. There was no evidence of any greater clinical benefit for any doses in between this range. Side-effects from aspirin are lowest in those using lower dosages. Hence, the available evidence supports daily doses of aspirin in the range of 75–150 mg for the long term prevention of serious vascular events in high risk patients. Although there is no clinical trial evidence of treatment beyond a few years, it would be both prudent and safe to continue aspirin therapy for life. For patients with acute coronary disease, unstable angina or non ST segment elevation myocardial infarction, Clopidogrel has been shown to reduce the composite outcome of CV death, myocardial infarction and stroke during the year following the hospitalisation (CURE Trial) [751]. To study the question of whether one anti-platelet therapy is better than another, and specifically aspirin, very large clinical trials will be needed. At this time only Clopidogrel at 75 mg/day has been tested in a single large trial against aspirin at 325 mg/day [752]. The overall result shows that the two drugs are equally effective at preventing major vascular complications in patients with recent myocardial infarction or ischaemic stroke. Clopidogrel however was more effective than aspirin among subjects enrolled because of symptomatic peripheral arterial disease. Clopidogrel has a better side effect profile than aspirin and therefore this drug should be considered an alternative to aspirin if the latter causes side effects.

In asymptomatic individuals with no evidence of cardiovascular disease a meta-analysis has shown that aspirin reduced the risk of the combined end point of non-fatal myocardial infarction and fatal CHD, but increased the risk of haemorrhagic strokes and major gastrointestinal bleeding. The net benefit of aspirin increases with increasing cardiovascular risk and therefore estimating total risk of CVD is an absolute pre-requisite to initiating anti-platelet therapy [753,754].

If the total CVD risk is $\geq 5\%$ then prophylactic aspirin is appropriate as long as the blood pressure has been controlled as closely as possible to the goal of $< 140/90$ mmHg. In lower risk subjects in the population a small absolute vascular benefit by aspirin may be offset by the slightly greater absolute risk of bleeding complications. When aspirin cannot be tolerated alternative anti-platelet therapy such as Clopidogrel should be considered.

Beta-blockers

In a meta-analysis of beta-blockers following myocardial infarction, there was evidence of a significant reduction in all cause mortality, cardiovascular death and in particular sudden cardiac death, as well as non fatal re-infarction [755]. The benefits of beta-blockade are greatest in older patients (more than 60 years) and in patients at increased risk of reinfarction and death (e.g. patients with LV dysfunction or arrhythmias or both). Beta-blockers have also been shown to reduce all cause mortality in patients with heart failure due to coronary heart disease [756]. Therefore a beta-blocker should be considered in all patients with CHD, providing there are no contra-indications, for the following reasons: to relieve symptoms of myocardial ischaemia, to lower blood pressure to < 140/90 mmHg, as prophylaxis following myocardial infarction and in the treatment of heart failure. In post-MI patients with contra-indications to beta-blockers and no evidence of heart failure, verapamil may be considered based on the results of single large clinical trial [757].

ACE inhibitors

Several clinical trials have shown that ACE inhibitors in patients with symptoms or signs of heart failure, or left ventricular dysfunction, due to CHD will significantly reduce the risk of death, recurrent myocardial infarction and progression to persistent heart failure [758–767,720]. Short term studies of ACE inhibitors in the acute phase of myocardial infarction have also shown the risk of death can be reduced within the first day of treatment. More recently ACE inhibition has been shown to reduce the risk of myocardial infarction and cardiovascular mortality in two large clinical trials in respectively high risk people (aged 55 years or older, at high risk of CV complications characterised by the prevalence of diabetes, hypertension, stroke and obstructive peripheral vascular disease) and in patients with stable CHD without apparent heart failure [260,768].

Anti-coagulation

Systemic anti-coagulation with coumarins is not indicated prophylactically in all patients with coronary artery disease. However, anti-coagulation is appropriate in selected patients following myocardial infarction at increased risk of thrombo-embolic events including patients with large anterior myocardial infarction, left ventricular aneurysm or thrombus, paroxysmal tachyarrhythmias, chronic heart failure and those with a history of thrombo-embolic events [769].

6) Implementation strategies**Implementation of evidence-based treatments: the role of guidelines and recommendations**

As shown in previous chapters, the risk to develop a first or recurrent manifestation of atherosclerotic disease can

be lowered by changes in lifestyle and by pharmacotherapeutic interventions. The Euroaspire I and II studies have demonstrated that a more complete implementation of existing guidelines will increase life expectancy and quality of life in most European countries.

Guidelines, recommendations and expert consensus documents are all intended to help the clinician choose the appropriate therapy for a patient with a certain medical condition. As a rule such documents are based on the evidence provided by the outcome of controlled clinical trials or, if this is not available, on consensus between experts.

Despite the fact that guidelines and recommendations exist for the treatment of most common conditions in cardiology, it has been found in national and international hospital-based surveys, that many patients do not receive the therapy appropriate for their condition. On the other hand, several small and large outcomes studies show that under well-controlled conditions almost all patients may well receive appropriate therapy [770,771,772]. In this chapter, we use the term “implementation” as indicating the goal, that each patient receives treatment in accordance with the existing guideline for the diagnosis under consideration, unless a medical reason exists to withhold the appropriate therapy [773,774]. In this sense, implementation is either complete, or incomplete.

Barriers to the implementation of evidence-based treatment guidelines

Incomplete implementation of the appropriate therapy may have several causes. Some causes have to do with inadequacies of medical management, some with circumstances not within control of doctors, and sometimes the patient just does not fit the profile [775]. Recently, three types of barriers to the implementation of evidence-based treatment guidelines have been suggested: a physician-related, a patient-related, and a healthcare-related barrier [776]. Table 26 shows these barriers in more detail.

Physician-related barriers to the implementation of evidence-based treatment

Lack of knowledge of the existence of a particular guideline may result in the application of a less than appropriate therapy. It is of great importance that the existence of guidelines is widely communicated and that existing guidelines are easily accessible. The internet provides an excellent tool, but it is also conceivable that guideline information is installed in smaller hand-held devices. Still, the physician has to develop the routine to check the guideline when a new diagnosis is to be matched by therapy. At the same time, the guideline providing institution has the responsibility to ensure that existing guidelines are up-to-date as well as state-of-the-art.

A guideline is based on the available scientific evidence. The guideline however, does not necessarily always fit the

Table 26 Barriers to the implementation of evidence-based treatment

Physician-related:	Lack of knowledge Guidelines difficult to interpret Time constraints
Patient-related:	Concern for possible side effects of medication Polypharmacy and compliance Time and financial constraints
Health care-related:	Difficulties engaging in health-modifying behaviour Uninsured and underinsured individuals Lack of systematic approach to chronic illnesses Budgetary restraints

situation of a given patient. Even under ideal circumstances, the guideline may be difficult to interpret. On top of this, a guideline may be difficult to interpret because of unwanted ambiguity. The communicative aspects of any guideline should be given sufficient attention.

When the availability of time is the critical factor, as will be the case in many hospitals and primary care practices, and when guideline application is not part of an established routine, patients may not always receive guideline-conformed medical care.

Lastly, a physician can have good reasons to withhold the therapy suggested by a guideline. Or the patient may have reasons to refuse a certain treatment. The available reports on the implementation of guidelines give little information on the underlying rationale for not following the guideline.

Physician-related methods to improve implementation

A systematic review of the literature executed several years ago concludes that the application of guidelines in a setting of rigorous control gives the best chances to improve clinical practice [777]. A recent study of the care of patients with acute myocardial infarction concludes that the “implementation of guideline-based tools may facilitate quality improvement among a variety of institutions, patients and caregivers [778]”. The shared conclusion here is, that a guideline in itself is not the ultimate instrument to improve clinical care. The guideline needs a tool, or a setting, to realise its full potential.

One way to implement a guideline in a well defined clinical setting, for example the treatment of acute coronary syndromes, can be to use the daily multidisciplinary group rounds [779]. Another way is to create a “tool kit” and engage nurse and physician opinion leaders as well [778].

Treatment protocols, developed from evidence-based guidelines can be used in circumstances where strict adherence to the rules for limited periods of time is essential for the quality of the care, for example in the intensive care unit.

A novel way to implement guidelines in patients with uncomplicated illnesses who are undergoing procedures

or surgery, is the use of critical pathways. Critical pathways are management plans that “display goals for patients and provide the corresponding ideal sequence and timing of staff actions for achieving those goals with optimal efficiency [780]”. Recently, the use of critical pathways for the implementation of evidence-based treatments has been critically reviewed [781]. At this moment, more research into the added value of the use of critical pathways, clearly is necessary.

Patient-related options to improve implementation

Patient-related barriers to implementation in which the physician can play a role are related to polypharmacy and compliance with medication, and to behavioural changes. For behavioural changes in particular, the reader is referred to the chapter on “Behaviour change and management of behavioural risk factors” (chapter 5.1 of these guidelines).

Health care-related barriers to the implementation

Some of the health care system related barriers cannot be changed by the individual physician for whom these guidelines are written; other can be influenced by a better organisation in primary care practice and in the hospital.

The role of the National Societies

The members of the Third Joint Task Force on Cardiovascular Disease Prevention in Clinical Practice expect that the National Societies and individual physicians will be actively engaged in the process to make these guidelines (or adapted ones) part of the standard daily clinical practice.

The Third Joint Task Force also fully subscribes to the need of a continuous evaluation of the relation between guideline developments, implementation programmes, and daily practice as addressed by the European Society of Cardiology [782].

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