Task Force Report

Prevention of coronary heart disease in clinical practice

Recommendations of the Second Joint Task Force of European and other Societies[†] on Coronary Prevention

†European Society of Cardiology, European Atherosclerosis Society, European Society of Hypertension, International Society of Behavioural Medicine, European Society of General Practice/Family Medicine, European Heart Network

Prepared by David Wood, Guy De Backer, Ole Faergeman, Ian Graham, Giuseppe Mancia and Kalevi Pyörälä together with members of the Task Force

Summary of Recommendations

Since the first Joint European Societies — European Society of Cardiology (ESC), European Atherosclerosis Society (EAS) and European Society of Hypertension (ESH) — Task Force recommendations on coronary heart disease prevention in clinical practice were published in 1994 new scientific evidence has emerged in both secondary and primary coronary prevention, particularly in relation to lipid lowering. Therefore, a second Task Force was convened by the three major societies, including professional representatives from behavioural medicine, primary care and the European Heart Network to revise the recommendations.

The Task Force has summarized the most important clinical issues on coronary heart disease prevention on which there is good agreement in order to give cardiologists and physicians — in hospital, the office and the community — and other health care professionals, the best possible advice to facilitate their work on coronary heart disease prevention. The priority for physicians is still to concentrate on patients with overt coronary heart disease, or other atherosclerotic disease, and other high risk individuals. The potential for preventive action is greatest in these groups and we need to achieve considerable improvements on existing clinical practice. The present recommendations are specifically intended to encourage the development and revision of national guidelines on coronary prevention.

Key Words: Coronary heart disease, primary prevention, secondary prevention, risk factors, atherosclerosis.

For coronary prevention to become an integral part of everyday clinical practice national societies of cardiology, atherosclerosis and hypertension, in collaboration with other professional organisations within each country, must take responsibility for developing their own guidelines, appropriately reflecting their political, economic, social and medical circumstances.

The common challenge for cardiologists, physicians and other health professionals throughout Europe is to realise the potential for coronary prevention for all our patients, and to contribute to the wider public health efforts to reduce the enormous burden of cardiovascular disease.

Medical priorities

In the context of a comprehensive population strategy — to reduce tobacco use, encourage healthy food choices and increase physical activity for the whole population — the medical priority is to focus on those who have developed symptoms of coronary heart disease or other major atherosclerotic disease, and those who are at high risk of developing such diseases in the future.

The priorities for preventive cardiology are:

1. Patients with established coronary heart disease or other atherosclerotic disease.
2. Healthy individuals who are at high risk of developing coronary heart disease or other atherosclerotic disease, because of a combination of risk factors — including smoking, raised blood pressure, lipids (raised total cholesterol and low density lipoprotein

(LDL)-cholesterol, low high density lipoprotein (HDL)-cholesterol and raised triglycerides) raised blood glucose, family history of premature coronary disease — or who have severe hypercholesterolaemia or other forms of dyslipidaemia, hypertension or diabetes.
3. Close relatives of patients with early onset coronary heart disease or other atherosclerotic disease, and of healthy individuals at particularly high risk.
4. Other individuals met in connection with ordinary clinical practice.

Objectives of coronary heart disease prevention

The overall objective of coronary heart disease prevention, both in patients with clinically established coronary heart disease, or other atherosclerotic disease, and high risk individuals is the same: to reduce the risk of major coronary heart disease, or other atherosclerotic disease events, and thereby reduce premature disability, mortality and prolong survival. In these recommendations goals have been set not only for lifestyle change but for the management of blood pressure, blood lipids and diabetes in secondary and primary prevention of coronary disease (Table 1).

Absolute multifactorial coronary heart disease risk as a guide to lifestyle intervention and drug treatments

Patients who present with symptoms of coronary heart disease, or other atherosclerotic disease, declare themselves to be at very high absolute risk of a further vascular event. Therefore they require the most intensive lifestyle intervention and, as necessary, drug therapies in order to achieve risk factor goals.

As coronary heart disease is multifactorial in origin it is important in healthy individuals to estimate absolute risk (the risk of developing coronary heart disease, either a non-fatal event or coronary death, over the next 10 years) by taking into account all the major risk factors. See colour Coronary Risk Chart (Fig. 1, between pages 1437 and 1440). Those at highest multifactorial risk can be identified and targeted for lifestyle intervention and, where appropriate, drug therapies. Physicians should always use absolute coronary heart disease risk when making a clinical judgement about using drugs to treat blood pressure, and blood lipids, rather than just considering the level of any one risk factor alone. An absolute coronary heart disease risk which exceeds 20% over the next 10 years, or will exceed 20% if projected to age 60, and which is sustained despite professional lifestyle intervention, is sufficiently high to justify the selective use of proven drug therapies.

Secondary prevention

Patients with coronary heart disease or other atherosclerotic disease

Lifestyle
Lifestyle changes depend on the readiness of coronary and other high risk patients to modify their behaviour. When patients develop symptoms of coronary heart disease, or are found to be at high risk, this is an ideal opportunity to review lifestyle. Many will consider making appropriate changes and, with professional and family support, can do so for life.

Stop smoking tobacco. Patients should be professionally encouraged and supported to stop smoking all forms of tobacco for life. A physician can, with sustained advice, help patients to quit. Avoidance of passive smoking would also be prudent. Nicotine replacement therapies can be initially helpful for some patients, particularly those who are heavily addicted to nicotine. Other family members sharing the same household can support patients to stop smoking, and reduce the risks of taking up this habit again by not smoking themselves.

Make healthy food choices. All patients should receive professional advice on food and food choices which make up a diet associated with the lowest risk of coronary heart disease or other atherosclerotic disease. Physicians should emphasize the importance of diet in relation to weight reduction, lowering blood pressure and blood cholesterol, in the control of blood glucose in diabetic patients, and in reducing the propensity to thrombosis. Diet is an integral part of the patient's overall management. The role of the family is particularly important in this context as the person primarily responsible for buying and preparing food must be informed of the need for healthy food choices and how these can be practically achieved. The relevance of physical activity in helping weight control and favourably modifying other risk factors should be explained. Many dietary factors are related to the risk of coronary heart disease and other atherosclerotic disease. For a patient with atherosclerotic disease the dietetic goals are:

- To reduce total fat intake to 30% or less of total energy intake, the intake of saturated fat to no more than one third of total fat intake, and the intake of cholesterol to less than $300 \text{ mg . day}^{-1}$.
- To achieve the reduction in saturated fats by replacing them in part with monounsaturated and polyunsaturated fats from both vegetable and marine sources, as well as with complex carbohydrates.
- To increase the intake of fresh fruits, cereals and vegetables.
- To reduce total calorie intake when weight reduction is needed.
- To reduce salt and alcohol use when blood pressure is elevated.

Table 1   Lifestyle and therapeutic goals for patients with CHD, or other atherosclerotic disease, and for healthy high risk individuals

Patients with CHD
or other atherosclerotic disease.

Healthy high risk individuals.
Absolute CHD risk ≥20% over 10 years, or will exceed 20% if projected to age 60.

Lifestyle

Stop smoking, make healthy food choices, be physically active and achieve ideal weight.

Other risk factors

Blood pressure <140/90 mmHg. Total cholesterol <5.0 mmol/l (190 mg/dl)

LDL-cholesterol <3.0 mmol/l (115 mg/dl)

When these risk factor goals are not achieved by lifestyle changes, blood pressure and cholesterol lowering drug therapies should be used.

Other prophylactic drug therapies

Aspirin (at least 75mg) for all coronary patients, those with cerebral atherosclerosis and peripheral atherosclerotic disease.

ß-blockers in patients following myocardial infarction.

ACE inhibitors in those with symptoms or signs of heart failure at the time of myocardial infarction, or with chronic LV systolic dysfunction (ejection fraction <40%).

Anticoagulants in selected coronary patients.

Aspirin (75 mg) in treated hypertensive patients and in men at particularly high CHD risk.

Screen close relatives

Screen close relatives of patients with premature (men <55 yrs, women <65 yrs) CHD.

Screen close relatives if familial hypercholesterolaemia or other inherited dyslipidaemia is suspected.

Patients who have hypertension, hypercholesterolaemia or other forms of dyslipidaemia, or diabetes can benefit from specialist dietary advice. Appropriate dietary changes can favourably influence all these risk factors, and reduce the need for drug therapies.

Increase physical activity. All patients should be professionally encouraged and supported to increase their physical activity safely to a level associated with the lowest risk of vascular disease. Aerobic exercise (e.g. walking, swimming or bicycling) for 20–30 min 4–5 times a week is recommended. Physicians should emphasize the importance of physical activity in giving the patient a sense of well being. Being physically active helps to reduce weight (together with healthy food choices), increase HDL cholesterol, lower triglycerides and the propensity to thrombosis. Once again the family is important in supporting an active lifestyle.

Other cardiovascular risk factors

Overweight and obesity
Patients who are overweight (body mass index (BMI) $> 25 \, kg \cdot m^{-2}$) or obese (BMI $> 30 \, kg \cdot m^{-2}$), and particularly those who have central obesity, are at increased risk and should be professionally supported to lose weight using an appropriate diet and increased physical activity. Weight reduction will also help to reduce blood pressure, blood cholesterol and blood glucose. Waist circumference is a useful clinical index of obesity and for monitoring weight reduction. A waist circumference $\geq 94 \, cm$ in men and $\geq 80 \, cm$ in women is an indication to lose weight and $\geq 102 \, cm$ in men and $\geq 88 \, cm$ in women requires professional advice on weight reduction.

Blood pressure
In coronary patients the blood pressure goal is consistently below 140/90 mmHg. If this goal is not achieved with lifestyle changes, drug therapy should be used. For patients with angina preference should be given to beta-blockers, or if not tolerated or effective, to long-acting calcium channel blockers, as both drug classes will lower blood pressure and relieve symptoms. Following acute myocardial infarction preference should be given to beta-blockers as this drug class will also reduce the risk of recurrent disease. Angiotensin converting enzyme (ACE) inhibitors can also be used particularly in patients with significant left ventricular systolic dysfunction.

Blood lipids
The blood cholesterol goals are a total cholesterol consistently below $5 \cdot 0 \, mmol \cdot l^{-1}$ (190 mg $\cdot$ dl^{-1}), and an LDL cholesterol below $3 \cdot 0 \, mmol \cdot l^{-1}$ (115 mg $\cdot$ dl^{-1}). Concentrations of HDL-cholesterol and triglycerides are not used as goals of therapy.

However, an HDL-cholesterol $< 1 \cdot 0 \, mmol \cdot l^{-1}$ (40 mg $\cdot$ dl^{-1}) and fasting triglycerides $> 2 \cdot 0 \, mmol \cdot l^{-1}$ (180 mg $\cdot$ dl^{-1}) are markers of increased coronary risk. If the total and LDL-cholesterol goals are not achieved with lifestyle changes then drug therapy should be used. Preference should be given to HMG Co-A reductase inhibitors (statins) as this class of lipid lowering drugs has the strongest evidence in coronary heart disease patients for reducing coronary morbidity, mortality and prolonging survival. There is also evidence that statins will reduce the risk of stroke in coronary patients.

Blood glucose
Although it is not known whether good blood glucose control reduces the risk of recurrent disease in diabetic patients with coronary heart disease or other atherosclerotic disease, it does favourably influence microvascular disease and other diabetic complications. The goals for adequate glucose control in Type 1 (insulin-dependent) diabetes are: fasting blood glucose $5 \cdot 1 – 6 \cdot 5 \, mmol \cdot l^{-1}$ (91–120 mg $\cdot$ dl^{-1}); post-prandial (peak) glucose; $7 \cdot 6 – 9 \cdot 0 \, mmol \cdot l^{-1}$ (136–160 mg $\cdot$ dl^{-1}); HbA$_{1C}$ $6 \cdot 2 – 7 \cdot 5\%$; and avoidance of serious hypoglycaemias. In the majority of patients with Type 2 (non-insulin-dependent) diabetes even lower goals, extending to the non-diabetic range, can be safely achieved. For some patients, particularly the elderly, less stringent goals have to be accepted.

Other prophylactic drug therapies
In addition to drugs needed to supplement lifestyle management of blood pressure, lipids and glucose the following drug classes, which can each reduce morbidity and mortality in coronary heart disease patients, should also be considered.

- Aspirin (at least 75 mg), or other platelet modifying drugs, in virtually all patients.
- Beta-blockers in patients following acute myocardial infarction.
- ACE inhibitors in patients with symptoms or signs of heart failure at the time of myocardial infarction, or with persistent left ventricular systolic dysfunction (ejection fraction $< 40\%$).
- Anticoagulants following myocardial infarction for selected patients at increased risk of thromboembolic events, including those with large anterior myocardial infarction, left ventricular aneurysm or thrombus, paroxysmal tachyarrhythmias, chronic heart failure and those with a history of thromboembolic events.

Screen close relatives
Close relatives of patients with premature coronary heart disease (men < 55 years and women < 65 years) should be screened for coronary risk factors as they are at increased risk of developing coronary heart disease.
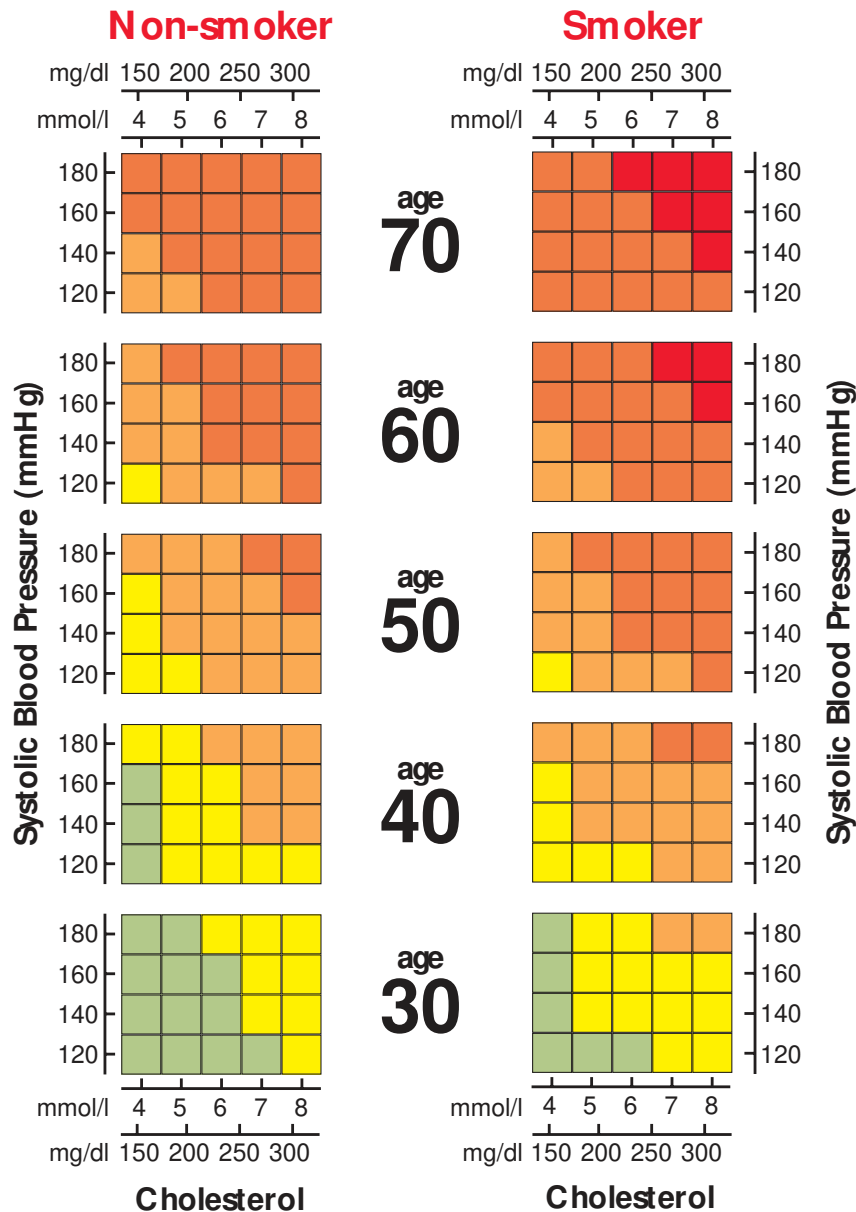
Figure 1   Coronary risk chart for primary CHD prevention.

Risk Chart
Coronary Heart Disease

WOMEN
Risk of Coronary Heart Disease

Non-smoker — **Smoker**

Charts by age (70, 60, 50, 40, 30), showing Systolic Blood Pressure (mmHg) on vertical axis (120, 140, 160, 180) and Cholesterol on horizontal axis (mmol/l: 4 5 6 7 8; mg/dl: 150 200 250 300).

Cholesterol

- **CHD risk is higher than indicated** in the chart for those with:-
  - Familial hyperlipidaemia
  - Diabetes: risk is approximately doubled in men and more than doubled in women
  - Those with a family history of premature cardiovascular disease
  - Those with low HDL cholesterol. These tables assume HDL cholesterol to be 1.0 mmol/l (39 mg/dl) in men and 1.1 (43) in women
  - Those with raised triglyceride levels >2.0 mmol/l (>180 mg/dl)
  - As the person approaches the next age category.

- **To find a person's relative risk**, compare their risk category with that for other people of the same age. The absolute risk shown here may not apply to all populations, especially those with a low CHD incidence. Relative risk is likely to apply to most populations.

- **The effect of changing** cholesterol, smoking status or blood pressure can be read from the chart.

Primary prevention

Individuals at high risk of developing coronary heart disease or other major atherosclerotic disease

Estimation of coronary risk

The absolute risk of developing coronary heart disease (non-fatal coronary heart disease or coronary death) over the next 10 years can be estimated from the Coronary Risk Chart (Fig. 1, between pages 1437 and 1440) using gender, age, smoking status, systolic blood pressure and total cholesterol. For individuals whose absolute coronary heart disease risk is ≥20% over the next 10 years (or will exceed 20% if projected to age 60) intensive risk factor modification is recommended including, where appropriate, a selective use of proven drug therapies. Lifestyle intervention in this high risk group is particularly important.

Lifestyle

High risk individuals are especially encouraged to stop smoking, make healthier food choices and become physically active. Avoiding overweight, or reducing existing overweight, is important in primary prevention. With such lifestyle changes the need for lifelong drug therapy maybe obviated. Lifestyle recommendations given for coronary heart disease patients apply to these high risk individuals.

Blood pressure

Clinical trials of blood pressure lowering using different drugs have convincingly shown that the risks associated with rising blood pressure can be substantially reduced, particularly for stroke, but also coronary heart disease and heart failure. This risk reduction is likely to be due to the common factor of lowering blood pressure rather than any intrinsic property of the classes of antihypertensive agents used. As coronary heart disease accounts for the largest proportion of deaths due to cardiovascular disease the primary consideration in blood pressure treatment is reducing coronary heart disease risk.

A decision to treat blood pressure with drugs depends on the absolute coronary heart disease risk as well as systolic and diastolic pressure levels, and target organ damage (Fig. 2). For individuals with a sustained systolic blood pressure ≥180 mmHg and/or a diastolic ≥100 mmHg, despite lifestyle interventions, the risk of coronary heart disease, stroke and heart failure is so high that drug treatment is essential. Individuals with a systolic blood pressure (SBP) 160–179 mmHg and/or a diastolic blood pressure (DBP) between 95 and 99 mmHg often require drug treatment if these high blood pressure values are sustained. Those with more mild sustained blood pressure increases (SBP 140–159 and/or DBP 90–94 mmHg) may also require drug treatment but this will depend on the presence of other risk factors (an absolute coronary heart disease risk ≥20%

over 10 years, or ≥20% if projected to age 60) and whether or not there is target organ damage. In contrast, at the same pressure levels drugs will not usually be needed in someone who is at lower absolute coronary heart disease risk.

When starting blood pressure lowering therapy a treatment goal is set and the dose titrated up until it is achieved. Treatment is preferably started with one drug, and if necessary, a second or even third line anti-hypertensive agent is added to achieve the goal. A goal blood pressure clearly and consistently less than 140/90 mmHg is appropriate for primary prevention. For young individuals, patients with diabetes and for patients with renal parenchymal disease the blood pressure goal can be even lower.

Reduction in cardiovascular morbidity and mortality by antihypertensive treatment with diuretic-based (particularly thiazides) and beta-blocker-based regimens is well established. Similar evidence has recently been obtained for some calcium channel blocker-based regimens. In some of these trials, however, ACE-inhibitors and other drugs have also been used in the treatment regimens. Therefore several classes of drugs can be considered for antihypertensive treatment with the goal of adequate blood pressure reduction.

Blood lipids

Clinical trials of lipid modification by diet and different drugs have convincingly shown that coronary heart disease risk associated with rising cholesterol can be substantially reduced. This risk reduction is likely to be due to the common factor of modifying lipoproteins, principally lowering LDL cholesterol, rather than any intrinsic property of the lipid lowering agents used.

A decision to treat blood lipids with drugs depends on the absolute coronary heart disease risk as well as lipid levels, lipoprotein profile and family history of premature coronary heart disease or other atherosclerotic disease (Fig. 3). Patients with familial hypercholesterolaemia are at such high coronary heart disease risk of premature coronary artery disease that drug treatment is always necessary. Individuals who are at high coronary heart disease risk because of a combination of risk factors (absolute coronary heart disease risk ≥20% over 10 years, or ≥20% if projected to age 60), and whose cholesterol levels are not lowered by diet, require drug treatment of blood lipids. For such high risk individuals the goals are a total cholesterol consistently below $5 \cdot 0$ mmol . l^{-1} (190 mg . dl^{-1}) and an LDL cholesterol below $3 \cdot 0$ mmol . l^{-1} (115 mg . dl^{-1}). This view is supported by primary prevention trials of cholesterol lowering therapies which have shown benefit, by reducing coronary morbidity and mortality, when treating individuals with absolute coronary heart disease risks even lower than 20%. Concentrations of HDL-cholesterol $< 1 \cdot 0$ mmol . l^{-1} (40 mg . dl^{-1}) and fasting triglycerides $> 2 \cdot 0$ mmol . l^{-1} (180 mg . dl^{-1}) are markers of increased coronary heart disease risk.

When starting lipid lowering therapy the drug dose should be titrated up until the cholesterol goal

Primary Prevention

Guide to
Blood Pressure Management

Estimate absolute CHD risk * using the
Coronary Risk Chart

Use initial office blood pressure # to estimate coronary risk

Absolute CHD risk <20% and no target organ damage DBP 90-99 mmHg and/or SBP 140-179 mmHg	Absolute CHD risk ≥20% and/or target organ damage DBP ≥90 mmHg and/or SBP ≥140 mmHg	DBP ≥100 mmHg and/or SBP ≥180mmHg
Lifestyle advice for at least six months with repeat BP measurements	**Lifestyle advice for at least three months with repeat BP measurements**	**Lifestyle advice and drug therapy #**

BP <140/90 mmHg	DBP 90-94 and/or SBP 140-159 mmHg	DBP ≥95 and/or SBP ≥160 mmHg	DBP <90 mmHg and SBP <140 mmHg	DBP ≥90 mmHg and/or SBP ≥140 mmHg
Maintain lifestyle advice and follow-up at a minimum of 5 year intervals	**Reinforce lifestyle advice with annual follow-up**	**Drug # therapy and maintain lifestyle advice**	**Maintain lifestyle advice with annual follow-up**	**Drug # therapy and maintain lifestyle advice**

* High CHD risk ≥20% over 10 years or will exceed 20% if projected to age 60 years

 # Consider causes of secondary hypertension. If appropriate refer to a specialist

Figure 2   **Primary prevention guide to blood pressure management.**

Primary Prevention
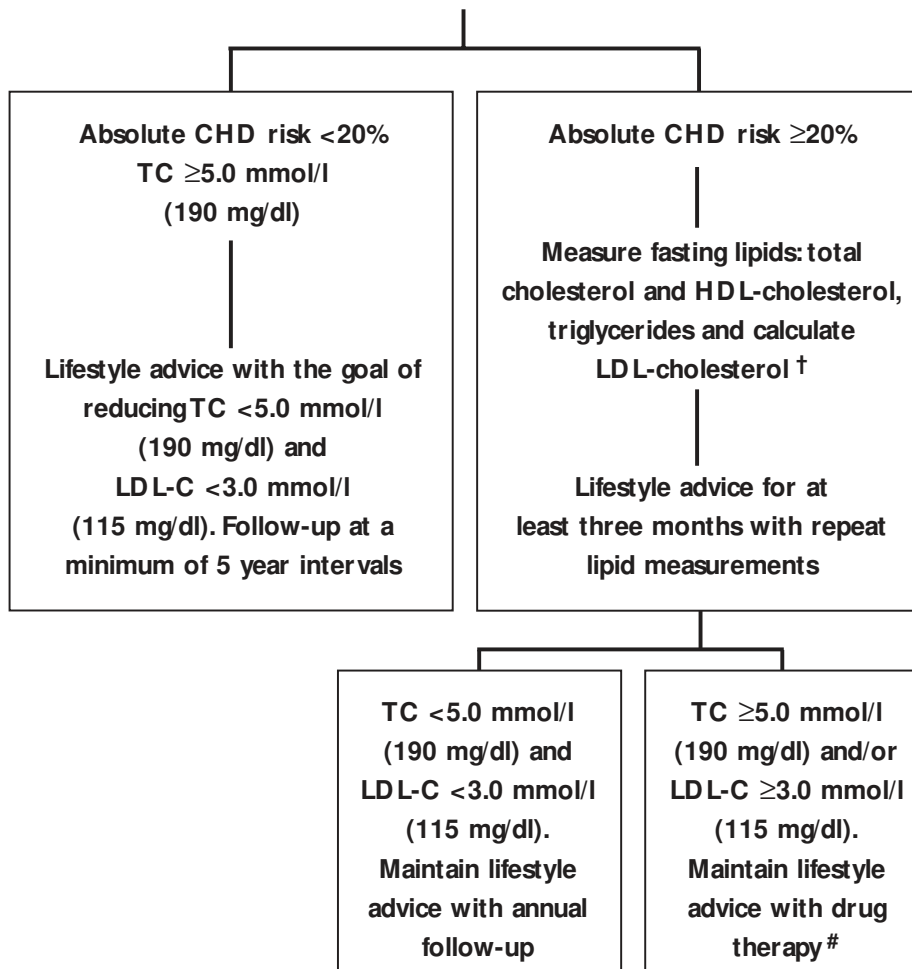
Guide to Lipid Management

**Estimate absolute CHD risk * using the
Coronary Risk Chart**

**Use initial total
cholesterol # to estimate coronary risk**

**Absolute CHD risk <20%
TC ≥5.0 mmol/l
(190 mg/dl)**

**Lifestyle advice with the goal of
reducing TC <5.0 mmol/l
(190 mg/dl) and
LDL-C <3.0 mmol/l
(115 mg/dl). Follow-up at a
minimum of 5 year intervals**

Absolute CHD risk ≥20%

**Measure fasting lipids: total
cholesterol and HDL-cholesterol,
triglycerides and calculate
LDL-cholesterol †**

**Lifestyle advice for at
least three months with repeat
lipid measurements**

**TC <5.0 mmol/l
(190 mg/dl) and
LDL-C <3.0 mmol/l
(115 mg/dl).
Maintain lifestyle
advice with annual
follow-up**

**TC ≥5.0 mmol/l
(190 mg/dl) and/or
LDL-C ≥3.0 mmol/l
(115 mg/dl).
Maintain lifestyle
advice with drug
therapy #**

* High CHD risk ≥20% over 10 years or will exceed 20% if projected to age 60 years

**† HDL cholesterol <1.0mmol/l (40 mg/dl) and fasting triglycerides >2.0 mmol/l
(180 mg/dl) are markers of increased coronary risk.**

**# Consider genetically determined hyperlipidaemias (total cholesterol usually
>8.0 mmol/l (above 300 mg/dl) with stigmata of hyperlipidaemia and a family history of
premature CHD) and causes of secondary hyperlipidaemia such as obesity, diabetes,
alcohol, hypothyroidism, liver and renal diseases. If appropriate refer to a specialist**

Figure 3 **Primary prevention guide to lipid management.**

is achieved. It may not be possible for all high risk individuals to achieve this goal on diet, or with a lipid lowering drug at the maximum dose, and therefore some will need combination drug therapy. Those with very high cholesterol or LDL cholesterol levels may still not achieve this goal, even on maximum therapy, but will still benefit to the extent to which cholesterol has been lowered.

There are four classes of drugs in current use (statins, fibrates, resins and niacin), and one or more drugs of each class has been shown to reduce coronary heart disease morbidity and mortality, but the evidence for efficacy and safety in primary prevention is strongest for the statins.

Blood glucose

At present there is no trial evidence on blood glucose control and the risk of coronary heart disease or other atherosclerotic disease in diabetic patients. In both Type 1 and 2 diabetes the degree of hyperglycaemia is associated with increased risk of atherosclerotic diseases. Good glucose control (as defined for patients with coronary heart disease) has beneficial effects on diabetic microvascular disease, and other diabetic complications, and thus this should be achieved, wherever possible, in all diabetics. At every level of a given risk factor — smoking, blood pressure and plasma lipids — and with every combination of such risk factors, the total coronary heart disease risk of a diabetic patient is much higher than the risk of a comparable non-diabetic. Therefore, it is particularly important to achieve the risk factor goals in diabetic patients.

Prophylactic drug therapies

Aspirin or other platelet modifying drugs are not usually indicated in the management of high risk individuals. There is evidence that low dose aspirin (75 mg) can reduce the risk of coronary heart disease in treated hypertensive patients whose blood pressure is well controlled, and in men at particularly high coronary heart disease risk. Prescribing aspirin to all high risk individuals is not recommended.

Screen close relatives

Close relatives of patients who are suspected to have familial hypercholesterolaemia, or other inherited dyslipidaemia, should have their lipids measured.

BACKGROUND

Introduction

Cardiovascular diseases, of which coronary heart disease is the most common, are the major causes of death in adults in their middle years and older 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.

A recent European Society of Cardiology Task Force on Cardiovascular Mortality and Morbidity Statistics in Europe describes this burden of cardiovascular diseases[1]. Coronary heart disease remains the leading cause of mortality in men over 45 years, and in women over 65 years throughout Europe, but there are enormous differences in disease experience between countries and within countries over time. Coronary heart disease shows a clear East–West gradient with a fivefold difference between countries, with the highest mortality rates in Eastern Europe. For the period 1970–1992, major differences between countries in the annual change of coronary heart disease mortality rates were observed in men aged 45–74 years. In Eastern European countries, particularly Romania, Poland, Yugoslavia, and the former East Germany, large increases have occurred. In contrast coronary heart disease mortality rates have decreased in Northern and Western European countries, particularly Belgium, the Netherlands and Finland and in some of the southern European countries, such as France and Italy. Of concern in southern Europe is the recent rise in coronary heart disease mortality observed in Greece. A similar mortality pattern is seen for women throughout Europe, although coronary heart disease mortality increased significantly in only three European countries, namely Romania, Poland and former East Germany.

In spite of falling coronary heart disease mortality in western European countries there has been no decrease in the absolute number of people who die from this disease. The number of chronically ill coronary heart disease patients may even be increasing in these countries due to an ageing population. In addition, medical treatments for coronary artery disease, revascularization and preventive medicine are all contributing to an increasing prevalence of survivors, and therefore rising numbers of patients who are at risk of recurrent disease, for example myocardial reinfarction and its complications such as heart failure. For this reason, and because of the increasing trends in coronary heart disease mortality in Eastern European countries, the overall burden of coronary heart disease, and other vascular diseases, is likely to increase in the forthcoming decade.

There are also marked socio-economic gradients in coronary heart disease morbidity and mortality within European countries[2,3]. These differences are partly explained by socio-economic differences in conventional risk factors, such as smoking, blood pressure, blood cholesterol and glucose. Smoking, for example, is more prevalent in lower social classes among both men and women in industrialized countries[4–8]. Another explanation for these findings is the poorer health habits and health knowledge in lower socio-economic groups. For example, men and women with low socio-economic status eat more fatty foods, but fewer vegetables or fruits, compared to those in higher socio-economic groups[9,10]. Unhealthy eating and over-eating combined

with lack of physical exercise increases the prevalence of obesity in persons with low socio-economic status[11,12]. However, psychosocial factors appear to be the most potent in explaining these socio-economic gradients. Heavy work strain, lack of control over the work situation, lack of social support as well as lack of capacity to cope with stressful factors encountered in life predict coronary heart disease events, particularly in men but also in some studies of women[13–16]. These factors are more prevalent in low socio-economic groups and they explain more than half of the social gradients in coronary disease in both men and women[17–19].

In seeking to prevent coronary heart disease and other atherosclerotic diseases 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 coronary heart disease 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 coronary heart disease 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 coronary heart disease in clinical practice[20]. 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 coronary heart disease in clinical practice.

Priorities for coronary heart disease prevention were given starting with patients with established coronary heart disease or other atherosclerotic disease. Patients who develop symptoms of atherosclerotic disease and its complications come under the care of cardiologists and other physicians in hospital and the community. As these patients are at high risk of non-fatal complications, or of dying from their disease, they were therefore given the first priority for prevention. The next priority for prevention was given to individuals in the general population who are at high risk of developing coronary heart disease or other atherosclerotic disease. In this context the risk was defined as multifactorial — namely the absolute risk of developing disease based on an assessment of all risk factors — and a Coronary Risk Chart was developed for the physician to calculate risk at a glance. This chart illustrated 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 emphasized the importance of multifactorial risk assessment in relation to the intensity of lifestyle intervention and, importantly, whether or not to use drug therapies, rather than the level of one risk factor alone. This approach acknowledges three important facts: that coronary heart disease has a multifactorial aetiology, that risk factors can have a multiplicative e ect, 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 coronary heart disease or other vascular disease, and those of high risk individuals in the population. Such relatives are themselves at increased risk of cardiovascular disease compared to the general population, particularly the first-degree blood relatives of patients with premature coronary heart disease. In addition, members of a family and especially an adult partner, sharing the same household, can favourably influence the adoption of a healthy lifestyle.

After the publication of these joint European Societies recommendations in October 1994 a meeting of 37 of the national cardiac societies a liated to the European Society of Cardiology was convened at the Heart House in Sophia Antipolis, France, in January 1995 to agree a strategy for the adoption, dissemination and implementation of these recommendations in daily clinical practice throughout Europe. This resulted in their publication and distribution in many European countries[21–42]. The American Heart Association issued a joint statement in the same year on 'Preventing Heart Attack and Death in Patients with Coronary Heart Disease', which was endorsed by the American College of Cardiology[43]. This also emphasized the importance of comprehensive risk factor intervention in patients with established coronary heart disease in order to reduce the risk of myocardial infarction, the need for revascularization procedures, improve quality of life and extend overall survival. In 1996 the 27th Bethesda Conference reiterated this view, endorsing the principle of matching the intensity of risk factor management with the hazard for coronary disease events, and advocating that cardiovascular risk factor management should be an integral part of the optimal care of patients with established disease, or at high risk of developing coronary or other atherosclerotic disease[44]. 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 far short of these recommendations. A nine country European survey (EUROASPIRE)[45] of 3569 patients with coronary heart disease, based on a survey (ASPIRE)[46] of secondary prevention originally undertaken in the United Kingdom, showed that there is considerable potential to improve risk-factor management. Almost one in five coronary heart disease patients

Table 2   Lifestyle and characteristics associated with increased risk of future coronary heart disease events

Lifestyles	Biochemical or physiological characteristics (modifiable)	Personal characteristics (non-modifiable)
Diet high in saturated fat, cholesterol and calories	Elevated blood pressure	Age
Tobacco smoking	Elevated plasma total cholesterol (LDL-cholesterol)	Sex
Excess alcohol consumption	Low plasma HDL-cholesterol	Family history of CHD or
Physical inactivity	Elevated plasma triglycerides	other atherosclerotic vascular disease at early age (in men <55 years, in women <65 years)
	Hyperglycaemia/Diabetes	Personal history of CHD or other atherosclerotic vascular disease
	Obesity	
	Thrombogenic factors	

had started to smoke cigarettes again following discharge from hospital after revascularization (coronary artery bypass grafting or angioplasty), acute myocardial infarction or myocardial ischaemia. Twenty-five percent were obese (body mass index $\geq 30 \, kg . m^{-2}$), 53% had raised blood pressure (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg), 44% had raised total plasma cholesterol (total cholesterol ≥ 5.5 mmol . l^{-1} [213 mg . dl^{-1}]) and 18% were diabetic. So a high prevalence of modifiable coronary risk factors was found in patients who have most to gain from effective risk factor interventions which are known to reduce coronary morbidity and mortality.

Since the 1994 European recommendations new scientific evidence has emerged. In particular the evidence for lipoprotein modification, in both secondary and primary coronary heart disease prevention, has become much stronger with the results of five major trials. Three of them — 4S[47], CARE[48] and LIPID (presented at the American Heart Association meeting in November 1997)[49] have been in secondary prevention and two — WOSCOPS[50] and AFCAPS/TexCAPS[51] — in primary prevention. Taken together these trials have shown that statin therapy can reduce the risk of non-fatal myocardial infarction, the need for coronary bypass surgery and angioplasty, and the risk of coronary death and death from all causes. The 4S and CARE trial results were the catalyst for the American Heart Association/American College of Cardiology Consensus panel statement on secondary prevention, and subsequent advice from the American Heart Association on when to start cholesterol lowering therapy in patients with coronary heart disease[52]. The American Heart Association also issued a guide to comprehensive risk factor intervention in the primary prevention of cardiovascular diseases[53]. Risk factor management in patients after coronary revascularization had already been the subject of a separate statement in 1994[54].

The European Societies also took the view, in the light of these new trials of lipid lowering and other available scientific evidence, that the 1994 recommendations on coronary prevention should be revised. Therefore, a second Task Force based on the three original societies was convened, and expanded to include the professional interests of behavioural medicine, primary care and the European Heart Network. The aim of these new joint recommendations is to summarize from a clinical view point the most important issues on coronary heart disease prevention on which there is good agreement and thereby to give cardiologists and physicians — in hospital, the office and the community — and other health care professionals, the best possible advice to facilitate their work on coronary heart disease prevention. The priority for physicians is still to concentrate on patients with overt coronary heart disease or other atherosclerotic disease, and on other high risk individuals, because the potential for preventive action is greatest in these groups and there is a great deal to do to improve on existing clinical practice.

Concept of risk

There is a wealth of evidence that lifestyles associated with 'western' culture — a diet rich in saturated fats and calories, tobacco smoking and physical inactivity — have an important role as causes of the mass occurrence of coronary heart disease in populations and as contributing factors to the risk of coronary heart disease in individuals within populations[55]. These lifestyles lead in many individuals to adverse changes in biochemical and physiological characteristics that enhance the development of atherosclerosis and associated thrombotic complications (Table 2). Recent research raises the possibility of early life influences contributing to the development of an adverse cardiovascular risk factor profile and coronary heart disease in later life[56]. There is also an important genetic component in the susceptibility of individuals to atherosclerosis and coronary heart disease, although its nature is so far understood only to a limited extent. In part this genetic susceptibility appears to be mediated through genetic determinants of biochemical and physiological risk characteristics, such as plasma lipids and blood pressure. Adverse lifestyles appear to interact with such genetic influences. The use of genetic markers to determine risk still remains in its infancy[57].
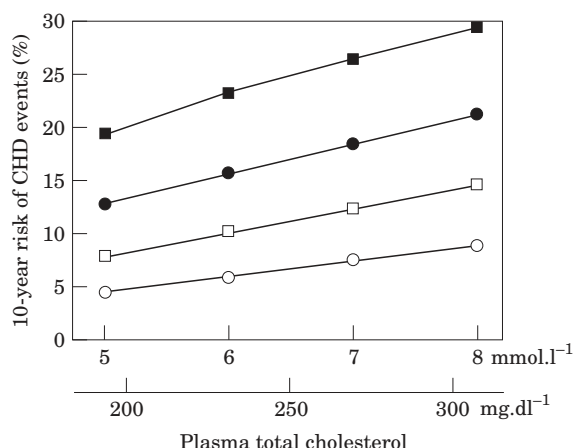
Figure 4 **The relationship of plasma total cholesterol level to 10-year risk of coronary heart disease (CHD) events in men and women aged 50, with and without risk factors based on a risk function derived from the Framingham Study. Men: ■ smoking, SBP 160 mmHg, □ no other risk factors; Women: ● smoking, SBP 160 mmHg, ○ no other risk factors.**

The term risk factor describes those characteristics found in healthy individuals to be independently related to the subsequent occurrence of coronary heart disease and, where modifiable, to be reversible. The term risk factor includes modifiable lifestyles and biochemical and physiological characteristics, as well as non-modifiable personal characteristics, such as age, sex and family history of early-onset coronary heart disease or other atherosclerotic disease (Table 2). When a person develops symptomatic coronary heart disease or other atherosclerotic disease, the modifiable risk factors continue to contribute to disease progression and prognosis.

The multifactorial aetiology of coronary heart disease and the contribution of all of these factors to the risk of developing a future coronary heart disease event is of great importance. For a proper assessment of coronary heart disease risk in an individual, the presence or absence and 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 the non-modifiable risk characteristics of each individual.

Figure 4 based on Framingham Study data[58] illustrates the multiplicative effect of risk factors. In an asymptomatic man with a moderate elevation of plasma cholesterol but without other risk factors the risk of coronary heart disease is relatively small, whereas in a man of the same age but with other risk factors the risk is much higher. Due to a protective effect of female sex, the risk of an asymptomatic woman is, in both instances, lower than that of a man with a corresponding risk factor pattern. Because age has a major influence on the absolute risk of coronary heart disease events, the short-term impact of any risk factor, or any combination of risk factors, increases with age. This does not, however, apply to people older than 80 or so years[59]. Patients

with clinically established coronary heart disease have at any level of a single risk factor, or at any combination of risk factors, a much higher overall level of risk of recurrent disease than asymptomatic persons. Because modifiable risk factors continue to be important to the subsequent risk of coronary heart disease events in patients with clinically established coronary heart disease, comprehensive action aimed at reducing risk factors is of great importance in the proper care of such patients.

Scientific basis for risk factor modification

Lifestyles and lifestyle-related modifiable risk factors listed in Table 2 are known to be associated with risk of coronary heart disease and other forms of athero-sclerotic disease, although the underlying mechanisms still remain incompletely understood. There is much evidence that favourable modification of lifestyles, and life-style related risk factors, reduces the risk of subsequent coronary heart disease events. Unifactorial randomized controlled trials of diet, blood pressure and cholesterol lowering have all shown significant reductions in cardiovascular morbidity and mortality. Yet, when multifactorial risk factor intervention has been attempted the results overall have been considerably less than expected from the single risk factor trials[60–66]. Within the World Health Organization Collaborative Group Study an analysis of the relationship between compliance with the intervention programme and coronary heart disease incidence confirmed that the multi-factorial prevention programme was effective to the extent that it was accepted[67]. The rationale for multi-factorial intervention is therefore not in doubt but such intervention needs to be at least as effective as the changes achieved in the single risk factor trials. The scientific evidence for risk factor interventions is now reviewed.

Diet

Diet is an important determinant of coronary heart disease risk. The effect of diet on the development of atherosclerosis and coronary heart disease is mediated through the influence of biological risk factors e.g. low density lipoproteins (LDL), high density lipoproteins (HDL), blood pressure and obesity.

Saturated fatty acids, especially those with 12–16 carbon atoms, increase LDL cholesterol[68]. Iso-caloric substitution of saturated fatty acids by unsaturated fatty acids lowers LDL cholesterol and does not affect HDL cholesterol. Substitution of saturated fatty acids by complex carbohydrates lowers both LDL and HDL cholesterol and does not improve the LDL/HDL cholesterol ratio. Trans fatty acids, which are formed by hydrogenation of polyunsaturated fatty acid rich oils,

Table 3   Population goals for nutrients and foods

Nutrient or food	Limits for population average intakes
Saturated (and trans) fatty acids (%E)	< 10
Polyunsaturated fatty acids (%E)	3–7
Dietary fibre (g . day^{-1})	27–40
Fruits and vegetables (g . day^{-1})	> 400
Legumes, nuts, seeds (g . day^{-1})	> 30
Cholesterol (mg . day^{-1})	< 300
Fish (g . day^{-1})	> 20
Salt (g . day^{-1})	< 6

Adapted from *Diet, nutrition, and the prevention of chronic diseases.* Report of a WHO Study Group 1990[69].

either naturally or in industrial processing e.g. margarine production, increase LDL cholesterol and lower HDL cholesterol. Finally, dietary cholesterol has a small LDL cholesterol elevating effect.

A healthy diet is therefore characterized as one which is low in saturated and trans fatty acids and low in dietary cholesterol. The total amount of saturated and trans fatty acids in the diet should be lower than 10% of energy and the dietary cholesterol intake < 300 mg . day^{-1} (Table 3)[69]. The intake of trans fatty acids in Western European countries is 0·5–2·0% of total energy intake (1·6–5·4 g . day^{-1}), being lowest in Mediterranean countries[70]. Currently, there is discussion about the optimal diet for lipoprotein levels[71]. Should it be a diet low in saturated fat and high in unsaturated fat or a low saturated fat diet rich in complex carbohydrates? The first will provide the best lipoprotein levels and an example is the traditional Mediterranean diet. An example of the second diet, low in saturated fat and high in complex carbohydrates, is the traditional Japanese diet. Both of these diets are associated with the best life expectancy in the world. For primary and secondary coronary heart disease prevention in Europe the best advice is to use a diet low in saturated fatty acids by replacing them in part with monounsaturated and polyunsaturated fatty acids, as well as with complex carbohydrates.

Polyunsaturated fatty acids can be divided into N-6 and N-3 polyunsaturated fatty acids. Linoleic acid, a fatty acid with 18 carbon atoms and two double bonds is the most well known representative of the N-6 polyunsaturated fatty acid family. This fatty acid is present in polyunsaturated fatty acid rich margarines. In most Western European countries the intake of linoleic acid is adequate. In countries characterized by a low linoleic acid intake in the past, for example Finland and Scotland, a low intake of this fatty acid (< 4% of energy) was associated with an increased risk of coronary heart disease[72,73]. At an average population intake of 6% of energy of linoleic acid there is no association with coronary risk.

α-Linolenic acid is the parent compound of the polyunsaturated fatty acids of the N-3 family and has 18 carbon atoms and three double bonds. This fatty acid is present in certain oils e.g. soybean oil and canola (rapeseed) oil, but also in wholemeal bread and fruits and vegetables. In a controlled trial, 600 post-myocardial infarction patients were randomized to either a Mediterranean α-linolenic acid enriched diet, or to a usual prudent post-infarction diet[74]. During the 5-year trial total mortality was reduced by as much as 70% and cardiac mortality by 76%. In another trial post-myocardial infarction patients were advised to eat oily fish three times a week[75]. This led to an intake of 300 mg . day^{-1} of eicosapentaenoic acid, another fatty acid of the N-3 family with 20 carbon atoms and five double bounds. The intake of this fatty acid in the control group was 100 mg . day^{-1}. This dietary intervention resulted in a 29% reduction in all-cause mortality and 33% reduction in cardiac mortality. These results suggest that a diet low in saturated fatty acids is not enough. It should also contain adequate amounts of α-linolenic and eicosapentaenoic acid. Probably an intake of 2 g . day^{-1} of α-linolenic acid and 200 mg . day^{-1} of very long chain N-3 polyunsaturated fatty acids from fish is adequate[76].

Evidence that a diet rich in fruits and vegetables may protect against coronary heart disease is accumulating[77]. Fruits and vegetables are rich sources of antioxidants. Currently there is a great interest in antioxidants because there is increasing evidence that oxidative modification of lipoproteins in the arterial wall plays a role in the formation of atherosclerotic lesions[78]. Observational population studies suggest that a high intake of antioxidant vitamins may be associated with a decreased coronary heart disease risk[79–81]. Also non-nutritive compounds for example flavonoids present in tea, red wine, apples and onions are strong antioxidants. In a cohort study it was shown that flavonoids were protective against coronary heart disease[82].

The effects of dietary supplementation of β-carotene on the incidence of lung cancer has been investigated in large randomized trials in high risk populations of smokers and asbestos workers and in physicians[83–85]. These studies showed that cardiovascular mortality was 9–26% higher among the β-carotene supplementation users compared with controls. In the ATBC trial there was also an increased risk of fatal coronary heart disease among cardiac patients who smoked and received either a supplementation of β-carotene, or the combination of α-tocopherol and β-carotene[86]. There was also a non-significant trend in increased death in the α-tocopherol group. In the CHAOS trial in which 2000 cardiac patients were supplemented daily with either 800 or 400 international units of vitamin E, a protective effect of supplementation was observed for the end-point non-fatal myocardial infarction[87]. No significant benefit was observed for either fatal myocardial infarction or all-cause mortality. These results show that the combination of smoking and supplementation with β-carotene and/or α-tocopherol is detrimental for health. But there is no convincing evidence, one way or the other, regarding

antioxidant supplementation in non-smoking coronary patients. The best advice for such patients is to consume a diet rich in vegetables and fruits.

The protective effect of a healthy diet, low in saturated fat and with a large amount of fruits and vegetables, in coronary patients was shown in a trial from India[88]. About 400 patients were randomized either to a healthy diet rich in plant foods or a control diet. Coronary patients who followed the healthy diet had a 42% reduction in cardiac mortality and a 45% reduction in all-cause mortality. The results form this trial are also supported by the results from observational studies. Men in Finland, Italy and the Netherlands who complied best to a healthy diet score based on the World Health Organization recommendation for prevention of chronic diseases[69] showed a 18% lower cardiovascular disease mortality and a 13% lower all cause mortality compared to men who had the worst diet score[89]. Similar results were obtained in a cohort study from Greece. All-cause mortality was lowest among the elderly following a traditional Mediterranean diet[90].

Evidence is accumulating that diet is also a determinant of blood pressure. A low salt diet can lower blood pressure and prevent the increase of blood pressure with age[91,92]. Furthermore, blood pressure may be influenced by other dietary components besides salt. In a randomized controlled trial vegetables and fruits lowered blood pressure, and further blood pressure lowering was obtained with the addition of low-fat dairy products[93]. Thus a diet rich in fruits and vegetables, and low-fat dairy products not only lowers LDL cholesterol but can also favourably influence blood pressure values.

Obesity is a rapidly growing threat to the health of populations in an increasing number of countries worldwide[94,95]. This is due to a fall of spontaneous and work-related physical activity and a readiness to over-consume high-fat or energy-dense foods. Under iso-energetic conditions, dietary fat does not promote the development of obesity more than other macro-nutrients[96]. However, at low levels of physical activity a high fat intake promotes the development of obesity[97].

Smoking

There is overwhelming evidence for an adverse effect of smoking on the risk of coronary heart disease and other atherosclerotic disease. Smoking is responsible for 50% of all avoidable deaths and one half of these are due to cardiovascular disease[98,99]. This adverse effect of smoking is related to the amount of tobacco smoked daily and the duration of smoking[100,101]. 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[102]. The risk of future cardiovascular disease is particularly high if smoking starts before the age of 15 years[103]. Passive smoking has now been shown to increase the risk of coronary heart disease and other smoking related diseases[104–106].

The impact of smoking on coronary heart disease risk is importantly modified by plasma lipid levels. Epidemiological studies have shown that in populations with low mean plasma cholesterol levels, such as the Japanese living on their home islands, coronary heart disease incidence remains very low despite a high prevalence of smoking[107]. However, when the Japanese adopt western dietary habits and their plasma LDL cholesterol levels increase, smoking also becomes an important coronary heart disease risk factor in this population[108]. 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[107]. 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 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[101], whereas in asymptomatic individuals up to 10 years are needed to reach the risk level of those who never smoked[103,109].

Alcohol

Alcohol consumption has a J-shaped or U-shaped relationship to the risk of all-cause mortality. Non-drinkers have a higher risk than light or moderate drinkers (10–30 g of ethanol daily, i.e. 1–3 standard measures of spirits, 1–3 glasses of wine, or 1–3 bottles of beer), and the risk then rapidly increases with increasing alcohol consumption. This increased risk is due to a large number of different causes of death related to heavy alcohol consumption, including accidents, suicides, cirrhosis of the liver, pancreatitis, several forms of cancer and alcoholic cardiomyopathy[110–112]. Reduced mortality of light or moderate drinkers is due to their lower mortality from coronary heart disease, independent of the type of drink[113–118]. Alcohol use increases plasma HDL cholesterol level and this may partly explain the protective effect of alcohol, but it has also been shown that alcohol has an anti-aggregatory effect on platelets[119] and a favourable effect on fibrinolytic factors[120]. The prevalence of hypertension and the risk of haemorrhagic stroke, however, increase with increasing alcohol consumption[121,122]. Furthermore, heavy drinking, particularly binge drinking, increases the risk of sudden arrhythmic death[123,124]. Because at a population level adverse social and health effects of alcohol tend to offset its possible beneficial effects on 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, 10–30 g of ethanol per day for men and 10–20 g of ethanol per day for women may be considered safe[122].

Obesity

Prospective epidemiological studies in western populations have shown that the relationship between body weight expressed in relation to height, usually in terms of body mass index (body mass index, weight (kg)/height (m)^2), and the risk of death from all causes is J-shaped. The thinnest people show some excess risk compared to those with 'normal' weight and those who are slightly overweight, but then as obesity increases all-causes mortality increases and this is largely due to an increase in cardiovascular mortality[125]. Prospective studies in both men and women have demonstrated that the risk of coronary heart disease already begins to increase at moderate levels of weight gain and overweight[126–131]. Overweight is also associated with an increased risk of stroke[130].

Obesity has an adverse influence on a number of other cardiovascular risk factors, including blood pressure, plasma LDL cholesterol, high density lipoprotein (HDL) cholesterol and triglycerides, and glucose tolerance, and this explains a large part of its effect on the risk of cardiovascular disease. Central adiposity, with an increased intra-abdominal fat mass, is associated with a particularly adverse profile of these risk factors, and is also associated with insulin resistance[132]. Prospective epidemiological studies have shown that central adiposity, assessed by waist to hip circumference ratio, is more strongly associated with the risk of coronary heart disease and other cardiovascular disease than general adiposity, assessed by body mass index[125,127,133,134].

Because of the adverse effects of obesity on other risk factors, and also due to its adverse haemodynamic effects, reducing weight is important in obese patients with coronary heart disease, and in obese healthy individuals with high levels of obesity-related risk factors.

Physical inactivity

Prospective epidemiological studies have shown that a sedentary lifestyle is associated with an adverse effect on the risk of death from all causes and cardiovascular disease and with an increased coronary heart disease risk[135–146]. Even a modest change in lifestyle, with the adoption of moderate physical activity in middle-age, or older age, can have a beneficial effect on mortality outcome, with regard to both cardiovascular and non-cardiovascular mortality, as well as on the risk of non-fatal coronary heart disease events[136,137,140]. This may be partly mediated through the relationship between the level of habitual physical activity and other determinants of coronary heart disease risk[147]. A high level of habitual physical activity helps to prevent people becoming overweight, as well as to reduce weight, and is also associated with lower levels of plasma LDL cholesterol and triglycerides and higher levels of plasma HDL cholesterol, as well as lower levels of blood pressure.

Maintaining regular physical activity and physical fitness, may also have a direct protective effect against cardiovascular disease independent of other risk factors. Regular exercise has been found to protect against the risks of strenuous exertion precipitating myocardial infarction[148,149].

Meta-analyses of randomized trials of cardiac rehabilitation in patients surviving an acute myocardial infarction, which include an exercise programme as part of a multi-factorial scheme, have shown that such rehabilitation may lead to a 20–25% reduction in overall and cardiovascular mortality[150,151]. Whilst this evidence is supportive of a beneficial effect of aerobic exercise, changes in physical activity in these programmes may have occurred concurrently with other changes in lifestyle, such as smoking cessation and the adoption of a healthy diet. Thus, the effects cannot necessarily be attributed to exercise alone.

Psychosocial factors

Psychosocial factors are viewed both as environmental stressors and as individual personality patterns or psychological reactions to stress. Exposure to stressors include both an acutely stressful life and chronic exposure to stressful work conditions. A particularly stressful work environment is characterized by both high demand and time pressure, and low control or decision latitude[15]. This pattern is often found in low status jobs, which may explain part of the socio-economic gradient in coronary heart disease. Individual behavioural responses to stressful environments include hostility and depression, but also unhealthy lifestyles like smoking, poor diet and lack of physical exercise.

To visualize interactive patterns of psychological risk factors, and relationships between psychosocial and standard risk factors, hypothetical models of causal mechanisms have been developed[152]. When applied to social gradients, these hypotheses suggest that early childhood socio-economic conditions may determine adult status. The adult social status influences both the socio-economic environment (unfavourable micro and macro economic aspects, insufficient health care utilization, poor social networks and working conditions) and the individual emotional reactions (lack of self-esteem and coping mechanisms, poor sense of coherence, hopelessness, depression, hostility and anger). These may in turn be reflected in unhealthy life style patterns (smoking, poor dietary habits, lack of physical activity and obesity) and thus unfavourably influence the pathogenesis of cardiovascular diseases[19].

The pathogenic effects of emotional factors, such as depression and hostility, on coronary heart disease morbidity[153–155] and mortality[156] have been reported to be partly independent of classical risk factors. In addition to being a primary risk factor, depression has been associated with a poorer prognosis following myocardial infarction[157].

Coronary heart disease risk factors do not provide a full explanation for the effects of psychosocial factors on coronary heart disease. For example, the relationship between hostility on coronary heart disease mortality in Finnish men was not mediated by blood pressure, LDL or HDL cholesterol[158]. Other possible biological pathways are suggested through the neuroendocrine and other stress mechanisms. For example, work stress[159] and social isolation[160] have been associated with a high risk haemostatic profile. Also imbalances of the autonomic nervous system, expressed as low heart rate variability or sustained elevated heart rate, have been associated with social isolation, depression[161,162] and anger[163].

It is important to emphasize that these psychosocial factors often coincide and therefore may have multiplicative effects. For example, studies have shown that the effects of psychosocial stress[158,164] on coronary heart disease morbidity and mortality are magnified when interacting with low socio-economic status.

These relationships between psychosocial factors and coronary heart disease have important implications for management, since treating the person or patient as a whole may mean influencing both the social environment, the work situation, and the individual's emotional reactions as well as lifestyle and health habits. A successful approach to these aspects of health may potentiate the effects and thus increase effectiveness of risk factor management. This may explain the relatively promising results of comprehensive behaviour modification programmes[165]. Because these trials have been multifactorial by design and included changes in lifestyles, such as diet, smoking and exercise, it is not possible to isolate the effects of specific behavioural modifications. This may not even be appropriate from a prevention viewpoint, as psychosocial and behavioural treatment programmes may potentiate the effects of standard lifestyle interventions[166,167].

Blood pressure

The importance of elevated blood pressure as a risk factor for coronary heart disease, heart failure, cerebrovascular disease and renal failure in both men and women has been demonstrated in a large number of epidemiological studies[168–171]. 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, dyslipidaemia etc.)[57] and taken together these make the overall cardiovascular risk disproportionately high[58,170].

Lifestyle interventions for mildly elevated blood pressure have been evaluated in randomized controlled trials[172–180]. These trials have used different interventions including dietary sodium reduction, correction of overweight, reduction of alcohol intake, diets based on oily fish, increased physical activity and cessation of smoking. Blood pressure can be reduced by these interventions, in the context of a clinical trial, and the reduction can be maintained[181]. Furthermore, such life-style modifications can also decrease the number and doses of antihypertensive drugs to control blood pressure and make it unnecessary to restart medication in some where antihypertensive drug treatment has been stopped. The size of the trials, however, has been too small, and their duration too short, to provide evidence on the effect of life-style changes on cardiovascular morbidity and mortality.

Several large scale randomized controlled trials have convincingly demonstrated that blood pressure lowering by drugs reduces cardiovascular morbidity and mortality. A meta-analysis of these trials comprising a total of more than 40 000 individuals[182,183] has shown that over an average period of 5 years a mean diastolic blood pressure difference of 5–6 mmHg between treatment and control groups reduced the risk of stroke by about 40%. This is only slightly less than the increase in fatal and non-fatal stroke seen in epidemiological studies for a prolonged increase in diastolic blood pressure of 5–6 mmHg. Another meta-analysis comprising a total of about 14 000 individuals[184] showed that blood pressure lowering reduces the development of heart failure by about 50%. However, this meta-analytic approach has also shown[182] that the reduction in risk of coronary heart disease (fatal or non-fatal events) with a 5-year reduction of diastolic blood pressure of 5–6 mmHg is about 15%, which is definitively less than the 20–25% increase in coronary heart disease predicted from epidemiology for a prolonged 5–6 mmHg difference in diastolic blood pressure. Thus antihypertensive treatment does result in a substantial reduction in the increased risk of stroke and heart failure associated with hypertension. However, it only incompletely reduces the risk of coronary heart disease. The reasons for this are not clear, although the following are likely to be involved[185] (1) incomplete attention to and achievement of systolic blood pressure control, because systolic blood pressure is equal to, or more important than, diastolic blood pressure as a cardiovascular risk factor[186] (2) adverse effects of diuretics[187] and beta-blockers (i.e. the drugs mostly used in antihypertensive drug trials) on plasma lipids, insulin resistance and the development of diabetes (3) failure to achieve blood pressure reductions to values below 140/90 mmHg (systolic/diastolic) despite the continuous risk relationship between coronary heart disease (and other cardiovascular diseases) and blood pressure levels well within the normotensive range[188] and (4) inability of trials of relatively short duration to fully quantify benefits of antihypertensive treatment that may take decades to become manifest[189]. This last possibility has received

support from recent Framingham study data in which a group of hypertensive patients treated for two decades was compared with an untreated group. In those treated the absolute risk of cardiovascular mortality was reduced by 60%, with a reduction in all-cause deaths of 30%[190].

Hypertension is also a major risk factor in the elderly[168,169,186]. A number of randomized controlled trials have shown that antihypertensive drug treatment is clearly beneficial[191–195] and this benefit extends to the very elderly up to 80 years of age[191,193]. These trials have also shown that in isolated systolic hypertension, i.e. a form of hypertension common in the elderly population[196], which markedly increases cardiovascular risk[197] blood pressure lowering by drugs results in a clear-cut reduction in the number of cardiovascular fatal and non-fatal events[198,199]. Cardiovascular complications reduced by drug treatment are stroke, heart failure and coronary heart disease, with a reduction in all-cause mortality, both in individual trials[191] and in a meta-analysis[195].

Whether antihypertensive treatment is beneficial in hypertensive individuals aged more than 80 years is still not clear.

Following myocardial infarction, blood pressure elevation is associated with an increased risk of reinfarction and death[200–202]. No randomized controlled trial evidence is available on the effect of antihypertensive treatment in these circumstances. However, several classes of antihypertensive agents (beta-blockers, ACE inhibitors and calcium channel blockers but not of the dihydropyridine class) which reduce diastolic blood pressure by a few mmHg have shown secondary cardio-protection when given to patients following a myo-cardial infarction[203–205]. This evidence supports current clinical practice to use antihypertensive treatment in hypertensive patients with established coronary heart disease. Treatment should be given according to guidelines used in primary prevention but blood pressure should be lowered slowly and carefully because myo-cardial necrosis, coronary atherosclerosis and cardiac hypertrophy (due to hypertension) may render coronary autoregulation less effective in preserving organ perfusion when blood pressure is reduced[206].

Plasma lipids

In blood plasma, lipids such as cholesterol and trigly-cerides are bound to various proteins to form lipo-proteins. The degree to which lipoproteins cause atherosclerosis depends in part on their size. The small-est lipoproteins, HDL (high density lipoproteins), enter the artery wall quite easily, but they also leave the artery wall easily, and they do not cause atherosclerosis. In contrast, LDL (low density lipoproteins), IDL (inter-mediate density lipoproteins) and small species of VLDL (very low density lipoproteins) are small enough to enter the artery wall, and if they are chemically modified by oxidation, they are easily retained in the wall to cause atherosclerosis. The largest lipoproteins, chylomicrons

and large VLDL, are too large to enter the artery wall, and they are therefore not atherogenic. Instead, high concentrations of these large triglyceride-rich lipoproteins can cause pancreatitis.

LDL cholesterol

There is a strong and graded positive association between plasma total cholesterol (or LDL cholesterol) and risk of coronary heart disease events extending over a wide range of cholesterol concentrations[207–209]. The association applies to individuals without coronary heart disease as well as to patients with established coronary heart disease[210–215], and it applies to women as well as men, but the general level of coronary heart disease risk is lower in women. The association is considerably modified by other risk factors. Low HDL cholesterol[216–219] and non-lipid risk factors such as smoking, hypertension and diabetes aggravate the effect of LDL cholesterol substantially[220], especially when total and LDL cholesterol are only moderately elevated; 5 to 6·5 mmol.l^{-1} (190 to 250 mg.dl^{-1}) and 3 to 4·5 mmol.l^{-1} (115 to 175 mg.dl^{-1}) respectively. In patients with the fairly common heterozygous form of familial hypercholesterolaemia, LDL-cholesterol can be severely elevated, 7 to 10 mmol.l^{-1} (270 to 390 mg.dl^{-1}), and they are extremely elevated in the rare homozygous form, 12 to 20 mmol.l^{-1} (465 to 775 mg.dl^{-1}). At these concentrations LDL cholesterol causes early coronary heart disease even if there are no other risk factors.

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. Re-duction of LDL cholesterol must therefore be a prime concern in both primary and secondary prevention of coronary heart disease. This point of view has been strongly emphasized in previous European guidelines[20,221–223] and especially by the National Choles-terol Education Program in the United States[224], and it is central to the recommendations in the present document.

Triglycerides

Hypertriglyceridaemia is also associated with risk of coronary heart disease, but the association is not as strong as it is for LDL, and the relationship of trigly-cerides to atherosclerosis has been a source of confusion to clinicians. The confusion stems in part from an oversimplified extrapolation of epidemiological data into the clinical setting. In univariate analyses in most prospective studies, triglycerides up to 5 mmol.l^{-1} (about 450 mg.dl^{-1}) predict the risk of coronary heart disease[225], and this relationship is somewhat stronger in women and younger individuals. However, when stat-istical adjustment is made for the effects of other risk factors, HDL cholesterol in particular, the independent effect of plasma triglycerides becomes weaker or disappears[225–227].

This is largely due to differences in the metab-olism of HDL and VLDL. VLDL normally carry most of plasma triglyceride, and these lipoproteins are

metabolized very quickly. The half life of VLDL is less than one hour. HDL are metabolized much more slowly; the half-life is several days. VLDL and HDL are nevertheless metabolically closely linked, and HDL cholesterol concentrations are usually low when triglyceride (VLDL) concentrations are high. HDL cholesterol therefore becomes an inverse indicator of what has been going on in the metabolism of VLDL (triglycerides). HDL has appropriately been termed the 'memory box' of triglyceride metabolism. In the clinical setting, measurement of HDL cholesterol can be used as a long-term indicator of disturbances in triglyceride in the same way that glycosylated haemoglobin is used to indicate whether glucose concentrations have been normal during the preceding days and weeks.

Another reason for confusion about the role of triglycerides and coronary heart disease is that only part of plasma triglyceride is related to atherosclerosis. All lipoproteins contain triglyceride. The most triglyceride-rich lipoproteins are chylomicrons, synthesized by the mucosa of the small intestine, and very low density lipoproteins (VLDL), synthesized in the liver. LDL and high density lipoproteins (HDL) also contain small amounts of triglyceride. Very severe hypertriglyceridaemia can be due to chylomicrons and large forms of VLDL. They can cause pancreatitis, but they are not atherogenic, because they are too large to enter into the arterial wall[228]. In contrast, small forms of VLDL as well as intermediate density lipoproteins (IDL) and LDL are atherogenic. Hypertriglyceridaemia due to high concentrations in plasma of small VLDL and IDL therefore identifies an individual at risk of coronary artery disease. Familial combined hyperlipidaemia is a fairly common genetic dyslipidaemia, expressed in about half of members of affected families. The phenotype may vary, even within an individual over time, manifesting as any combination of raised cholesterol, raised triglycerides and low HDL cholesterol, and it exemplifies the importance of this combination of lipid abnormalities because the risk of coronary heart disease is markedly increased in these patients[229,230].

At a population level, recent meta-analyses[231] and epidemiological studies[226,227,232] have more clearly identified hypertriglyceridaemia as a risk factor for coronary heart disease. There is also now some trial evidence of the importance of reducing serum concentrations of VLDL, as observed in the BECAIT angiography trial[233]. LDL cholesterol was unaffected, and angio-graphic and clinical benefit seemed to be related to reductions in VLDL and fibrinogen and elevations of HDL.

HDL cholesterol
There is also a strong but inverse association between plasma HDL and the risk of coronary heart disease[216–219]. This has been shown for both men and women, in asymptomatic persons and patients with coronary heart disease: the lower the concentration of HDL, the greater the risk of coronary heart disease. How HDL are related to coronary heart disease is not entirely understood. As already described, concentrations of HDL tend to be low when triglyceride concentrations are high, and HDL cholesterol may to a large extent be a reciprocal measure of atherogenic lipoproteins such as VLDL. It is also possible, however, that HDL directly protects the arterial wall by transporting cholesterol from the artery wall to the liver, or by inhibiting oxidation of LDL. A third possibility is that low plasma concentrations of HDL identifies people with an atherogenic lifestyle, because HDL cholesterol is lowered by smoking, obesity and physical inactivity[234,235].

Gemfibrozil is a fibrate drug that increases HDL cholesterol. It also lowers LDL cholesterol moderately and triglycerides markedly. Gemfibrozil was used in the Helsinki Heart Study[236,237], which suggested that a beneficial effect on clinical coronary heart disease events could, at least in part, have been due to an increase in HDL cholesterol. The same observation pertains to the more recently published LOCAT angiography trial[238].

Epidemiological studies have observed that a combination of plasma triglycerides higher than $2 \, \text{mmol} \cdot \text{l}^{-1}$ [$180 \, \text{mg} \cdot \text{dl}^{-1}$] and HDL cholesterol lower than $1 \, \text{mmol} \cdot \text{l}^{-1}$ ($40 \, \text{mg} \cdot \text{dl}^{-1}$) predicts a high risk of coronary heart disease, especially if the ratio of cholesterol to HDL cholesterol is also greater than 5[239].

Other lipid factors
Apolipoprotein B. Apolipoprotein B is the major protein component of LDL, IDL, VLDL and chylomicrons. Since the latter are not present in plasma in the fasting state, almost all apolipoprotein B is in atherogenic lipoproteins. There is only one molecule of apolipoprotein B per lipoprotein particle. Apolipoprotein B is therefore a measure of the number of atherogenic lipoprotein particles in plasma, and it is a good indicator of risk of atherosclerosis[240].

Lipoprotein (a). Plasma concentrations of lipoprotein (a), abbreviated Lp (a), are largely resistant to modification, but high lipoprotein (a) identifies persons at increased risk of coronary heart disease[226,241]. Such persons are therefore in greater need of attention to modifiable risk factors, especially high concentrations of LDL cholesterol.

Lipoproteins and risk of coronary heart disease
In general, a 10% increase in LDL cholesterol is associated with an increase in the risk of coronary heart disease of about 20%[220]. It would therefore be expected that a reduction of LDL cholesterol of 10% would lead to a reduction in the risk of coronary heart disease of about 20%, and this has turned out to be the case in clinical trials of both primary and secondary prevention[213,214,242]. Meta-analyses indicate, moreover, that the greatest benefits from lowering serum cholesterol are achieved in individuals with the highest concentrations of serum cholesterol[243] and at highest overall risk[244].

Clinical evidence of the benefits of reducing serum cholesterol has been obtained from both angiographic trials and from trials with clinical end-points. In more than 20 trials, coronary angiograms were performed in about 6000 patients before and after reduction of serum cholesterol by diet, drugs or surgery. Results of the early angiographic trials[245] have been confirmed by later trials[233,238,246–253]. With the exception of the smallest of these trials[247], they have all demonstrated, by one kind of measurement or another, that reduction of cholesterol can significantly inhibit the further progression of coronary artery disease and in several cases regress lesions already present. The beneficial effect on angiographic variables was in all cases very small, and it was therefore remarkable that clinical events such as myocardial infarction were substantially and significantly reduced in several of these trials[233,245,249,250]. There are at least two possible explanations of this finding. The one most subscribed to is that cholesterol lowering, despite a very limited effect on lumen size, stabilizes the atherosclerotic plaque so that it becomes less liable to rupture and thereby cause occlusion and myocardial infarction. The other is that cholesterol lowering treatment affects endothelial function so that the vessel becomes less likely to contract in spasm. Whatever the mechanism, the results of the angiographic trials are very consistent with those of the major clinical trials.

When the first version of these recommendations was published, several clinical trials had already provided evidence that reduction of serum cholesterol would prevent coronary heart disease and the recurrence of coronary heart disease. Still, doubts remained about the overall effect of such an intervention. One concern was that one of the large early trials of cholesterol reduction with clofibrate had shown an increase in non-cardiovascular deaths in the treated group[254]. Another concern was that prospective epidemiological studies had shown the relationship between plasma total cholesterol and mortality from all causes is J-shaped. At high concentrations of plasma cholesterol, death rates are high due to an excess of cardiovascular deaths. At the lower end of the cholesterol distribution, however, there is also an excess of deaths, but they are non-cardiovascular and include deaths due to cancers, haemorrhagic stroke, trauma or violence, respiratory disease and gastrointestinal disease[208,220,255,256]. Whether these diseases cause cholesterol to fall or, conversely, low cholesterol somehow causes these diseases has been difficult to assess, but the epidemiological data is most consistent with the former possibility. Moreover, there are mechanisms by which, for example, cancers or depression may lower cholesterol. Nevertheless, it seemed that these important issues could only be resolved by results of large scale trials of very efficient cholesterol reduction, and it was considered important to test specifically whether reduction of serum cholesterol would reduce not only coronary heart disease events but also total mortality[257].

The Scandinavian Simvastatin Survival Study (4S)[47] addressed this question directly. The trial included 4444 men and women with coronary heart disease and average concentrations of serum cholesterol of 6·8 mmol . l^{-1} (263 mg . dl^{-1}). The primary end-point was total mortality. After 5·4 years, 11·5% of placebo patients had died vs 8·2% of patients treated with simvastatin. In relative terms, risk of dying was reduced by 30% due to a 42% reduction in coronary deaths.

The West of Scotland Coronary Prevention Study (WOSCOPS)[50] included 6595 men, 95% of whom were without coronary heart disease. Average cholesterol was 7·0 mmol . l^{-1} (272 mg . dl^{-1}). After 4·9 years of treatment with placebo or pravastatin, 7·9% of placebo men had developed a major coronary event vs 5·5% of the pravastain group. Relative risk of a major coronary event, the primary end-point of the study, was thereby reduced by 31%. Total deaths were reduced by 22%.

The Cholesterol and Recurrent Events Trial (CARE)[48] was, like the 4S, a secondary intervention trial of 4159 men and women with coronary heart disease and average plasma cholesterol concentrations of 5·4 mmol . l^{-1} (209 mg . dl^{-1}). After 5 years of treatment pravastatin reduced fatal and non-fatal coronary heart disease events by 24% ($P=0·002$). In absolute terms, the reduction was from 13·2% to 10·2%. Like the WOSCOPS, the CARE trial was not powered to test for an effect on total mortality, which was non-significantly reduced by 9%.

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) included 6605 healthy men and women with average total cholesterol (mean 5·71 mmol . l^{-1} [221 mg . dl^{-1}]) and below-average HDL cholesterol levels (mean for men 0·94 mmol . l^{-1} [36 mg . dl^{-1}] and for women 1·03 mmol . l^{-1} [40 mg . dl^{-1}])[51]. After 5·2 years of treatment with lovastatin, in addition to a low saturated fat, low cholesterol diet, the incidence of major acute coronary heart disease events (fatal or non-fatal myocardial infarction, unstable angina or sudden cardiac death) was reduced by 37% ($P<0·001$), in absolute terms from 10·9% to 6·8%. Total mortality was not changed, but the trial was not powered to test for an effect on total mortality.

In 4S, WOSCOPS and CARE, non-cardiovascular deaths were unaffected so that the reduction in total deaths was entirely due to a reduction in coronary deaths. Within the trial periods of about 5 years, treatment was largely without side-effects, and the incidence of cancer was the same in the placebo and the statin groups (96/89 in 4S, 106/116 in WOSCOPS, 161/172 in CARE and 259/252 in AFCAPS/TexCAPS). A detailed safety analysis has been published from the 4S[258]. These trials have therefore established that efficient reduction of serum cholesterol, at least for the duration of these trials, can reduce the risk of coronary heart disease safely.

The upper age limit for inclusion was 70 (4S), 64 (WOSCOPS) and 75 years (CARE and AFCAPS/TexCAPS), and treatment benefited older patients as much as younger patients. Coronary heart disease patients less than 75 to 80 years of age should therefore be treated if their life expectancy is not otherwise limited by debility or other disease.

There were no women in WOSCOPS. There were 19% women in 4S, and they had the same benefit of treatment as men. In CARE, 14% of patients were women, and they had a significantly better effect from treatment than men. Women with coronary heart disease should therefore be treated like men with coronary heart disease, but treatment of women without coronary heart disease has not been adequately studied. A detailed analysis of treatment effects in the elderly and in women has been published from the 4S[259].

In CARE, the occurrence of stroke was a pre-defined end-point. Pravastatin reduced stroke significantly by 31% in CARE ($P = 0.03$). Similar results were seen in 4S and WOSCOPS, and meta-analyses suggest that statin therapy does reduce stroke[260,261], but these results need to be confirmed in a large prospective trial. In all three trials, treatment reduced the need for coronary bypass surgery and percutaneous transluminal coronary angioplasty (37% in 4S and WOSCOPS and 27% in CARE). Myocardial infarctions and other cardiac morbidity decreased, as did the need for hospital admissions, coronary bypass surgery and coronary angioplasty. Economic analyses have therefore indicated significant advantages from this form of prevention, if it is reserved for individuals at high risk of developing coronary heart disease[262] or patients who already have coronary heart disease[263]. The cost of a year of life saved was 13 995 pounds sterling in the group at highest risk in WOSCOPS[262] and 5502 pounds sterling in the patients with coronary heart disease in 4S[263]. Costs of this magnitude are generally considered acceptable, but costs are very sensitive to the degree of baseline risk: the higher the risk, the lower the cost[264].

For patients at lower risk, costs per year of life saved will be much higher, and it will be important to identify patient groups most likely, and least likely, to benefit from treatment. Diabetic patients are a very high risk group, and a post hoc analysis from the 4S indicates that it is particularly important to reduce lipids in patients with non-insulin-dependent diabetes mellitus with coronary heart disease[265].

Two other large clinical trials of secondary prevention with bezafibrate[266] and pravastatin[49] are expected to be published in 1998. Preliminary reports from the pravastatin secondary prevention trial indicate that the results will be consistent with those of the published trials of statins in secondary coronary heart disease prevention[47,48]. A preliminary report from the bezafibrate trial indicates no significant overall benefit from bezafibrate treatment in secondary prevention (presented at the XXth Congress of the European Society of Cardiology). Earlier clinical trials of fibrate treatment[254,267] have also not yielded results as clear-cut as those involving the other classes of lipid lowering drugs, principally the statins.

Diabetes

Both major types of diabetes mellitus, Type 1 (insulin-dependent) diabetes and Type 2 (non-insulin-dependent) diabetes are associated with a markedly increased risk of coronary heart disease, cerebrovascular disease and peripheral vascular disease[268–274]. Diabetes is a particularly strong cardiovascular risk factor in women and markedly diminishes the relative protection of female sex against atherosclerotic disease. The excess cardiovascular risk associated with diabetes is only partly explained by the adverse effect of diabetes on cardiovascular risk factors, and a large part of this excess risk must be caused by the direct effects of hyperglycaemia, or the diabetic state itself, through mechanisms which are not yet completely understood.

In patients with Type 1 diabetes who are in good glucose control plasma lipids and blood pressure levels remain normal. Poor glucose control and the advent of diabetic nephropathy are associated with plasma lipid abnormalities and elevated blood pressure[268,274]. The excess risk of coronary heart disease and other atherosclerotic disease in patients with Type 1 diabetes becomes evident after the age of 30 years and is particularly high in patients with poor glucose control and/or diabetic nephropathy[269].

Type 2 diabetes is associated with more profound abnormalities in cardiovascular risk factors than Type 1 diabetes. Even the precursor stage of Type 2 diabetes, in which the person has impaired glucose tolerance diagnosed by an oral glucose tolerance test, is associated with a cardiovascular risk factor pattern characteristic of Type 2 diabetes; namely elevated plasma triglycerides and low plasma HDL cholesterol, increased prevalence of hypertension, central type of obesity and hyperinsulinaemia, reflecting insulin resistance of the peripheral tissues, particularly skeletal muscle[268,270–274]. This adverse pattern of cardiovascular risk factors, which may last for many years in the impaired glucose tolerance phase of the progression towards diabetes, explains why many patients at the time of diagnosis of Type 2 diabetes already have clinically manifest coronary heart disease or other atherosclerotic disease.

The American Diabetes Association has recently recommended a revision of the diagnostic criteria of diabetes and this is particularly relevant for the diagnosis of Type 2 diabetes[275]. A provisional report of a World Health Organization Consultation Group[276] supports this revision, although this is still under consultation. In the 1985 World Health Organization criteria[277] a fasting blood glucose criterion for diabetes was ≥ 6.7 mmol . l^{-1} (120 mg . dl^{-1}), corresponding to a plasma glucose ≥ 7.8 mmol . l^{-1} (140 mg . dl^{-1}), but in the new American Diabetes Association criteria the diagnostic threshold for fasting blood glucose has been lowered to ≥ 6.1 mmol . l^{-1} (110 mg . dl^{-1}), corresponding to a plasma glucose ≥ 7.0 mmol . l^{-1} (126 mg . dl^{-1}). The observation that diabetic retinopathy becomes more prevalent above this fasting blood glucose level was the primary reason for the American Diabetes Association's lower fasting blood glucose criterion. Observations from long-term prospective epidemiological studies of the association between fasting blood glucose and

cardiovascular and coronary heart disease mortality risk give further support to this downward revision of fasting blood glucose criterion for diabetes[278].

Prospective epidemiological studies on large cohorts of diabetic patients have shown that the degree of hyperglycaemia is associated with the risk of coronary heart disease and other atherosclerotic disease in both Type 1 and Type 2 diabetes[270,279–282]. The Diabetes Complications and Control Trial (DCCT) which showed that good glucose control is important for the prevention of diabetic microvascular complications in Type 1 diabetes, also demonstrated a 60% decline in macrovascular events, although this decline was not statistically significant because of a small number of such events[283]. So far no direct trial evidence is available on the effect of glucose control on the risk of coronary heart disease and other atheroscleorotic disease in Type 2 diabetes. The United Kingdom Prospective Diabetes Study[284], a large multicentre study comprising about 5000 patients with Type 2 diabetes, is investigating the effect of improved glucose control achieved by different treatment modalities (chlorpropamide, glibenclamide, insulin and metformin). This study has been going on for more than 10 years and will report its results in autumn 1998.

Hyperglycaemia after myocardial infarction and stroke has been shown to be associated with a poor prognosis[270,271]. In a Scandinavian trial more than 600 diabetic patients with myocardial infarction were randomized either to aggressive blood glucose lowering with insulin, or to their usual treatment, both during the hospital admission and one year after it[285]. One-year mortality was significantly reduced by 25% in the insulin-treated group and this benefit became apparent after the acute phase rather than during it.

Subgroup analyses on diabetic patients with myocardial infarction included in large randomized controlled trials suggest that the treatment benefit obtained from long-term treatment with prophylactic drugs, such as aspirin, beta-blockers and ACE inhibitors is similar in-diabetic and non-diabetic patients[270,286].

Approximately 20% of patients with clinically established coronary heart disease have diabetes[45] and this proportion will increase, if the new blood glucose criteria recommended by the American Diabetes Association are widely adopted in European clinical practice.

Epidemiological evidence indicates that conventional cardiovascular risk factors have the same impact in diabetic patients as in non-diabetic individuals, and because diabetic patients are at any given risk factor levels at a much higher absolute risk of serious cardiovascular events than non-diabetic individuals[287–289], the benefit expected from risk factor reduction in diabetic patients could be particularly great[290]. Although no trials on the effect of blood pressure lowering in diabetic patients are available, subgroup analyses on diabetic patients included in the Hypertension Detection and Follow-up Program (HDFP) and the Systolic Hypertension in the Elderly (SHEP) study have shown a 34–38% reduction in cardiovascular mortality and morbidity in diabetic patients. This suggests that the relative risk reduction achieved in diabetic patients is at least as good as in non-diabetic individuals[291,292]. The Hypertension Optimal Treatment (HOT) trial showed the importance of active blood pressure lowering in diabetic patients[293]. In the treatment group randomized to a diastolic blood pressure target ≤ 80 mmHg the risk of major cardiovascular event was halved in comparison with that of the target group ≤ 90 mmHg.

Trials to investigate the effect of cholesterol lowering on the risk of coronary heart disease and other atherosclerotic disease in diabetic patients are in progress, addressing both secondary and primary prevention. Subgroup analyses on diabetic patients have, however, recently been published from two large secondary prevention trials of cholesterol lowering using statins — the Scandinavian Simvastatin Survival Study (4S)[265] and the Cholesterol and Recurrent Events (CARE) trial[48]. In the 4S (baseline total cholesterol levels 5·5–8·0 mmol . l^{-1} [213–310 mg . dl^{-1}]) the risk of major coronary heart disease events was reduced by 55% in diabetic patients and by 32% in non-diabetic patients. In the CARE trial coronary heart disease patients with lower baseline total cholesterol levels ($<6·2$ mmol . l^{-1} [240 mg . dl^{-1}]) the relative reduction in major coronary heart disease events was similar in diabetic and non-diabetic patients (25% vs 23%).

Insulin resistance

Hyperinsulinaemia and insulin resistance have received increasing attention during the last decade as possible aetiological factors for atherosclerotic disease. Reaven pointed out in 1988[132] that hyperinsulinaemia clusters with several cardiovascular risk factors, including elevated plasma triglycerides, low HDL cholesterol, impaired glucose tolerance, elevated blood pressure and central type of obesity. Individuals showing components of this risk factor cluster are characterized by a decreased sensitivity of peripheral tissues, particularly skeletal muscles, to the action of insulin. This clustering of risk factors is termed the insulin resistance syndrome or metabolic syndrome[272]. Increased plasminogen activator inhibitor-1 (PAI-1) level is a further potentially important thrombogenic component of this syndrome[294,295]. It is not yet clear whether or not this syndrome is a homogenous entity, but it has become evident that individuals with components of this syndrome have an increased risk of developing Type 2 diabetes, and even without developing diabetes, they have an increased risk of coronary heart disease or other atherosclerotic disease[296].

Other factors

Homocysteine
Raised plasma homocysteine is associated with increased risk of coronary heart disease[297] although the risk estimates are greater in cross sectional[297] than in

prospective studies[298,299]. An elevated plasma total homocysteine substantially increases the risk associated with smoking, hypertension and hyperlipidaemia[300]. Folic acid reliably reduces plasma total homocysteine but whether this reduces coronary heart disease risk is unknown. This question is being addressed in several ongoing randomized controlled trials. For the present careful attention to conventional risk factors in individuals with a raised plasma total homocysteine is warranted.

Genetic factors also modulate total plasma homocysteine levels. Most frequent of these is the thermolabile variant of methylenetetrahydrofolate reductase[301]. A raised plasma total homocysteine associated with this mutation is folate sensitive and it may be that this mutation is a risk factor in folate-depleted individuals[302].

Thrombogenic factors

An elevated plasma fibrinogen level has, in several prospective studies, been shown to be an independent predictor of coronary heart disease risk[303–305]. Smoking, exercise and raised plasma triglyceride levels are associated with an elevation in plasma fibrinogen[306], as are genetic influences[307], particularly polymorphisms in the beta fibrinogen gene[308], which appear to be associated with increased coronary heart disease risk.

Several other factors participating in blood coagulation have been associated with increased coronary heart disease risk. Factor VII levels are predictive of myocardial infarction in some[309,310] but not all[311] studies. Plasminogen activator inhibitor-1 (PAI-1) has been noted to be associated with increased risk of recurrent myocardial infarction[312,313]. A polymorphism of the PAI-1 gene was associated with an increase in PAI-1 levels and increased risk of myocardial infarction in Swedish[314] but not in French people[315]. To date, measurement of these factors has not been widely used in risk assessment.

Increased platelet aggregation is associated with an increased risk of clinical coronary heart disease[316,317]. The methods used for the assessment of platelet aggregation are not very consistent and are unsuitable for use in risk stratification. Platelet activation may be a risk factor for acute myocardial infarction and is associated with acceleration of glycoprotein IIb/IIIa receptor expression[318]. Aspirin is of proven benefit in the secondary prevention of myocardial infarction, and the more recent use of glycoprotein IIb/IIIa receptor antagonists has been associated with improved results after coronary artery stent implantation. A polymorphism of the glycoprotein IIb/IIIa receptor gene has been associated with acute myocardial infarction in a case control study[319], and prospectively with coronary stent thrombosis[320]. Compelling evidence from randomized controlled trials now exists on the beneficial effect of antiplatelet drugs (chiefly aspirin) in the prevention of cardiovascular events (non-fatal myocardial infarction, non-fatal stroke or vascular death) in patients with clinically established coronary heart disease or other atherosclerotic disease[321]. Meta-analyses of these trials have shown that in such patients the use of aspirin in a dosage of 75 to 325 mg per day reduces cardiovascular events by about one quarter. With the exception of well-controlled treated hypertensive patients[293] and men at particularly high coronary heart disease risk[322] there is no unequivocal evidence on the balance of risk or benefits for the use of aspirin in the primary prevention of coronary heart disease.

Markers of inflammation

Experimental and clinical studies suggest that inflammatory processes may have a role in the pathogenesis of atherosclerosis and clinical manifestations of atherosclerotic disease. Slight elevations of plasma C-reactive protein, a marker of inflammation, using new sensitive assays, predict an increased risk of coronary heart disease events in patients with unstable and stable angina pectoris[323]. Prospective epidemiological studies of initially asymptomatic individuals have shown an association between elevated C-reactive protein levels and the risk of coronary heart disease events[324–328], stroke[325] and peripheral vascular disease[329], independently of traditional risk factors. It has been suggested that cytokines, interleukin-6 and tumour necrosis factor alpha, which regulate C-reactive protein, could be mediators in the association between other laboratory markers of inflammation, such as increased leukocyte count and reduced plasma albumin, and coronary heart disease risk[330]. The association between elevated plasma fibrinogen and coronary heart disease risk may also, in part, reflect an ongoing inflammatory process, because fibrinogen is an acute phase reactant[331]. An association between elevated plasma levels of intercellular adhesion molecule ICAM-1 and coronary heart disease risk has also been demonstrated, suggesting that cellular mediators of inflammation have a role in atherogenesis[332]. The possible role of markers of inflammation in the clinical assessment of cardiovascular risk remains, however, to be determined by future research.

There has been a surge of 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 coronary heart disease and other atherosclerotic disease. However, the results of clinical and epidemiological studies on this issue are still conflicting and difficult to interpret. The evidence for the association between *C. pneumoniae* and coronary heart disease is somewhat stronger than that found for *H. pylori* and cytomegalovirus[333]. *C. pneumoniae* particles have been found in coronary atherectomy specimens, and not in normal coronary arteries[334], but the sequence of infection and the development of atherosclerotic lesions still remains uncertain. Two small preliminary antibiotic treatment trials aimed at *C. pneumoniae* eradication[335,336], reported positive results and have led to the planning of further trials.

Steroid hormone contraceptives and hormone replacement therapy

Studies carried out after the widespread introduction of the use of steroid hormone contraceptives showed that their use is associated with a 2–3 fold increase in coronary heart disease risk, and that this increased risk became particularly evident among women older than 35 years who also smoked cigarettes[337,338]. The high oestrogen dosage used in the earlier formulations of steroid hormone contraceptives may have been responsible for this increased risk and lower doses do not appear to have this effect, although the final proof for that is still pending. Therefore it is still prudent to advise steroid hormone contraceptive users to quit smoking. The use of steroid hormone contraceptives in patients with hyperlipidaemia, hypertension or diabetes requires careful consideration and follow-up because steroid hormone contraceptives may interact with these risk factors. A recent World Health Organization Scientific Group report[339] confirms these observations. It notes that the incidence and mortality rates of all cardiovascular disease (stroke, acute myocardial infarction and venous thrombo-embolic disease) in women of reproductive age are very low. Any increase in incidence or mortality attributable to the use of combined oral contraception is very small if users do not smoke.

Premature menopause (before age 45) due to oophorectomy or occurring naturally is known to lead to an increase in coronary heart disease risk[340–342] and this may be reversed by hormone replacement therapy. More recently a controversy has developed about the possible role of hormone replacement therapy after a normal menopause in the reduction of the age-related increase in coronary heart disease risk. Observational epidemiological studies have demonstrated a smaller coronary heart disease risk in women receiving hormone replacement therapy with oestrogen than in women not receiving it[343–345]. Although attempts have been made to adjust for possible confounding factors in the data analyses of these studies, the possibility cannot be excluded that women receiving hormone replacement therapy were particularly health conscious. Oestrogen replacement therapy has been shown to have beneficial effects on the plasma lipid profile of postmenopausal women by increasing HDL cholesterol level and decreasing LDL cholesterol level[346–349].

Because unopposed administration of oestrogen to post-menopausal women is associated with some increase in the risk of endometrial cancer[350,351], addition of progestogen to hormone replacement therapy has been recommended. There is also some concern about the possible increase of breast cancer risk during long-term hormone replacement therapy[352–354]. To answer all these open questions about the benefits and risks of post-menopausal hormone replacement therapy, large-scale randomized controlled trials are currently in progress.

Genetics

Genetic information may be divided into three categories: information on family history, information on phenotypes, and information on genotypes. These three types of information may be useful to identify patients who are at high risk of developing coronary heart disease; whereas information on phenotypes and genotypes may be useful in guiding the therapeutic approach.

Family history. The importance of a family history of coronary heart disease 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[355]. In this study, the relative risk of death from coronary heart disease in men, according to the age at which their twin died from coronary heart disease, decreased from eight in monozygotes and four in dizygotes in the age range 36–55 years, to four in monozygotes and two 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 coronary heart disease attributable to genetics was maximal in the age range 55–75 years.

A detailed family history of coronary heart disease, or other atherosclerotic disease should be part of the assessment of all patients with coronary heart disease and in the identification of high risk individuals. The risk of coronary heart disease increases (i) when an individual is closely related to a family member who has developed coronary heart disease. A history of coronary heart disease in a first degree relative (parent, 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) if the percentage of family members with coronary heart disease increases; and (iii) the younger the age at which family members develop coronary heart disease. Risk factor screening should be considered in the first degree relatives of any patient developing coronary disease at an early age; before 55 years in men and 65 years in women. A family history of premature coronary heart disease should also be taken into account in assessing the risk of developing the disease in a healthy individual. Lifestyle advice and, where appropriate, therapeutic management of risk factors should be offered to members of families where coronary disease is particularly highly prevalent.

Phenotypes. Some measurable traits (phenotypes) can be strongly genetically determined. This is the case, for example, for plasma lipoprotein (a), a factor which is associated with the risk of coronary heart disease. Variability of the apolipoprotein (a) gene accounts for 90% of the variability of plasma lipoprotein (a) in normal populations. The heritability of plasma LDL cholesterol is lower (about 50%) and furthermore can not be explained by the polymorphism of a single gene.

Nevertheless very high levels of cholesterol, (usually >8·0 mmol . l^{-1}; above 300 mg . dl^{-1}) frequently characterize familial hypercholesterolaemia, a monogenic disorder, caused by mutations in the LDL receptor gene. The frequency of this disorder, about 1/500 in most populations, may be much larger in some populations which recently increased in size (French Canadians, Afrikaners), as a consequence of the so-called founder effect. Familial hypercholesterolaemia is associated with a very high risk of coronary heart disease and may account for up to 2% of coronary heart disease occurring before age 60 in most industrialized countries. Familial defective apolipoprotein-B, caused by apolipoprotein-B mutations, also has a frequency of about 1/500 and produces a similar but less severe clinical picture. A high blood cholesterol in an individual, and particularly if there is a family history of premature coronary heart disease, should lead to systematic screening of the close relatives. Molecular genetic testing can be useful in the assessment of such families. Currently it is possible to demonstrate a mutation in the gene for the LDL receptor, or the gene for apolipoprotein-B, but this is a specialist task. Such specialist services are available in several European countries but each country should have its own programme for genetic testing for familial hypercholesterolaemia because the spectrum of mutations varies between countries. The clinical observation of a very abnormal trait in an individual that is known to increase the risk of coronary heart disease, and which cannot be explained, should be systematically sought in first degree relatives. Such traits could, for example, be high plasma triglycerides or lipoprotein (a) levels, or a low plasma HDL cholesterol level.

The pathophysiology of coronary heart disease is characterized by a mixture of chronic processes — mainly dyslipidaemia, hypertension, endothelial dysfunction, diabetes, cardiac and vascular hypertrophy, atherosclerosis — and acute events, such as plaque rupture, thrombosis and vasoconstriction — which each have their own genetic and environmental determinants. Hundreds, if not thousands of molecules may contribute to this disease process, 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 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.

Genotypes. A gene may predispose to coronary heart disease 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. It is postulated that common polymorphisms, with frequent alleles that have relatively small effects and interact with each other and environmental factors, are likely to account for most of the genetic component of coronary heart disease. Conversely, rare monogenic disorders associated with a considerable increase in absolute risk, such as familial hypercholesterolaemia, are only observed in a small proportion of patients with coronary heart disease.

Several coronary heart disease genes have already been investigated, in relation to apolipoproteins (apolipoprotein B, apolipoprotein CIII, apolipoprotein (a), apolipoprotein E), lipoprotein lipase, cholesteryl ester transfer protein, fibrinogen, PAI-1, ACE, angiotensin II receptor, paraoxonase, methylenetetrahydrofolate reductase and glycoprotein IIIa. The implication of the polymorphisms of some of these genes in cardiovascular diseases still needs confirmation, and a large number of other candidate genes have not yet been adequately investigated.

The apolipoprotein E polymorphism is an example of a common polymorphism, and despite a relatively weak effect at the individual level, may explain 5–8% of the attributable risk of coronary heart disease in the population[356]. The ACE polymorphism has probably been the most extensively studied polymorphism so far in relation to preclinical phenotypes and cardiovascular end-points[357]. 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[358], the restenotic process after stent angioplasty[359,360], the evolution of cardiac function after myocardial infarction[361] or the survival of patients with congestive heart failure[362]. Interestingly, other candidate gene polymorphisms may also have the characteristic of being response modifiers to a number of stimuli. The fibrinogen gene polymorphism may affect the plasma fibrinogen response to cigarette smoking, physical training or acute phase reaction[363–365]; the cholesteryl ester transfer protein polymorphism modifies the relationship between alcohol consumption and plasma HDL cholesterol[366], the methylenetetrahydrofolate reductase polymorphism may affect the relationship between folate intake and plasma homocysteine[367,368], and the α-adducin polymorphism between that of salt intake and blood pressure[369]. These interactions are not yet fully established and characterized. However, they offer interesting prospects for coronary heart disease prevention through the identification of responders to deleterious factors or beneficial ones (drugs for example) by genotyping appropriate candidate genes.

The genetic variants predisposing to coronary heart disease may be frequent in the population but further research is required to investigate their simultaneous effect on the risk of developing coronary heart disease. In the future, gene–gene and gene–environment interactions will be characterized in large observational studies, and new genes contributing
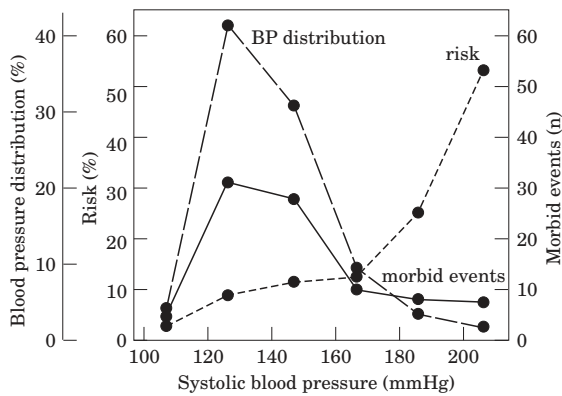
Figure 5 **Systolic blood pressure (BP) distribution, risk of coronary heart disease or stroke, and number of such morbid events in relation to blood pressure during 13·5-- year follow-up of 855 men aged 50 at entry. Reproduced with permission[370].**

to disease will be discovered by linkage analysis (mostly in a ected sib–pair studies) based on thousands of patients. What the future contribution of molecular genetics will be to the management of common cardiovascular diseases is di cult to predict. In the longer term understanding disease aetiology in these terms may be essential in identifying high-risk individuals and adapting therapeutic management to the individual's genetic make-up.

Strategies of coronary heart disease prevention; patients, high risk persons, population

The 1982 report of the World Health Organization Expert Committee on Prevention of Coronary Heart Disease[55] 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, 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.

Secondary prevention targeted at patients with established coronary heart disease and the high-risk strategy targeted at healthy individuals at high risk are an integral part of clinical practice. The clinical approaches and the population approaches for coronary heart disease prevention are complementary, but the population strategy is fundamental to reducing the burden of cardiovascular disease in Europe. As illustrated in Fig. 5, using systolic blood pressure as an example, most cases of coronary heart disease and

stroke occur among the large number of people in whom blood pressure is only modesty elevated, not among the small number with a very high blood pressure level[370]. Therefore, public health e orts to lower risk factors in the population by lifestyle changes are essential. In this public health context preventive work in clinical practice becomes much easier because people in society as a whole are changing lifestyles in a healthier direction.

Patients with symptomatic coronary heart disease present to cardiologists and other physicians and this o ers a unique opportunity for preventive action. In clinical practice healthy high-risk persons will also be identified because of their lifestyle, e.g. smoking cigarettes or obesity, or through the detection of hypertension, hyperlipidaemia, diabetes, or a combination of risk factors. A substantial number of such persons can be identified in daily clinical practice, without resort to comprehensive cardiovascular screening of the population, if physicians are alerted to the need to detect, assess and treat such high risk individuals. With regard to slowing the progression of coronary atherosclerosis and its clinical complications the distinction between primary prevention in healthy high-risk persons and secondary prevention in patients with established coronary heart disease is to some extent artificial. Many asymptomatic persons with multiple risk factors will have occult atherosclerotic lesions in their coronary arteries like patients with established coronary heart disease. Preventive action aimed at risk factor reduction through lifestyle changes, and where appropriate the use of drug therapies, will be similar.

Preventive action directed to patients with established coronary heart disease and high-risk persons can lead to contact with their families, other blood relatives and friends and therefore the message about coronary heart disease is spread through the society.

Priorities in coronary heart disease prevention in clinical practice

In European countries the number of patients with established coronary heart disease is large and the number of healthy individuals at high coronary heart disease risk is enormous. Understandably the medical community may feel that the tasks of coronary heart disease prevention are too overwhelming and impossible to accomplish in their everyday work. Therefore, it is useful to define priorities for coronary heart disease prevention in clinical practice, and these are set out in Table 4. This list of priorities proposes the order in which preventive action should be directed to the di erent 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 coronary heart disease, or other atherosclerotic

Table 4   Priorities of coronary heart disease prevention in clinical practice

1.   Patients with established coronary heart disease or other artherosclerotic disease
2.   Healthy individuals who are at high risk of developing coronary heart disease or other atherosclerotic disease, because of a combination of risk factors — including smoking, raised blood pressure, lipids (raised total cholesterol, and LDL-cholesterol, low HDL-cholesterol and raised triglycerides) raised blood glucose, family history of premature coronary disease — or who have severe hypercholesterolaemia, or other forms of dyslipidaemia, hypertension or diabetes
3.   Close relatives of
        patients with early-onset coronary heart disease or other atherosclerotic disease
        healthy individuals at particularly high risk
4.   Other individuals met in connection with ordinary clinical practice

disease, and the next place to healthy individuals at high risk of coronary heart disease. Patients who present with coronary heart disease 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 coronary heart disease 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 coronary heart disease and those of high risk individuals. In primary health care and in the private practice of cardiologists and internists preventive action may finally be extended to o ering risk assessment and appropriate advice to individuals not belonging to these priority groups.

Finally, physicians should not underestimate their power as opinion leaders to inform and influence public health decisions which can facilitate healthy lifestyles at a population level in their society.

ESTIMATION AND MANAGEMENT OF CORONARY HEART DISEASE RISK

General principles in the estimation of coronary heart disease risk

As coronary heart disease is multifactorial in origin it is important, in estimating coronary heart disease risk for an individual, to consider all the risk factors simultaneously. Traditionally, risk factor guidelines have focused on single factor assessment, particularly in the management of high blood pressure or hyperlipidaemia. This has resulted in undue emphasis being placed on elevations of single risk factors rather than on the overall level of risk based on a combination of risk factors. In practice, physicians deal with the whole patient rather than one aspect of his or her risk. Clusters of risk factors may have a multiplicative e ect and an individual with a number of modest risk factors may be at considerably greater risk than a person with one very high risk factor.

Patients with clinically manifest coronary heart disease have already declared themselves to be at high risk of further coronary heart disease events. In such patients, the 10-year risk of a coronary heart disease event (non-fatal or fatal coronary heart disease) is usually over 20%, and for many of them over 40%. Intensive risk factor modification is therefore advised for all such patients. For healthy individuals, calculation of total coronary heart disease risk was advocated in the 1994 European recommendations on coronary prevention and a simplified method of deriving an approximate 10-year coronary heart disease risk, based on a risk function derived from the Framingham study[58], was presented in the form of a Coronary Risk Chart[20]. A new colour version of this chart is shown in Fig. 1 (between pages 1437 and 1440) and Fig. 6 (in black and white) and a separate black and white chart for diabetic patients (Fig. 7) between pages 1461 and 1466. These Coronary Risk Charts are simple to use. An individual's absolute risk of developing a coronary heart disease event (angina, non-fatal myocardial infarction or coronary death) over the next 10 years is found by locating the appropriate box in the Coronary Risk Chart. Systolic blood pressure in mmHg is recorded vertically, and total cholesterol level in $mmol . l^{-1}$ or $mg . dl^{-1}$ is recorded horizontally. With knowledge of age, sex and smoking status, an estimate of the absolute 10-year risk of developing coronary heart disease may be read o immediately.

Total cholesterol is used rather than total cholesterol/HDL cholesterol ratio. The 1991 Framingham function incorporated both total cholesterol and the total cholesterol/HDL cholesterol ratio. Although this ratio improves coronary heart disease risk prediction, particularly in women, HDL cholesterol is not routinely measured across Europe, whereas a measurement of total cholesterol is easily available in every European country. Therefore, the decision to use total cholesterol only was primarily made to ensure the widest possible application of the chart across Europe. The chart assumes an HDL cholesterol level of $1{\cdot}0\,mmol . l^{-1}$ ($39\,mg . dl^{-1}$) for men, and $1{\cdot}1\,mmol . l^{-1}$ ($43\,mg . dl^{-1}$) for women. A further consideration was that a chart based on the ratio would have to assume an average European cholesterol value. Whilst this might be reasonable in a single homogeneous population, it was not felt to be appropriate for Europe

Table 5 Examples showing the impact of a single risk factor, multiple risk factors and clinically established coronary heart disease on the absolute risk of developing a coronary heart disease event over 10 years

Sex	Age (years)	Plasma cholesterol (mmol . l^{-1})	Systolic blood pressure (mmHg)	Smoking	Clinical CHD	Minimum estimate of the 10-year risk
Male	50	7	120	−	−	10%
Male	50	6	140	+	−	20%
Male	50	7	120	−	+	> 20%
Male	50	6	140	+	+	> 40%

in view of the large differences in average cholesterol levels between countries. Compared to the 1994 Coronary Risk Chart the range of total cholesterol has been increased by including 4·0 mmol . l^{-1} (about 150 mg . dl^{-1}). This is because a cholesterol goal of 5·0 mmol . l^{-1} (about 190 mg . dl^{-1}) for secondary and primary coronary heart disease prevention is now recommended and therefore the cholesterol range has been extended below this level in the new chart. As before, age and cholesterol levels have been rounded off to whole digits and systolic blood pressure to 10 mmHg. As an individual approaches the next highest category for these variables, risk will rise accordingly. Systolic blood pressure is still used, since this is an even better predictor of cardiovascular events than diastolic pressure.

It should be stressed that certain individuals will be at higher risk than is evident from the coronary risk chart. It has been emphasized already that those with clinically established coronary heart disease or other atherosclerotic disease have declared themselves to be at very high risk, over 20% and often over 40%, over the next 10 years, and this chart is not intended for them. Risk is also higher than indicated in patients with familial hyperlipidaemia, diabetes (see Fig. 7), those with a family history of premature cardiovascular disease, and those with low HDL cholesterol or raised triglycerides levels.

The Framingham risk function has certain limitations. As with other functions, it over-estimates risk in young people. Furthermore, the application of one Coronary Risk Chart, based on a high-risk middle-aged north American population, to European populations at different levels of coronary heart disease risk poses a problem. Whilst the Framingham function predicts absolute risk reasonably well in high risk populations it may overpredict absolute risk in low-risk European populations. Estimates of relative risk derived from the chart are, however, likely to be quite robust for all European populations.

With these caveats, the Coronary Risk Chart has several functions:

(1) An individual's absolute risk of developing a coronary heart disease event over the next 10 years can be read from the chart without any calculations.

(2) Although young people are generally at lower risk this will rise steadily as age increases. The chart can be used by following the tables upwards to illustrate the effect of lifetime risk by observing the increased risk with 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.

(3) Relative risk can readily be estimated by comparing the risk in one cell with any other in the same age group. As mentioned, absolute risk may vary considerably from one population to another but the magnitude of relative risk will usually remain fairly constant.

(4) The chart can be used to predict the effect of changing from one risk category to another. Thus, one can readily show an individual the reduction in risk associated with stopping smoking, reducing blood pressure or reducing blood cholesterol level.

In general, even low risk individuals should be offered lifestyle advice to maintain their low risk status. Advice should be intensified with increasing risk, and a level of ≥20% 10-year coronary heart disease risk should signal intensive risk modification efforts. In the Management of Risk chapter it is emphasized that more intensive advice for all risk factors is required for a young person if the coronary heart disease risk projected to age 60 will exceed 20%. A preliminary examination of prospective cohort studies from different parts of Europe shows wide regional variations in the proportion of individuals whose coronary heart disease risk exceeds 20%. In 60-year-old men the range is from virtually zero to over 40%. The proportions for women are between one tenth and one quarter that of men.

Table 5 illustrates the impact of single and multiple risk factors on absolute coronary heart disease risk with a few examples. An asymptomatic man aged 50 years with multiple moderate elevations of risk factors is shown to have an absolute coronary heart disease risk twice as high as an asymptomatic man with the same age with a marked elevation of a single risk factor.

The Coronary Risk Charts illustrate how the risk of developing coronary heart disease can be simply calculated. Ideally, such charts should be constructed
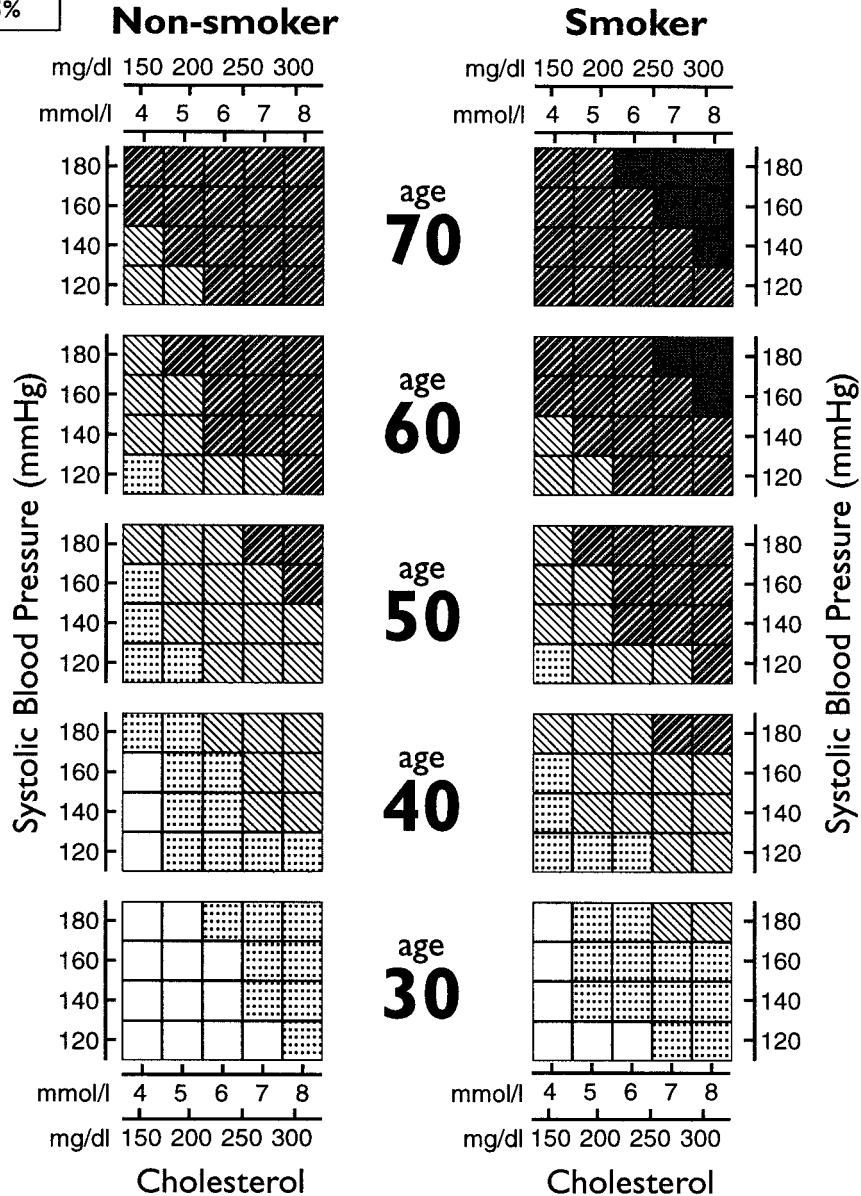
Coronary Risk Chart

Primary Prevention of Coronary Heart Disease

MEN

Risk of Coronary Heart Disease

Non-smoker

Smoker

Figure 6 Coronary risk chart for primary CHD prevention (black and white version).

How to use the Coronary Risk Chart for Primary Prevention

The chart is for estimating coronary heart disease (CHD) risk for individuals who have not developed symptomatic CHD or other atherosclerotic disease. Patients with CHD are already at high risk and require intensive lifestyle intervention and, as necessary, drug therapies to achieve risk factor goals.

- **To estimate a person's absolute 10 year risk of a CHD event**, find the table for their gender, smoking status and age. Within the table, find the cell nearest to their 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.

- **High risk individuals are defined as those whose 10 year CHD risk exceeds 20% or will exceed 20% if projected to age 60.**

Coronary Risk Chart

Primary Prevention of Coronary Heart Disease

WOMEN
Risk of Coronary Heart Disease

10 Year Risk Level

Very high	■	over 40%
High	▨	20% to 40%
Moderate	▧	10% to 20%
Mild	▦	5% to 10%
Low	□	under 5%

Non-smoker

mg/dl 150 200 250 300
mmol/l 4 5 6 7 8

Smoker

mg/dl 150 200 250 300
mmol/l 4 5 6 7 8

age 70

age 60

age 50

age 40

age 30

Systolic Blood Pressure (mmHg)

mmol/l 4 5 6 7 8
mg/dl 150 200 250 300
Cholesterol

mmol/l 4 5 6 7 8
mg/dl 150 200 250 300
Cholesterol

- **CHD risk is higher than indicated** in the chart for those with:-
  - Familial hyperlipidaemia
  - Diabetes: risk is approximately doubled in men and more than doubled in women
  - Those with a family history of premature cardiovascular disease
  - Those with low HDL cholesterol. These tables assume HDL cholesterol to be 1.0 mmol/l (39 mg/dl) in men and 1.1 (43) in women
  - Those with raised triglyceride levels >2.0 mmol/l (>180 mg/dl)
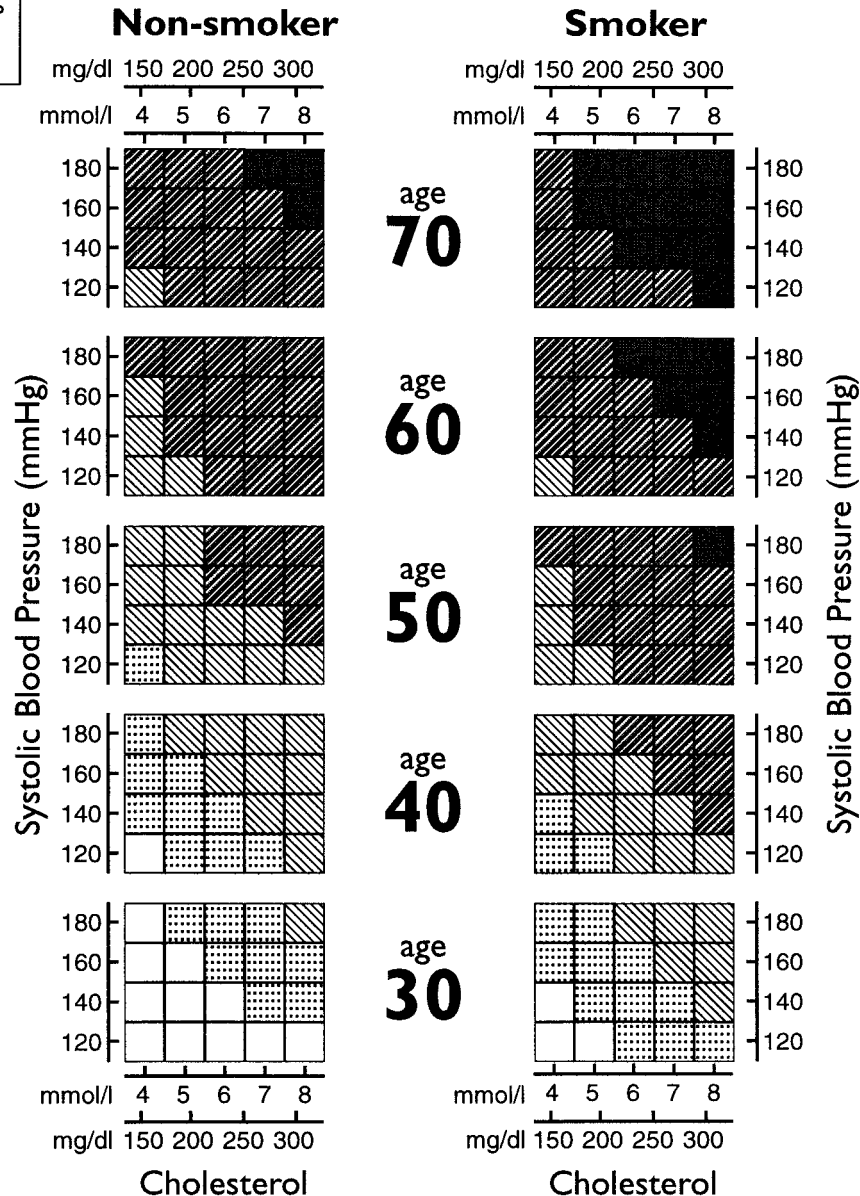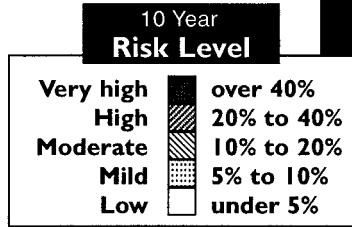 - As the person approaches the next age category.

- **To find a person's relative risk,** compare their risk category with that for other people of the same age. The absolute risk shown here may not apply to all populations, especially those with a low CHD incidence. Relative risk is likely to apply to most populations.

- **The effect of changing** cholesterol, smoking status or blood pressure can be read from the chart.

Coronary Risk Chart

Primary Prevention of Coronary Heart Disease

10 Year Risk Level		
Very high		over 40%
High		20% to 40%
Moderate		10% to 20%
Mild		5% to 10%
Low		under 5%

MEN WITH DIABETES
Risk of Coronary Heart Disease

Non-smoker

mg/dl 150 200 250 300
mmol/l 4 5 6 7 8

Smoker

mg/dl 150 200 250 300
mmol/l 4 5 6 7 8

age **70**

age **60**

age **50**

age **40**

age **30**

Systolic Blood Pressure (mmHg)

mmol/l 4 5 6 7 8
mg/dl 150 200 250 300

Cholesterol

How to use the Coronary Risk Chart for Primary Prevention

The chart is for estimating coronary heart disease (CHD) risk for individuals who have not developed symptomatic CHD or other atherosclerotic disease. Patients with CHD are already at high risk and require intensive lifestyle intervention and, as necessary, drug therapies to achieve risk factor goals.

- To estimate a person's absolute 10 year risk of a CHD event, find the table for their gender, smoking status and age. Within the table, find the cell nearest to their 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.

- High risk individuals are defined as those whose 10 year CHD risk exceeds 20% or will exceed 20% if projected to age 60.

Figure 7   Coronary risk chart for primary CHD prevention in diabetes mellitus.

Coronary Risk Chart

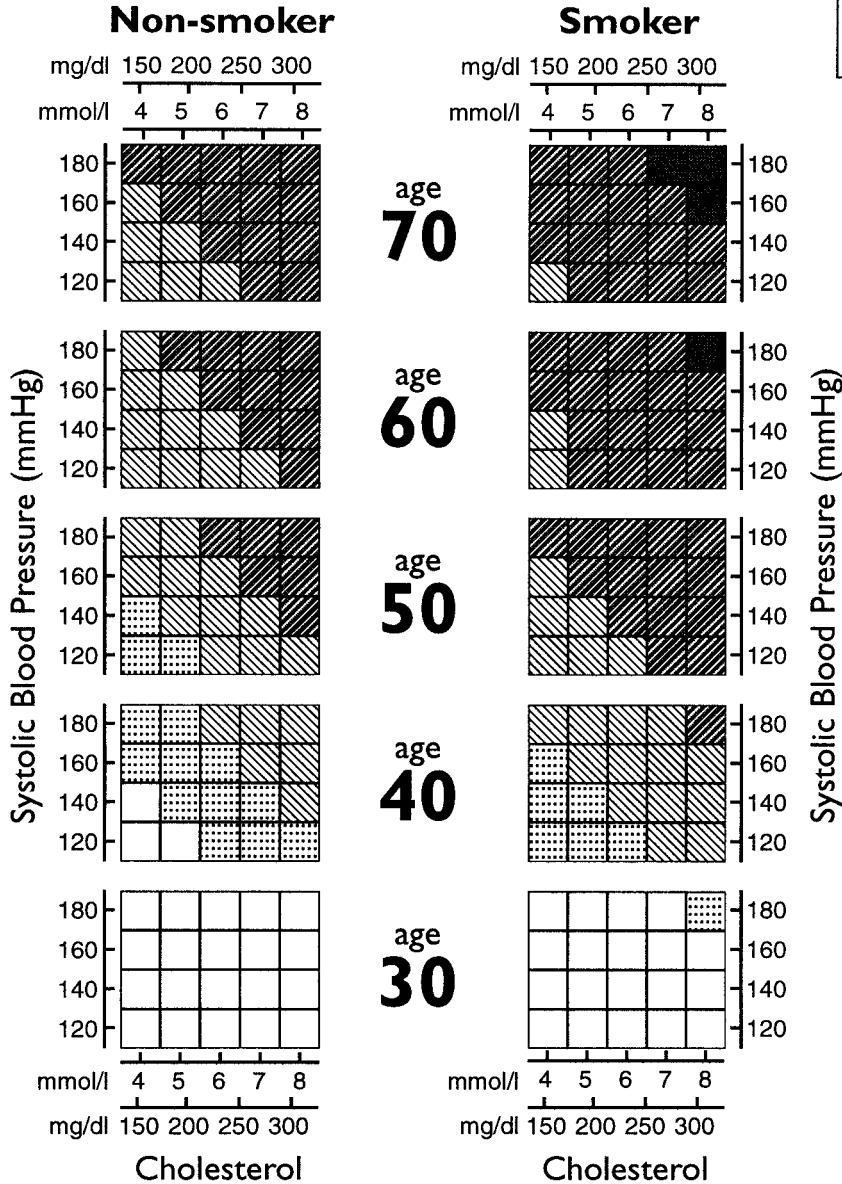## Primary Prevention of Coronary Heart Disease

WOMEN *WITH DIABETES*
Risk of Coronary Heart Disease

10 Year Risk Level

Very high	■	over 40%
High	▨	20% to 40%
Moderate	▧	10% to 20%
Mild	▤	5% to 10%
Low	☐	under 5%

Non-smoker

mg/dl 150 200 250 300
mmol/l 4 5 6 7 8

Smoker

mg/dl 150 200 250 300
mmol/l 4 5 6 7 8

Systolic Blood Pressure (mmHg)

age **70**
age **60**
age **50**
age **40**
age **30**

180 160 140 120

mmol/l 4 5 6 7 8
mg/dl 150 200 250 300
Cholesterol

mmol/l 4 5 6 7 8
mg/dl 150 200 250 300
Cholesterol

- **CHD risk is higher than indicated** in the chart for those with:-
  - Familial hyperlipidaemia
  - Those with a family history of premature cardiovascular disease
  - Those with low HDL cholesterol. These tables assume HDL cholesterol to be 1.0 mmol/l (39 mg/dl) in men and 1.1 (43) in women
  - Those with raised triglyceride levels >2.0 mmol/l (>180 mg/dl)
  - As the person approaches the next age category.

- **To find a person's relative risk**, compare their risk category with that for other people of the same age. The absolute risk shown here may not apply to all populations, especially those with a low CHD incidence. Relative risk is likely to apply to most populations.

- **The effect of changing** cholesterol, smoking status or blood pressure can be read from the chart.

from the results of prospective cohort studies undertaken in the population to which the risk chart is to be applied. A coronary risk chart developed by each country is therefore recommended.

Objectives of coronary heart disease prevention

The overall objective of coronary heart disease prevention both in patients with clinically established coronary heart disease or other atherosclerotic disease and high risk individuals is the same: to reduce the risk of subsequent major coronary heart disease events or other vascular events and thereby reduce mortality and prolong survival. There are some differences in the identification and management of patients with coronary heart disease or other atherosclerotic disease compared to healthy high-risk individuals, although as described earlier, there can be considerable overlap in risk between these two groups. These differences in the objectives for secondary and primary coronary heart disease prevention will be pointed out below.

Risk factor goals for maintenance of health and prevention of coronary heart disease are based on a knowledge of the attributes of individuals who, in observational studies, remain free from coronary heart disease. Additional information comes from international comparisons of coronary heart disease rates in relation to risk factors, change in coronary heart disease mortality over time, and from intervention studies involving both community projects and randomized controlled trials, and is also derived from clinical observation, autopsy data, animal feeding experiments, metabolic and genetic studies. This wealth of scientific knowledge has led to ideal goals for prevention of coronary heart disease and other atherosclerotic disease including a diet compatible with ideal weight and a plasma cholesterol level of less than $5 \, \text{mmol} \cdot \text{l}^{-1}$ ($190 \, \text{mg} \cdot \text{dl}^{-1}$), regular leisure exercise, the avoidance of all forms of tobacco, and a blood pressure less than 140/90 mmHg for most people.

In general risk factor goals should be framed in terms of working towards such ideals. Modest reductions in multiple risk factors are likely to reduce coronary heart disease risk more than aggressive reduction of a single risk factor while ignoring others; this can be appreciated from the Coronary Risk Charts. Thus, even modest success in terms of risk factor reduction may be associated with a useful and substantial reduction in risk and should stimulate a positive and encouraging attitude from physicians. From these considerations, it will be apparent that the objective should be to reduce absolute coronary heart disease risk as far as possible, based on multiple risk factor intervention. In any given age group lifestyle changes should be encouraged which will reduce absolute coronary heart disease risk (see Coronary Risk Charts) towards the lowest level possible for a person in that age group. In younger people, this would be less

than a 5% ten year risk of a coronary heart disease event, while in older people it will be nearer to 10%.

Secondary prevention

The overall objective in patients who present with symptoms of coronary heart disease — stable angina, an acute ischaemic episode without evidence of infarction, or acute myocardial infarction — is to reduce the progression of atherosclerotic coronary disease, and the risk of superimposed thrombotic phenomena, and thereby to reduce the risk of a further non-fatal major ischaemic event or coronary heart disease death. The same applies for patients with other forms of atherosclerotic disease. To define the specific objectives of preventive action for each patient, antecedents of the disease must first be addressed in relation to the patient's lifestyle — smoking, dietary and physical activity habits — and their personal risk factor profile in terms of obesity, blood pressure, plasma lipids, and so on. Secondly, in patients with coronary heart disease the prophylactic use of drugs known to reduce the risk of major coronary ischaemic events and mortality (aspirin, beta-blockers, lipid-lowering drugs, ACE inhibitors, anticoagulants) has to be considered. In selected patients a myocardial revascularization procedure may also be needed on prognostic grounds. The use of aspirin has to be considered in patients with other forms of atherosclerotic disease as well. Third, given the importance of the family history of coronary heart disease, and other atherosclerotic disease, the closest relatives of patients who develop atherosclerotic disease at a relatively young age should be screened and action taken to reduce their risk of developing symptomatic disease.

The specific lifestyle and therapeutic goals are:

(1) To modify the patients lifestyle
   To facilitate changes in the patient's lifestyle in relation to giving up smoking, eating a healthier diet and having regular physical activity. The patient should be helped to:
   (i) Stop smoking tobacco completely
   (ii) Make healthy food choices to reduce the dietary intake of fat to 30% or less of total energy intake, the intake of saturated fat to no more than one third of total fat intake, and the intake of cholesterol to less than 300 mg/day; to achieve the reduction in saturated fats by replacing them in part with monounsaturated and polyunsaturated fats from both vegetable and marine sources as well as with complex carbohydrates; to increase the intake of fresh fruits, cereals and vegetables; to reduce total calorie intake when weight reduction is needed; and to reduce salt and alcohol use when blood pressure is elevated.
   (iii) Increase physical activity
(2) To modify the patient's risk factors
   To achieve a more favourable risk factor profile through the above lifestyle changes and, where

appropriate, with drugs which are known to reduce the risk of coronary heart disease.

(i) When the patient is overweight (body mass index $> 25 \, kg \cdot m^{-2}$), to reduce weight through appropriate diet and regular physical activity, and thereby reduce blood pressure, total and LDL-cholesterol, increase HDL cholesterol, and improve glucose tolerance and insulin sensitivity.

(ii) If the patient's blood pressure is elevated (systolic blood pressure $\geq 140 \, mmHg$ and/or diastolic blood pressure $\geq 90 \, mmHg$), to reduce it by lifestyle measures and, when appropriate, with antihypertensive drugs, as described in more detail in the Management of Risk chapter.

(iii) In patients with hypercholesterolaemia or more complex forms of dyslipidaemia, to reduce total plasma cholesterol to $< 5 \cdot 0 \, mmol \cdot l^{-1}$ (190 mg $\cdot$ dl^{-1}) and LDL-cholesterol to $< 3 \cdot 0 \, mmol \cdot l^{-1}$ (115 mg $\cdot$ dl^{-1}) and favourably modify other plasma lipids, as described in more detail in the Management of Risk chapter. This is done primarily by dietary measures, but in patients with clinically established coronary heart disease, lipid-lowering drugs will often be required.

(iv) In diabetic patients to achieve and maintain as good blood glucose control as possible as described in more detail in the Management of Risk chapter.

(v) To reduce the propensity to thrombosis by stopping smoking (which lowers fibrinogen), modifying dietary fats as proposed above (influencing favourably factor VII and platelet function) and the use of prophylactic drugs such as aspirin and, where considered appropriate, anticoagulants. In women using steroid hormone contraceptives it may be necessary to reconsider the modality of contraception.

(3) To use other prophylactic drug therapies.
To start and maintain treatment with other prophylactic drugs known to reduce the risk of a further major ischaemic event, as described in more detail in the Management of Risk chapter.

(i) Aspirin (at least 75 mg) in virtually all patients with coronary heart disease or other atherosclerotic disease.

(ii) Beta-blockers in selected patients following myocardial infarction, particularly for those with electrical or mechanical complications.

(iii) ACE inhibitors in selected patients following myocardial infarction with symptoms or signs of heart failure or with persistent left ventricular systolic dysfunction.

(iv) Anticoagulants following myocardial infarction for selected patients at increased risk of systemic embolization.

(4) To screen the patient's closest relatives
Screening the closest relatives (parents, siblings, o spring and other relatives as appropriate) of patients with premature coronary heart disease (men < 55 years and women < 65 years) is important because such relatives may be at increased risk of cardiovascular disease due to adverse lifestyles or genetically influenced risk factor levels (e.g. familial dyslipidaemias).

Primary prevention in healthy high-risk persons

The overall objective of coronary heart disease prevention in healthy high-risk persons is to reduce their risk of developing clinically manifest coronary heart disease, or other forms of atherosclerotic disease. Asymptomatic middle-aged individuals with adverse lifestyles and several associated risk factors may actually be at as high risk of coronary heart disease death or a major non-fatal ischaemic event as patients who have recovered from an acute myocardial infarction without significant myocardial damage or persisting myocardial ischaemia.

Basically, for these healthy high-risk persons the goals of preventive action aimed at lifestyle changes are similar to those described above for secondary prevention. As to improvement and maintenance of physical fitness through regular physical activity, in healthy persons there is more latitude for the development of a more vigorous programme than in patients with symptomatic coronary heart disease. In risk factor modification, appropriate lifestyle changes should always take precedence, but with regard to blood pressure and plasma lipids, in persons who are at particularly high risk and do not respond adequately to lifestyle measures, drug therapy should be considered, as recommended in the Management of Risk chapter. Trial evidence does not give support to the use of aspirin in asymptomatic persons with the exception of treated hypertensive patients and men at particularly high coronary heart disease risk.

In those instances where genetically determined severe dyslipidaemia (e.g. familial hypercholesterolaemia, familial combined hyperlipidaemia) has been diagnosed, the person's closest relatives should be screened for the presence of the same disorder.

Estimation of risk

Estimation of the absolute risk of future coronary heart disease events, as described in the beginning of this chapter, requires:

(i) Taking account of the personal non-modifiable characteristics: age, sex, family history, personal history of coronary heart disease or other atherosclerotic disease. Family history of premature coronary heart disease or other atherosclerotic disease is of particular importance in identifying among healthy persons those who need more extensive evaluation of their risk factor status.

Table 6   Assessment of obesity using body mass index[371]

Body mass index (kg . m^{-2})	WHO classification	Popular description
<18·5	Underweight	Thin
18·5–24·9	'Normal' weight	'Normal' weight
25·0–29·9	Grade 1 overweight	Overweight
30·0–39·9	Grade 2 overweight	Obese
>40·0	Grade 3 overweight	Morbidly obese

(ii) An interview for the identification of adverse lifestyles (smoking, poor dietary habits, physical inactivity).

(iii) Measurement of risk factor levels (weight, blood pressure, plasma lipids, blood glucose)

(iv) Exercise testing, as appropriate

The following brief description of the assessment of risk factors follows the usual order of their assessment in a clinical setting.

Smoking

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?

Degree of obesity

Weight with adjustment for height using body mass index calculated as weight (kg)/height (m) squared, is recommended by the World Health Organization Expert Committee[371] for assessing the degree of obesity as shown in Table 6.

In addition to the degree of obesity, attention has to be paid to the distribution of body fat because central obesity, with the accumulation of fat to the trunk and abdominal cavity, is associated with a high prevalence of lipid abnormalities; in particular hypertriglyceridaemia and low HDL cholesterol, hypertension and abnormal glucose tolerance — the cluster of risk factors associated with insulin resistance — leading to increased risk of coronary heart disease and other atherosclerotic disease.

Calculation or use of a nomogram is needed to obtain body mass index and therefore it is not commonly used by physicians in their clinical practice. The ratio of hip to waist circumference is widely used in epidemiology as an index of central obesity, but this requires two measurements and a calculation. There is now, however, good evidence from population-based epidemiological studies that waist circumference is a useful index of obesity. This is because waist circumference is closely related to body mass index but relates

Table 7   'Action levels' for waist circumference in men and women[372]

	Non-obese	Action level 1 (Alerting zone)	Action level 2 (Professional advice needed)
Men	<94 cm	94–101 cm	≥102 cm
Women	<80 cm	80–87 cm	≥88 cm

better than body mass index to risk factor levels, because it also contains information about the central distribution of body fat[372]. Therefore, measurement of waist circumference with the person standing, midway between the lowest rib and the iliac crest, can be recommended for clinical assessment of the degree of obesity and in follow-up during weight reduction. 'Action levels' recommended for waist circumference are shown in Table 7. A waist circumference in action level 1 should be a signal to avoid weight gain or lose weight, and to increase physical activity. Individuals with a waist circumference in action level 2 should seek advice from health professionals for weight reduction.

Blood pressure

The large physiological variations in blood pressure[373] mean that to diagnose hypertension in an individual requires repeated blood pressure measurements on several separate occasions. If systolic and/or diastolic blood pressure 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 starting treatment. If systolic and/or diastolic blood pressure is initially more markedly elevated repeated blood pressure measurements taken on separate occasions 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 treatment does not appear to be necessary because their cardiovascular risk is probably low[374].

Blood pressure measurement is carried out in the sitting position from the right or the left arm, after the patient has rested for 5 minutes. At the initial visit blood pressure values from the contralateral arm should also be obtained and, as appropriate, in both thighs using a cuff of adequate size. 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 diastolic blood pressure 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.

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 proved and their use can not 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 (and home blood pressure can increase the patient's perception of the problem and compliance to treatment) but insufficient information on their prognostic value makes them 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[375]. This is also the case for so-called 'white coat hypertension'[376], a condition in which blood pressure is raised only in the presence of the physician[377] and to a lesser extent of a nurse[378]. If it is acknowledged that the upper limit of normality for home and 24 h average blood pressure is much lower than 140/90 mmHg[379,380] then white coat hypertension (more properly termed 'isolated clinic hypertension') probably comprises a small proportion of the hypertensive population[381]. It is not yet known, however, whether this condition is an innocent phenomenon or a marker of increased cardiovascular risk that should be monitored and treated[381].

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[382]. 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.

Plasma lipids

Atherosclerosis is due to invasion of the artery wall by low density lipoproteins (LDL), intermediate density lipoproteins (IDL) and small species of VLDL (very low density lipoproteins). Large VLDL and chylomicrons do not enter the artery wall, and high density lipoproteins (HDL) are associated with a low risk of atherosclerosis. Cholesterol and triglycerides are lipid components of all these various lipoproteins, and measurements of cholesterol or triglycerides therefore do not accurately reflect the particular lipoproteins that cause atherosclerosis. On the other hand, direct measurements of LDL, IDL and small VLDL are not practicable. Apolipoprotein B is a protein common to these three classes of lipoproteins, and 'apolipoprotein B' is in principle a good measurement of risk, but standardization of methods is still a problem for routine clinical use. The choice of measurements of plasma lipids for evaluation of coronary heart disease risk, and for monitoring the effects of therapy, has to be based on pathophysiological relevance, economy and practical laboratory technology.

Most laboratories measure cholesterol, triglycerides and the part of cholesterol carried in HDL, namely HDL cholesterol. With these three measurements, the part of cholesterol carried in LDL can be calculated according to the Friedewald formula:

In $mmol . l^{-1}$:
$$LDL\ cholesterol = total\ cholesterol - HDL\ cholesterol - (0.45 \times triglycerides)$$
In $mg . dl^{-1}$:
$$LDL\ cholesterol = total\ cholesterol - HDL\ cholesterol - (0.2 \times triglycerides)$$

The calculation is based on the assumption that triglycerides are less than $5\ mmol . l^{-1}$ ($450\ mg . dl^{-1}$).

The accuracy of this estimation of LDL cholesterol can be reduced due to a summation of possible analytical errors in the various lipid measurements. For the time being, however, the Friedewald calculation is a cheaper and more reliable estimation of LDL cholesterol than commercially available direct measurements of LDL based on immunoseparation[383].

Measurements of total and HDL cholesterol can be made from a venous blood sample taken in the non-fasting state using conventional laboratory methods. Cholesterol determinations made from plasma (with EDTA as anticoagulant) are about 3% lower than those made from serum. Measurements made in a desk-top machine on samples obtained by finger-pricks require a well trained operator and careful maintenance, calibration and external checking of the quality of measurement.

Due to biological and laboratory variation, a reliable assessment of habitual plasma total cholesterol concentrations requires measurements on three different occasions. Total cholesterol can be measured in a venous blood sample drawn in the non-fasting state and used to estimate absolute coronary heart disease risk from the Coronary Risk Charts. However, measuring total cholesterol alone gives an incomplete picture of coronary heart disease risk and therefore it is more desirable to measure total cholesterol, HDL-cholesterol and triglycerides after a fast of 12 h. This should be done in the three top priority groups listed in Table 4. The LDL cholesterol concentration can be calculated from the Friedewald formula.

Risk of coronary heart disease is best evaluated by taking into account plasma concentrations of

cholesterol in both LDL and HDL. The ratio of LDL-cholesterol to HDL-cholesterol is in principle a good indicator of risk. It should be apparent from the Friedewald formula above, however, that 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/HDL cholesterol as an assessment of risk. A total cholesterol/HDL cholesterol ratio greater than 5 indicates increased coronary heart disease risk and is particularly useful in the middle part of the cholesterol distribution (5 to 6·5 mmol . l^{-1} or 190–250 mg . dl^{-1}).

Plasma triglycerides can vary substantially and rapidly, for example due to changes in intake of food or alcohol. Triglycerides over 2 mmol . l^{-1} (180 mg . dl^{-1}) signal the need for repeated measurements in the fasting state.

Concentrations of total cholesterol, LDL cholesterol and HDL cholesterol fall, and triglycerides may rise, in patients with acute disease such as an acute myocardial infarction[382,384,385] or following cardiac surgery. The changes in cholesterol may persist for up to 3 months after an acute myocardial infarction, but a measurement made within 24 h from the onset of symptoms will usually reflect pre-morbid concentrations. Therefore, total cholesterol should be measured from the first venous blood sample drawn on admission to hospital. As this measurement is likely to underestimate the true concentration of cholesterol before the myocardial infarction, it is important to measure fasting lipids in all patients not later than 12 weeks after the acute event.

Blood glucose

Because previously undetected Type 2 diabetes may be an important underlying factor for coronary heart disease and other atherosclerotic disease, determination of fasting blood glucose should be included in the laboratory examinations made at the time of presentation. Blood glucose may be elevated in connection with myocardial infarction or other acute coronary heart disease events as a response to the stressful situation, or due to glucose-containing intravenous fluids, and therefore an elevated blood glucose detected in those circumstances requires further follow-up.

When risk assesment is being carried out on asymptomatic individuals who have a family history of Type 2 diabetes, it is appropriate to include determination of fasting blood glucose in the laboratory tests or even to perform an oral glucose tolerance test, with blood glucose determinations at 0 and 2 h after an oral glucose load of 75 g, for the detection of undiagnosed diabetes or impaired glucose tolerance. According to the revised American Diabetes Association criteria[275] the fasting blood glucose criterion for diabetes is $\geq$6·1 mmol . l^{-1} (110 mg . dl^{-1}) on repeated examinations and using plasma glucose determinations $\geq$7·0 mmol . l^{-1} (126 mg . dl^{-1}). The diagnostic criteria for impaired glucose tolerance in individuals with normal fasting glucose are: 2 h venous blood glucose 6·7–10·0 mmol . l^{-1} (120–180 mg . dl^{-1}), 2 h plasma glucose 7·8–11·1 mmol . l^{-1} (140–200 mg . dl^{-1}).

Physical activity and exercise capacity

A brief interview concerning the person's physical activity at work and leisure gives the basis for assessing his or her general level of physical activity and the need to give advice for an increase in physical exercise. An exercise test using a bicycle ergometer or treadmill provides an objective estimate of the exercise capacity of the individual and thus supplements the information obtained from the interview. Exercise testing is widely used in assessing patients with coronary heart disease for various reasons: to detect myocardial ischaemia, to stratify for risk of a further major ischaemic event, to select for coronary arteriography, to assess the impact of revascularization or assess the response to anti-anginal drug therapy. Thus, an objective estimate of the exercise capacity is available for the majority of patients with coronary heart disease.

The European Society of Cardiology Working Group on Exercise Physiology, Physiopathology and Electrocardiography has formulated guidelines for exercise testing in patients with symptoms suggestive of coronary heart disease or with known coronary heart disease[386].

Diet

Dietary advice is an essential part of the prevention for patients with coronary heart disease and asymptomatic high-risk individuals. Information about the patient's usual diet and eating habits and identification of dietary faults form the basis for dietary advice. A detailed dietary interview cannot easily be incorporated into the physician's practice schedule and most physician's training does not encompass this aspect of lifestyle. Assistance from a dietician or a nurse specially trained for dietary interviews and counselling is of considerable value.

Management of risk

Behavioural change

Prochaska and DiClemente have proposed a 'stages of change' model[387,388] which argues that everyone is not equally ready to change their behaviour at a given point in time even if they have all been invited to have screening and risk factor modification. They maintain

that it is important to assess the individual's behaviour, thoughts, attitudes and beliefs concerning their perceived ability to change, their behaviour over the past 6 months, as well as the environmental context in which they will attempt to change, and maintain the lifestyle change.

Five stages are proposed: pre-contemplation, contemplation, preparation, action and maintenance. In the pre-contemplation stage, individuals do not intend to change their high-risk behaviour in the foreseeable future, i.e. over the next 6 months. Individuals can be in this stage because (a) they are unaware of the long-term consequences of their behaviour; (b) they are discouraged about their ability to change and do not want to think about it; (c) they are defensive due to social pressure to change. Pre-contemplation is a very stable stage. As a group they evaluate the pros of their risk behaviour as greater than the cons.

Contemplation is the stage where people seriously intend to change their behaviour within the next 6 months. Despite their intentions, however, they typically stay in this stage for long periods of time, e.g. 2 years or more. They talk about change, but keep putting it off. Those who substitute thinking for acting are called chronic contemplators. Contemplators evaluate the pros and cons of their behaviour as about equal; hence there is considerable ambivalence about changing.

People in these first two stages should not enter behaviour change programmes, e.g. smoking cessation, dietary or exercise programmes. Most current smokers are in these stages. Instead they should be provided with information, motivation and advice that will help them move to the next stage, in which behavioural change is seriously considered.

In the preparation stage, individuals intend to take action in the near future, typically within the next month. They have a plan of action, and have usually made some modest behavioural change, such as reducing the number of cigarettes smoked per day or slightly modifying diet. In this stage there are both behavioural and intentional criteria; the cons are evaluated as greater then the pros. In this stage, cues to action should be provided, such as the demonstration of associations between lifestyle and symptoms, illness in other family members, social pressures and so on.

Overt behavioural change within the past 6 months characterizes the action stage, which is highly unstable and where the greatest risk for relapse may occur. The criterion for achieving this stage is to have actually changed behaviour, e.g. stopped smoking, as opposed to reducing smoking or switching brands to lower tar, etc. During this period most of the processes of change come into play and the intrapersonal (e.g. perceived self-efficacy), interpersonal (e.g. social support) and environmental (e.g. unavoidable exposure to smoking environments) factors associated with these processes are principal determinants of whether the newly quit smoker proceeds to the next stage (maintenance) or regresses to the earlier stage. Obviously this is

the critical period where all intervention strategies must focus on the above-mentioned processes. A wide variety of instructive materials are usually available from national Heart Associations and Foundations including tailored self instruction programmes, support groups and counselling strategies.

Maintenance is considered from 6 months after an individual has changed behaviour until about 5 years of continuous maintenance have elapsed. (NB: most smoking cessation programmes consider 6 months to one year continuous abstinence as 'success'). For example, smokers who successfully move from action to maintenance demonstrate a gradual decrease in overall temptation and lower use of cognitive/experiential processes, and a heightened confidence and greater use of behavioural techniques such as stimulus control, counter-conditioning, helping relationships and contingency management. Mapping out templates of change associated with successful recovery could allow comparisons to be made across smoking and alcohol problems to highlight the general principles underlying successful addictive behaviour change.

In summary, behaviour change programmes achieve much higher success rates when they assess the state of readiness of the individual to commit to the change process. The 'stages of change' model reviewed here is becoming increasingly employed by health care professionals who are concerned with treating and/or referring patients for appropriate assistance, as it proves its value in providing services to those who are ready to benefit from them.

Smoking

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 coronary heart disease, or other atherosclerosis disease and in connection with an invasive treatment, such as coronary artery bypass grafting or percutaneous transluminal coronary angioplasty. 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 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. A review of 28 major trials

of advice from North American physicians to stop smoking showed that one year after brief advice cessation rates were 3–13%, while after more intensive interventions cessation rates increased to 19–38%[389,390]. Readers are referred to specific recommendations describing the principles of brief advice and other interventions for smoking cessation in clinical practice[391–393]. 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 patch have been widely used in helping quitters to go through the difficult initial weeks or months of smoking cessation. Meta-analyses of trials of nicotine replacement therapy have shown that the use of nicotine gum or patches double the cessation rates compared with placebo[394]. 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[395], but caution in the use of nicotine replacement therapy is still required. It is imperative to tell patients that they should not smoke while they are using these nicotine delivery preparations, because doing so may lead to an exacerbation of symptoms.

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.

Dietary changes

All patients with coronary heart disease, or other atherosclerotic disease, and high risk individuals, should receive professional advice on food and food choices which make up a diet associated with the lowest risk of atherosclerotic disease. Physicians should emphasize the importance of diet in relation to weight reduction, lowering blood pressure and blood cholesterol, in the control of blood glucose in diabetic patients and in

reducing the propensity to thrombosis. Diet is an integral part of risk management. The role of the family is particularly important in this context as the person primarily responsible for buying and preparing food must be informed of the need for healthy food choices and how these can be practically achieved. The relevance of physical activity in helping weight control, and favourably modifying other risk factors should be explained.

The goals of dietary counselling have to be defined on an individual basis, taking account of overweight as well as plasma lipids, blood pressure levels, and diabetes. For patients and high risk individuals food choices should be modified so that the total dietary intake of fat is reduced to 30% or less of total energy intake, the dietary intake of saturated fat to no more than one third of total fat intake and the intake of cholesterol to less than $300 \, \text{mg} \cdot \text{day}^{-1}$, with an increase in the use of monounsaturated and polyunsaturated fats from both vegetable and marine sources, and complex carbohydrates from fresh fruits, cereals and vegetables[74,75,88–90]. Appendix Table 1 gives examples of food choices for a healthy lipid-lowering diet. Foods have been grouped into three broad categories: 'recommended foods', 'foods for use in moderation' and 'foods for only exceptional use'. These food categories will need modification for each European country to take account of national dietary habits and available foods. In presenting these food categories the object is to encourage those individuals whose diet is mainly composed of 'foods for only exceptional use' and 'foods for use in moderation' to change their food choices towards 'recommended foods' sensibly supplemented with 'foods for use in moderation' to give a palatable, nutritionally balanced and healthy diet.

The intensity of dietary changes will be influenced by plasma LDL cholesterol and other lipid abnormalities. For overweight individuals calorie restriction is also necessary.

Alcohol should also be considered in the context of dietary advice. Whilst moderation in the use of alcohol should always be advised further restriction may be necessary in those who are overweight (to reduce calories) particularly in hypertensive patients. The intake of salt (sodium chloride) should also be reduced to less than $5 \, \text{g} \cdot \text{day}^{-1}$ in hypertensive patients.

By emphasizing the importance of diet physicians can encourage patients and high risk individuals, with their families, to achieve the above dietary goals. To give this advice professionally physicians require appropriate diet literature, and other practical educational materials, in order to translate dietary goals into practical eating habits. For some patients a more thorough assessment of dietary habits is required together with specialized counselling which is beyond the competence of most physicians. For patients with severe dyslipidaemias, diabetes or obesity which is unresponsive to physician advice the professional guidance of a dietician is required.

Table 8 *Suitable target heart rates during exercise, according to age*[223]

Age (years)	Heart rate per minute*
20–29	115–145
30–39	110–140
40–49	105–130
50–59	100–125
60–69	95–115

*Corresponds to 60–75% of the average maximum heart rate for age.

Reduction of overweight

Reduction of overweight is not easy, but if achieved the outcome is in many respects rewarding. 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. As mentioned above, a calorie-restricted lipid-lowering diet is the central component in weight reduction. Suitable regular physical activity adapted to the individual fitness and health status helps in weight reduction and in the maintenance of reduced body weight. A realistic goal for weight reduction should be agreed between the physician and the patient. A weight loss of 0·5–1 kg per week is a suitable rate until the weight goal is achieved.

Physical activity

Regular aerobic physical activity has favourable effects on body weight, blood pressure, plasma lipids, glucose tolerance, and insulin sensitivity and may also have a direct protective effect against the triggering of acute cardiac events. Furthermore, regular exercise has favourable psychological effects. Very few occupations in the modern industrialized society require a workload compatible with the maintenance of good cardiovascular fitness. Therefore having enough aerobic exercise during leisure-time has become an important part of a healthy lifestyle and coronary heart disease prevention[141].

Physical activity recommendations have to define the intensity, duration and frequency of exercise. The intensity of exercise for healthy individuals is best defined in terms of target heart rate during peak exercise, 60–75% of the average maximum heart rate for the person's age being the preferred target heart rate (Table 8). This target heart rate is easily achieved by exercises involving the use of large muscle groups. Brisk walking, jogging, cycling, mowing, swimming, tennis, volley ball, cross-country skiing, aerobic dancing, and skipping (rope jumping) are examples of such activities and exercises.

The duration of physical activity should preferably be 30–40 min, including a 5–10 min warm-up phase before the 20–30 min aerobic phase and a 5–10 min cool-down phase at its end, and as frequent as 4–5 times weekly. Alternatively, with increasing duration of aerobic exercise, 2–3 times weekly is sufficient.

When a previously sedentary person starts to become physically active, both the intensity and duration of aerobic exercise have to be set low initially and then increased with improving fitness.

Physical activity recommendations for patients with clinically established coronary heart disease have to be based on a comprehensive clinical judgement including the results of exercise testing. 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 of activity should initially be set low and increased gradually according to the limits imposed by exercise-induced symptoms. The target heart rates for aerobic exercise given in Table 8 for healthy individuals are not applicable for patients receiving beta-blocking drugs and in general the intensity targets for exercise should not be over ambitious for patients with anginal symptoms.

Patients recovering from an acute myocardial infarction or other ischaemic cardiac events and, similarly, patients following angioplasty or recovering from coronary artery bypass grafting should be given advice about a suitable, gradually increasing physical activity programme. Many patients can do this on their own, when they get clear prescriptions and encouragement from their physician. Written material and audiocassettes or videos are useful supplements to verbal advice.

Many patients with coronary heart disease will benefit from an organized rehabilitation programme provided by a multidisciplinary team. Such a programme may be provided on an ambulatory basis, or as an in-patient at special rehabilitation units, as is the tradition in central European countries. Such rehabilitation programmes, in addition to supervised physical exercise, give a good opportunity for a comprehensive evaluation of the patient's coronary heart disease risk factor status and advice and measures aimed at risk reduction.

Detailed recommendations on exercise prescription and rehabilitation for cardiac patients, as well as on counselling for recreational and vocational activities have been formulated by the European Society of Cardiology Working Group on Rehabilitation[396] and other expert groups in this field[397].

Blood pressure

Guidelines on the management of hypertension vary slightly in their definitions of hypertension and its subdivision into borderline, mild, moderate or more severe stages[398,399]. As stated in the 1996 World Health Organization Expert Committee Report on hypertension control[400] all definitions of hypertension are

by necessity arbitrary because the risk of cardio-vascular 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.

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, transient ischaemic attacks, stroke, renal insu ciency etc) makes hypertension severe, regardless of the blood pressure level. The co-existence of other cardiovascular risk factors (smoking, increased plasma cholesterol, diabetes, family history of early cardiovascular disease) greatly adds to the risk associated with a mild blood pressure elevation (see Coronary Risk Charts). This is independent of the absence or presence of clinically established cardiovascular disease or end-organ damage. Markers of end-organ damage such as left ventricular hypertrophy, a marked reduction in glomerular filtration rate, proteinuria and retinal haemorrhages and/or exudates with or without papilloedema are also associated with an increased risk at any given blood pressure level. Thus, in hypertensive patients an electrocardiogram, a chest X-ray, a serum creatinine value, a urine analysis and a fundus oculi examination should always be obtained. Echocardiography has recently 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[401–403]. This has also been the case for microalbuminuria in diabetic patients[404] and in non-diabetic patients[405]. An echocardiogram, and one or more determinations of the presence or absence of microalbuminuria, should thus also be undertaken whenever possible. The clinical value of other possible markers of end organ damage such as increased carotid artery wall thickness at ultrasonography, and reduced arterial distensibility, remain to be determined.

Whom to treat?

Although most randomized therapeutic trials on hypertension have defined and treated patients on the basis of diastolic blood pressure values only, there is now a consensus that systolic blood pressure values should also be taken into account in defining and managing hypertension because (1) in epidemiological studies, cardiovascular risk is as strongly, or even more strongly, associated with systolic blood pressure as with diastolic blood pressure values, and (2) some of the intervention

studies on hypertension indicate that cardiovascular events correlate more closely with achieved systolic blood pressure than diastolic blood pressure. Favourable results of recent trials on isolated systolic hypertension have also added to the evidence about the importance of systolic blood pressure in risk assessment[198,199]. Therefore, in recent recommendations on the management of hypertension systolic blood pressure and diastolic blood pressure get equal attention.

Figure 2 outlines the suggested approach to blood pressure management in primary coronary heart disease prevention, based on the following risk stratifications for systolic blood pressure and diastolic blood pressure values (1) in patients presenting with severe hypertension — the possibility of secondary hypertension (renovascular hypertension, renal disease, primary aldosteronism, phaeochromocytoma) should be considered and a hypertension specialist should be consulted. (2) Individuals in whom the overall coronary heart disease risk is ≥20% over 10 years, or will exceed 20% when projected to age 60, blood pressure should be kept <140/90 mmHg by lifestyle counselling and, if needed, pharmacological treatment (3) in hypertensive individuals in whom the overall coronary heart disease risk is <20% the decision on whether and how quickly to start treatment will depend on the magnitude of the blood pressure increase above normal, the existence of subclinical cardiovascular disease and/or the presence of end-organ damage. If systolic blood pressure is ≥180 mmHg and/or diastolic blood pressure ≥100 mmHg lifestyle counselling and pharmacological treatment should be instituted with minimal delay. This should also be the case for modest elevations in blood pressure (diastolic blood pressure ≥90 mmHg and/or systolic blood pressure ≥140 mmHg) in the presence of subclinical disease and/or end-organ damage. If on the other hand, blood pressure is only 'mildly' elevated (diastolic 90–99 mmHg and/or systolic 140–179 mmHg) and there is no subclinical disease or end-organ damage present, blood pressure should be repeatedly measured over a period long enough to overcome the problem of spontaneous blood pressure variability and enable a more precise evaluation of the patient's 'usual' blood pressure. If after this period (during which lifestyle counselling will have been given) diastolic blood pressure remains ≥95 mmHg and/or systolic blood pressure ≥160 mmHg drug treatment should be instituted. If diastolic blood pressure falls between 90–94 mmHg or systolic blood pressure to between 140–159 mmHg lifestyle counselling should be continued together with frequent blood pressure measurements. If values fall to <90 diastolic and <140 systolic it would be prudent to continue lifestyle counselling and measure blood pressure at least every 5 years. (4) Individuals with a systolic blood pressure <140 mmHg and a diastolic blood pressure <90 mmHg do not normally need antihypertensive treatment. Some guidelines, however, emphasize that diastolic blood pressures between 85–89 mmHg carry an increased cardiovascular risk as compared to lower values and define this condition as 'high normal'. An

optimal level of blood pressure may therefore be <85 mmHg for diastolic and <120 mmHg for systolic and this is more likely to be the case for young adults (<20 years) in whom the damage of life time exposure to an even slightly elevated blood pressure may be greater. In individuals with diabetic nephropathy and renal parenchymal disease antihypertensive drug treatment must definitely be started at a diastolic blood pressure <90 mmHg because of the evidence that renal protection is achieved at values <85 and even down to 80 mmHg[406–409]. This may also be the case when renal damage is due to essential hypertension, particularly in black people[408].

Systolic and diastolic blood pressure usually parallel one another across each cardiovascular risk stratum. In some instances, however, a disparity may occur in that diastolic blood pressure may be in a higher or lower risk stratum than systolic blood pressure. Diastolic blood pressure may also be normal when systolic blood pressure is definitely elevated. Isolated systolic hypertension may be found in adolescents and young people, but it is particularly common in the elderly. 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 systolic blood pressure results in considerable benefit in terms of reduced cardiovascular morbidity and mortality from cerebrovascular and cardiac complications[198,199]. 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 systolic blood pressure is persistently ≥160 mmHg regardless of the diastolic blood pressure value.

How to treat?

Lifestyle. 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 emphasized above, it should always be advised for patients who are receiving antihypertensive drugs, because the dosage of antihypertensive drug 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 5 g . day^{-1}; restriction of alcohol consumption to no more than 10–30 g . day^{-1} 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^{-1} ethanol in women (1–2 of these drinks . day^{-1}); 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 pressor effect of smoking may raise daytime blood pressure[410] 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 childbearing age. Postmenopausal hormone replacement therapy does not usually influence blood pressure levels, but frequent monitoring of blood pressure is needed if such therapy is initiated in hypertensive women.

Antihypertensive drugs

Randomized trials of antihypertensive treatment have demonstrated the benefits of lowering blood pressure by antihypertensive drugs[399,411]. Although these trials have used diuretics and beta-blockers as first-choice agents, in all of them, blood pressure control has eventually been achieved with the use of several additional agents, with a substantial proportion of patients taking combination treatment with two or three drugs[412]. Furthermore, in most trials the benefit has been related to the degree of blood pressure reduction. The lower the achieved systolic or diastolic blood pressure, the greater the reduction in the rate of cardiovascular complications[413]. Thus no evidence is available that benefits are due to diuretics and beta-blockers rather than to the lowering of blood pressure per se[399]. This has received support from recent evidence in placebo-controlled prospective trials that antihypertensive treatments based on calcium antagonists also reduce cardiovascular morbidity and mortality[199,414]. Furthermore, a large controlled trial has recently shown antihypertensive treatments based on an ACE inhibitor affect cardiovascular morbidity and fatal events in a comparable way to that obtained by traditional drugs[415].

Several classes of drugs can be recommended as first-line treatment of mild hypertension. They may be listed in order of proven benefit based on morbidity and mortality trials as follows: diuretics, beta-blockers, calcium antagonists, ACE inhibitors and alpha-adrenoceptors blockers. When the first drug chosen leads to side effects, or is not sufficiently effective, a drug from a different pharmacological class should be administered. When the first drug chosen is only partially effective adding another drug from another pharmacological class is necessary. Combinations with proven efficiency and favourable tolerance profile are (1) a diuretic with a beta-blocker, an ACE inhibitor, or an alpha-blocker, (2) a beta-blocker and a dihydropyridine calcium antagonist and (3) an ACE inhibitor and a calcium antagonist.

Diuretics and ACE inhibitors should be given preference in patients with overt heart failure;

beta-blockers or calcium antagonists in patients with angina pectoris; beta-blockers in patients with a previous myocardial infarction and ACE inhibitors in those with a previous myocardial infarction who have left ventricular dysfunction; ACE inhibitors, calcium antagonists or alpha-blockers in individuals with a high cardiovascular risk profile due to dyslipidaemia and/or insulin resistance. Recently, the armamentarium of antihypertensive drugs has expanded with the addition of the antagonists of the angiotensin II receptors. These drugs are well tolerated which may favourably a ect patients' compliance to treatment. Their use as first choice in the treatment of hypertension, however, should wait for completion of trials on their ability to reduce cardiovascular morbidity and mortality and/or prevent or regress end-organ damage.

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 diastolic blood pressure should be reduced to 90 mmHg. Lower values down to 80 mmHg are desirable or needed in young hypertensive patients and in patients with diabetic nephropathy (or renal damage from any cause) in whom renal protection may occur at values even less than 80 mmHg. The blood pressure to be achieved should also be low in diabetic hypertensive patients without evidence of nephropathy because in the HOT study[293] the diabetic hypertensive subgroup randomized to a diastolic blood pressure goal of <80 mmHg had about 50% less cardiovascular morbidity and mortality than the subgroup randomized to a diastolic blood pressure goal of <90 mmHg. The systolic blood pressure goal is less certain but a reduction to values around 140 mmHg, or 130 mmHg in young people and those with diabetes, if well tolerated, also seems desirable. The possibility that excessive blood pressure fall may lead to an increased morbidity and mortality, i.e. the so called J shape phenomenon[416,417] is currently regarded as unlikely because of (1) the epidemiological evidence that in the general and elderly population cerebrovascular and coronary morbidity are linearly related to diastolic blood pressure down to about 70 mmHg[168] and (2) the evidence from a randomized controlled trial on isolated systolic hypertension in the elderly that cardiovascular morbidity is reduced when the diastolic blood pressure is reduced to less than 70 mmHg[198] and (3) the HOT study in which hypertensive patients were randomized to achieve a diastolic blood pressure of 90 mmHg or less, 85 mmHg or less, and 80 mmHg or less has provided little evidence for a J-curve phenomenon, within diastolic blood pressure values in the range of 70 to 90 mmHg, on either intention-to-treat or on-treatment results[293]. 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[399,411,418]. 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, especially in patients strictly observing 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[418]. Increasing compliance to antihypertensive treatment and achieving a wider blood pressure control in the population thus represents a major goal for clinical practice in the future.

Plasma lipids

The Coronary Risk Charts show that, at the concentrations of cholesterol given, overall risk depends critically on age, sex and the burden of other risk factors. Coronary heart disease is rare in populations with total cholesterol less than $3–4$ mmol . 1^{-1} (115–155 mg . dl^{-1}), even in the presence of other risk factors. Conversely, coronary heart disease is inevitable in untreated patients with the severest forms of familial hypercholesterolaemia, even in the absence of other risk factors.

However, most patients encountered in clinical practice have cholesterol concentrations in the range given in the chart. In this range, management recommendations must be based not only on lipid measurements but also on an assessment of absolute coronary risk. A cholesterol of $5–6$ mmol . 1^{-1} (190–230 mg . dl^{-1}) may require drug therapy in a patient at high overall coronary heart disease risk, whereas a cholesterol of $7–8$ mmol . 1^{-1} (270–310 mg . dl^{-1}) may be left untreated in an individual at low overall risk.

Figure 3 outlines the recommended approach to lipid management in primary coronary heart disease prevention. The first step is to assess total coronary risk and to identify those components of risk that can be modified. If the 10-year risk of coronary heart disease exceeds 20%, or will exceed 20% if the patient's risk factor combination is projected to age 60, intensive lifestyle advice is required for all risk factors including lipids. For the whole population the ideal total

cholesterol should be less than 5 mmol . l^{-1} (190 mg . dl^{-1}), with an LDL cholesterol below 3·0 mmol . l^{-1} (115 mg . dl^{-1}), and lifestyle with a particular emphasis on diet is the only justified approach. Most patients with coronary or other atherosclerotic disease have a 10-year risk greater than 20% of coronary heart disease, and in many of them the risk exceeds 40%. The majority of these patients need lipid lowering drug treatment as well as intensive dietary counselling.

Exclusion of secondary hyperlipidaemias
Hyperlipidaemias 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, hypothyroidism, diseases of the kidney and liver and diabetes, particularly in the presence of a nephropathy. Exclusion requires clinical assessment and a small battery of clinical chemical tests such as thyroid stimulating hormone, alanine aminotransferase, gamma glutamyl transferase, albumin, glucose and glycosylated haemoglobin and creatinine in plasma; a measurement of erythrocyte volume; and glucose and protein in urine.

Where possible, patients with diseases such as familial hypercholesterolaemia will also benefit from specialist evaluation of the feasibility of molecular genetic diagnosis.

Monitoring
The primary purpose of lifestyle and therapeutic interventions to modify plasma lipids is reduction of LDL cholesterol and related atherogenic lipopoproteins. Cholesterol and LDL cholesterol are accordingly the most important measurement to monitor. In some clinical situations, particularly treatment of severe hypertriglyceridaemia to prevent pancreatitis, it is of course more relevant to measure and follow triglycerides.

Goals
Physiological concentrations of LDL cholesterol are probably around 1–2 mmol . l^{-1} (40–80 mg . dl^{-1}), but whether there is clinical benefit from dietary or drug treatment to lower LDL below 3·3 mmol . l^{-1} (125 mg . dl^{-1}) has recently become an issue for debate. The debate arises from post hoc analyses of the results of the CARE[419] and of the WOSCOPS[213]. These analyses suggested that below this threshold there would be no further clinical benefit from cholesterol lowering, whereas the corresponding post hoc analysis of the 4S data indicated no such threshold. The latter result is consistent with results of observational epidemiology[420]. Until results of trials designed to answer this question become available, a conservative approach is to choose an LDL concentration of 3 mmol . l^{-1} closely equivalent to 115 mg . dl^{-1} as a goal of therapy. The corresponding concentration of total cholesterol is approximately 5 mmol . l^{-1} (about 190 mg . dl^{-1}).

These two values are recommended as goals of dietary and, if necessary, drug therapy for patients with coronary heart disease and for patients at high risk of

developing coronary heart disease. High risk of coronary heart disease is defined as ≥20% over 10 years or will exceed 20% when projected to age 60. The same goals apply to healthy persons at lower and very low overall coronary heart disease risk, but in these cases they should be pursued by following the usual dietary recommendations directed to the general population.

This recommendation differs from that of most earlier guidelines, in which a set of different goals have been given depending on the degree of risk. There are two reasons for the current recommendation. The first is pathophysiological. There is no reason to think that the atherogenecity of a given concentration of plasma cholesterol or LDL cholesterol depends on whether a myocardial infarction has occurred. The second reason is simplicity. A total cholesterol <5 mmol . l^{-1} and an LDL cholesterol <3 mmol . l^{-1} are easy to remember. The accuracy of conversion to mg . dl^{-1} has also been sacrificed for reasons of simplicity. A cholesterol of 5 mmol . l^{-1} = 193 mg . dl^{-1}, but there is no substantial loss of biological meaning by rounding that number down to 190. Similarly, 3 mmol . l^{-1} = 116 mg . dl^{-1}, which can be rounded off to 115 mg . dl^{-1}.

This recommendation for total cholesterol and LDL cholesterol goals requires two qualifications. First, the intensity with which these goals are pursued must be tempered by the calculation of absolute coronary heart disease risk. It is obviously more important to reach these goals in a patient with coronary heart disease or in an individual with a 10-year coronary heart disease risk ≥20% than it is in an individual with a 10-year risk of less than 20%. Secondly, goals cannot be reached with the same ease by all patients. In the most common clinical situation requiring lipid lowering drugs, patients either have coronary heart disease or they are at high absolute risk of coronary heart disease, and they have concentrations of plasma lipids that are only slightly abnormal. They can reach the above concentrations of cholesterol and LDL cholesterol fairly easily with diet and moderate doses of drugs. Where the cholesterol and LDL goals have not been reached it is important to titrate up the dose of lipid lowering therapy to the maximum, and certainly to use a dose no lower than the maximum used in the clinical trials which showed benefit from cholesterol lowering therapy. A minority of patients have severe disturbances of lipid metabolism due to genetic disorders such as familial hypercholesterolaemia. Even with dual or triple drug regimens, reaching a goal concentration of 3 mmol . l^{-1} (115 mg . dl^{-1}) of LDL-cholesterol can be very difficult. These patients will still benefit to the extent to which cholesterol has been lowered on maximum drug therapy even though they have not reached the treatment goals. For example, at the doses used in the trials of secondary and primary coronary prevention a reduction in total cholesterol and LDL-cholesterol of about 20% and 30%, respectively, would be achieved.

For reasons already given, there is insufficient evidence to justify goals for triglycerides and HDL-cholesterol. Instead, these measurements should be used

to identify individuals at high risk of coronary heart disease[421]. An HDL cholesterol concentration < 1 mmol (40 mg . dl^{-1}) and triglycerides > 2 mmol . l^{-1} (180 mg . dl^{-1}) identify those at higher risk. A ratio of total cholesterol to HDL cholesterol greater than 5 is also a marker of higher risk.

Measurements of triglycerides should also be used to guide the choice of drug therapy.

Treatment
Diet. All patients with coronary heart disease, and high risk individuals should follow the dietary recommendations already given.

Drugs. The current armamentarium of lipid-lowering drugs includes inhibitors of HMG CoA reductase (statins), fibrates, bile acid sequestrants (resins) and nicotinic acid and its derivatives. To various extents, they have all been used in angiographic trials demonstrating beneficial effects by reducing the progression of coronary disease. All four classes of drugs, but not all drugs within each class, have also been shown in trials to reduce myocardial infarction and sudden death. The most convincing evidence from angiographic as well as clinical end-point trials has nevertheless been obtained in the most recent trials using the most potent of the lipid lowering drugs, namely the statins. This class of drugs also has the best safety record to date and is the easiest to use. At present, the statins are therefore first line drugs.

Nicotinic acid and the resins have been used in several trials demonstrating reduction of coronary artery disease[422], but they can be difficult to use because of immediate side effects such as flushing in the case of nicotinic acid and constipation in the case of the resins. In contrast, fibrates are easy to use, and they have been shown to reduce progression of coronary artery disease and prevent myocardial infarction. There is still concern, however, that they may increase non-coronary mortality, and the publication of the results of a large clinical trial of bezafibrate in secondary prevention is therefore awaited with interest[266].

The statin drugs vary in the degree to which they can reduce LDL cholesterol. The physiological and epidemiological evidence suggests that LDL cholesterol should be lowered almost as much as possible, but the analyses of the relationship of lipid changes to clinical events in the large trials are in conflict with one another[213,214,419]. They are in any case based on post hoc analyses of the trial data, and a definitive answer to this question must come from prospective trials designed to test whether, for example, 20% or 40% reduction of cholesterol provides the best protection. Such trials are currently being launched. Other differences are in ancillary properties such as possible anti-thrombotic or antiproliferative effects, as demonstrated in laboratory or clinical experiments. Several of these properties are conceivably important, but it should be appreciated that the experimental basis for these observations is very small indeed compared to the major

trials with clinical end-points on which clinical practice should be based. These trials have demonstrated effective protection with statins in particular, but there is also evidence for nicotinic acid, the anion exchange resins and, with the above caveats, for some of the fibrate drugs.

Triglycerides greater than 10 mmol . l^{-1} are to a large extent due to chylomicrons, secreted from the small intestine. The most common causes of chylomicronaemia are diabetes and abuse of alcohol. Chylomicronaemias respond poorly to lipid lowering drugs. Triglyceride concentrations fluctuate very substantially, moreover, and it is difficult to assess the effect, if any, of treatment with lipid lowering drugs. Control of intake of alcohol and dietary fat and, if applicable, treatment of diabetes with insulin, are therefore more important than triglyceride lowering drugs. These drugs work best at concentrations of triglycerides between 2 and 10 mmol . l^{-1} (180–900 mg . dl^{-1}). This is counter-intuitive to many clinicians, because in most other situations, drugs are reserved for the severest cases.

Statins, resins and nicotinic acid effectively lower LDL cholesterol, whereas the effect of fibrates on LDL cholesterol is only moderate. HDL cholesterol is increased slightly or moderately by statins and resins and more substantially by nicotinic acid and especially the fibrates. Resins tend to increase triglycerides and are not suitable in combined (mixed) hyperlipidaemia unless a triglyceride-lowering drug is also given. Triglycerides are moderately lowered by statins and substantially by fibrates and nicotinic acid.

Since plasma lipoproteins, especially those carrying much triglyceride, respond differently to these drugs, the choice of drug in clinical practice should take account of triglyceride concentrations.

Resins should only be used when triglycerides are less than 2 mmol . l^{-1} (180 mg . dl^{-1}) or if given in conjunction with a triglyceride lowering agent. Statins are the first choice in patients with triglycerides up to 5 mmol . l^{-1} (450 mg . dl^{-1}). When triglycerides are between 5 and 10 mmol . l^{-1} (450–900 mg . dl^{-1}), 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^{-1} (900 mg . dl^{-1}), triglyceride lowering drugs are generally not useful. Instead triglycerides must be reduced by restriction of alcohol, treatment of diabetes with insulin, and severe restriction of long chain fat of both animal and vegetable origin.

Drugs can be used in combination. In familial hypercholesterolaemia, for example, a combination of resin and statin or even a triple-drug regime (statin, resin, nicotinic acid) may be needed to produce satisfactory reduction of LDL cholesterol.

An important practical question is when to start lipid lowering drug treatment after a myocardial infarction. As yet there are no trial data that mandate starting treatment in the acute phase of the disease or immediately thereafter. In principle, therefore, drug treatment could wait for up to 3 months when fasting lipids can be reliably estimated, with dietary intervention during this

Table 9 Glucose control assessment levels for Type 1 diabetes[424]

	Non-diabetic*	Adequate	Inadequate
HbA$_{1C}$ (DCCT standardized) % Hb	<6·1	6·2–7·5	>7·5
Self-monitored blood glucose			
Fasting/pre-prandial			
mmol . l^{-1}	4·0–5·0	5·1–6·5	>6·5
(mg . dl^{-1})	(70–90)	(91–120)	>120
Post-prandial (peak)			
mmol . l^{-1}	4·0–7·5	7·6–9·0	>9·0
(mg . dl^{-1})	(70–135)	(136–160)	>160
Pre-bed			
mmol . l^{-1}	4·0–5·0	6·0–7·5	>7·5
(mg . dl^{-1})	(70–90)	(110–135)	>135

*It can be dangerous to strive for non-diabetic levels.

period. In practice, however, many patients will no longer be under the care of a cardiologist when the effect of the dietary intervention on lipids should be assessed. This often means that drug treatment will never be considered. Some physicians are therefore starting drug treatment in hospital, usually with a statin drug, on the basis of the initial cholesterol level. Such early drug treatment should still be combined with effective dietary intervention. The strategy to ensure that goal concentrations of lipids are reached must obviously depend on the organisation of medical care in each country.

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

Blood glucose

There is convincing evidence from randomized controlled trials that good blood glucose control prevents or retards the occurrence of diabetic microvascular complications in patients with Type 1 diabetes[283]. There is also trial evidence showing that intensive insulin therapy prevents the progression of microvascular complications in patients with Type 2 diabetes[423]. Therefore, good glucose control is important in both types of diabetes for the prevention of microvascular complications. Trial evidence of the effect of good glucose control on risk of coronary artery disease or other atherosclerotic disease is so far not available, but epidemiological observations in prospective cohort studies of diabetic patients suggest that the degree of hyperglycaemia is associated with increased risk of different forms of atherosclerotic disease. 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 normalized 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 completely 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 (non-insulin-dependent) 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.

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.

Glucose control assessment levels for Type 1 diabetes defined by the European Type 1 Diabetes Policy Group[424] are shown in Table 9. Avoidance of serious hypoglycaemias is essential. In the majority of patients with Type 2 diabetes even lower goals, as shown in Table 10, extending to the non-diabetic range, can be safely achieved[425]. Ideal glucose control may be difficult, impossible and even unnecessary to achieve in certain patients, and in particular in the elderly. In such cases less stringent targets have to be accepted. Thus, individual targets should be established for each patient.

Smoking, blood pressure and plasma lipids have a similar effect on the risk of coronary artery disease and other atherosclerotic disease in diabetic patients as in non-diabetic individuals. However, at every level of a single risk factor and at every combination of risk factors the total cardiovascular risk of a diabetic patient

Table 10   Glucose control assessment levels for Type 2 diabetes[425]

	Good	Borderline	Inadequate
Blood glucose			
Fasting			
mmol . l^{-1}	3·5–5·5	5·6–6·5	> 6·5
(mg . dl^{-1})	(65–100)	(101–120)	> 120
Post-prandial (peak)			
mmol . l^{-1}	5·5–7·0	7·1–9·0	> 9·0
(mg . dl^{-1})	(100–125)	(126–160)	> 160
Plasma glucose			
Fasting			
mmol . l^{-1}	4·0–6·0	6·1–7·5	> 7·5
(mg . dl^{-1})	(70–110)	(111–135)	> 135
Post-prandial (peak)			
mmol . l^{-1}	6·0–8·0	8·1–10·0	> 10·0
(mg . dl^{-1})	(110–145)	(146–180)	> 180
HbA$_{1C}$ (DCCT standardized)			
% Hb	< 6·5	6·6–7·5	> 7·5

*No blood glucose value < 3·5 mmol . l^{-1} (65 mg . dl^{-1}) or plasma glucose value < 4·0 mmol . l^{-1}
(70 mg . dl^{-1}) at any time for insulin or sulphonylurea users to avoid serious hypoglycaemia.

is much higher than the risk of a non-diabetic person of the same age and sex. Therefore, in addition to good glucose control in diabetic patients the risk factor goals have to be more ambitious than in non-diabetic individuals. For blood pressure lowering in diabetic patients < 130/85 mmHg is the primary goal, and an even lower goal is desirable in the presence of nephropathy. For patients with isolated systolic hypertension of > 180 mmHg, usually elderly patients with Type 2 diabetes, the primary goal is a systolic blood pressure < 160 mmHg[424]. For those with a systolic pressure of 160–179 mmHg, the primary goal is a reduction of 20 mmHg. If these goals are achieved and well tolerated, further blood pressure lowering to 140 mmHg may be appropriate. Elevated triglycerides and low HDL-cholesterol are important markers of excess risk in patients with Type 2 diabetes but so far no trial evidence is available on the eect of correcting these aspects of diabetic dyslipdiaemia on the risk of atherosclerotic disease. With regard to LDL cholesterol, the minimum goal for diabetic patients with coronary artery disease is an LDL-cholesterol < 3·0 mmol . l^{-1} (115 mg . dl^{-1}). The American Diabetes Association has recently recommended that for diabetic patients with coronary artery disease or other atherosclerotic disease the LDL goal should be < 2·60 mmol . l^{-1} (100 mg . dl^{-1})[426]. For diabetic patients without coronary artery disease or other atherosclerotic disease who are at high coronary artery disease risk the minimun goal is an LDL-cholesterol < 3·0 mmol . l^{-1} (115 mg . dl^{-1}). If these goals are not reached with professional dietary therapy, cholesterol-lowering drug therapy is recommended.

The precursor stage of Type 2 diabetes, impaired glucose tolerance is already associated with an increased risk of coronary artery disease and other atherosclerotic disease. Therefore, if impaired glucose tolerance has been diagnosed, particularly in a person who has a family history of Type 2 diabetes, it is prudent to start diet therapy and weight reduction, as well as to increase physical activity, with the aim of improving glucose tolerance. Correction of other cardiovascular risk factors is equally important for such persons as it is for patients with clinically manifest Type 2 diabetes.

Other prophylactic drug therapy

In patients with coronary heart disease the following drugs, or classes of drugs, have been shown in single trials or meta-analyses to reduce total mortality. Therefore, in addition to the use of drugs which may be needed to control symptoms, manage blood pressure, lipids and glucose, the following should also be considered.

• Aspirin[321,427], (at least 75 mg) or other platelet modifying drugs, in virtually all patients with coronary heart disease or other atherosclerotic disease. The meta-analysis of antiplatelet trials following myoardial infarction provides convincing evidence of a significant reduction in all-cause mortality, vascular mortality, non-fatal reinfarction of the myocardium and non-fatal stroke. In the trials which used aspirin, the most widely tested doses ranged between 75 and 325 mg per day. There was no evidence of any greater clinical benefit for doses of 160–325 mg compared to 75 mg daily. Nor was any other antiplatelet regimen in this overview more eective than daily aspirin in this dose range. Side eects from aspirin use, principally gastrointestinal bleeding and peptic ulceration, are lowest in those using 75 mg or less daily. Therefore, for secondary coronary heart disease prevention a maintenance dose of 75 mg of aspirin is recommended for all patients following myocardial infarction and those with other clinical manifestations of coronary artery disease: unstable angina and stable angina. 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. When aspirin cannot be tolerated alternative antiplatelet therapies should be considered. For patients with stroke or transient ischaemic attacks aspirin at a dose of at least 75 mg daily is recommended and should also be considered for other high risk patients with peripheral arterial disease.

- Beta-blockers[428] in patients following acute myocardial infarction. In a meta-analysis of beta-blockers following myocardial infarction there was evidence of a significant reduction in all-cause mortality, and in particular sudden cardiac death, as well as non-fatal reinfarction. This clinical benefit was greatest in those patients with left ventricular dysfunction, or supraventricular or ventricular tachyarrhythmias. Therefore, a beta-blocker should be considered in patients with no contraindications following myocardial infarction, and particularly for patients at high risk because of mechanical or electrical complications. When a beta-blocker is contraindicated, verapamil, a non-dihydropyridine calcium antagonist may be considered, because there is trial evidence to indicate that this drug can reduce the risk of reinfarction and cardiovascular death[429].
- ACE inhibitors[430–439] in selected patients following acute myocardial infarction. ACE inhibitors in patients with symptoms or signs of heart failure at the time of acute myocardial infarction, those with a large myocardial infarction and in those with chronic left ventricular systolic dysfunction, will significantly reduce all-cause mortality and the risk of progressing to persistent heart failure. In the absence of clinical heart failure an assessment of left ventricular function by echocardiography is required. Patients following myocardial infarction with an estimated ejection fraction <40% would be eligible for treatment with an ACE inhibitor.
- Anticoagulation[440] following myocardial infarction for selected patients at increased risk of thromboembolic events, including patients with large anterior myocardial infarction, left ventricular aneurysm or thrombus, paroxysmal tachyarrhythmias, chronic heart failure and those with a history of thromboembolic events.

In high-risk individuals, such as treated hypertensive patients whose blood pressure is well controlled[293] and men at particularly high coronary heart disease risk[322], aspirin (75 mg) should be considered.

CLINICAL IMPLEMENTATION

Clinical opportunities for coronary prevention

Physicians are in an ideal position to encourage healthy lifestyle changes in a large section of the community. A majority of people visit their doctor once a year and research has shown that doctors are considered by society to be a credible and important source of information about the causes of coronary heart disease and other atherosclerotic disease, and how these diseases can be prevented. Some doctors view health promotion and disease prevention as an integral part of their role and many patients would like their physicians to advise them on lifestyle change. Starting with patients with established coronary heart disease, and other atherosclerotic disease, physicians can facilitate all aspects of secondary prevention and rehabilitation[441–444] and this will inevitably lead to contact with family members who may themselves be at high risk. Specialists in hypertension, lipids and diabetes have the same opportunity to take a multifactorial approach and address all risk factors. This will ensure that whichever risk factor is identified in a patient the risk factor intervention will be multifactorial and not just treating blood pressure alone, or blood lipids alone or only aiming for glucose control in diabetes. Other specialists such as neurologists managing patients with cerebral ischaemia or those looking after patients with peripheral arterial disease or renal disease, also have the same opportunity to broaden their assessment and management of these patients to reduce the risk of coronary heart disease and its complications. Opportunistic screening of all patients met in connection with ordinary clinical practice, whatever the reason for seeking medical advice, will yield yet more high risk individuals for primary prevention.

In other words, the opportunities for physicians to take preventive action in relation to coronary heart disease, or other atherosclerotic diseases, in current clinical practice are already considerable and yet this potential is not being realized. Even in patients with established coronary heart disease risk factor recording in medical records is incomplete and management of risk factors such as obesity, blood pressure or blood lipids is inadequate when compared to the standards set by professional guidelines[45,445]. For many patients with hypertension, or dyslipidaemia or diabetes, who are being managed with drug therapies, risk factor goals are not being reached. Physicians do not in their daily clinical practice routinely screen for cardiovascular risk factors, other than blood pressure, and even when they do so appropriate follow-up and action does not always occur. Physicians report that it is difficult to practice preventive medicine in routine clinical practice and several barriers have been described at the patient, doctor, healthcare organisation and community or society levels to explain this.

Patient level. Patients are sometimes not motivated to change, although lack of knowledge, lack of access to care and cultural factors might influence such attitudes. Whereas compliance and adherence to lifestyle modifications and drug therapies will never be perfect, their maximisation is clearly important if any risk factor reduction programme is to be effective.

Physician level. Primary care physicians and cardiologists are often more motivated in acute than preventive care because of the immediate gratification from a patient's improvement or better reimbursement for acute care services. Physicians have acknowledged limitations in training, skills and experience that prevent treatment approaches specifically for risk factor reduction. Patients, even if treated, may not reach recommended goals because of a variety of factors: patient non-compliance, inappropriate drugs, too low a dose of drug and severity of elevated levels of risk factors and possible lack of conviction from incomplete knowledge.

Organisational level. The interface between hospital and primary care and/or specialist and generalist communication is another area where preventive care is easily disrupted. Sometimes patients are discharged from the hospital without specific risk factor management recommendations, on the specialist's assumption that the generalist will address the problem. Such practice may imply for the generalist that these instructions are not important. Patients are not followed up systematically after hospitalization since hospital sta often do not interact with patients and their primary care providers after hospital discharge. Also, surveys of physicians have suggested that the prescription practices of internists and family practitioners di er from those of cardiologists regarding drug therapy after acute myocardial infarction, because the former are less aware of, or less certain about, key advances in the secondary prevention of coronary heart disease[46]. Also the lack of clear, national or local guidelines for preventive action confuse specialists and generalists alike.

Community level. The lack of reimbursement for both risk factor management, and specifically for drug therapies, is a shared barrier to providing such care by hospital and primary care physicians despite e cacy of these interventions exceeding that of other treatments with full reimbursement but marginal e cacy. Also the lack of clinical standards (based on performance surveys and identification of barriers) make justification of additional cost of preventive care di cult.

Physicians are in a powerful position to address many of these barriers but only if they consider preventive cardiology to be an integral and important part of a comprehensive cardiology service, both in hospital and the community. Physicians can motivate their patients to make lifestyle changes and comply with drug therapies. Physicians can address their own education and training and can encourage such discussions amongst other health professionals who contribute to coronary heart disease prevention. Physicians can also tackle the organisational barriers to e ective risk factor management which exist within hospitals, and between hospitals and the community. Physicians also have a political voice and can put prevention of coronary heart disease and other atherosclerotic diseases on the national agenda and argue for real resources for preventive cardiology.

Preventive cardiology

The organization of preventive care for coronary patients, high risk individuals and their families will di er from one European country to another, reflecting the wide diversity of medical provision, social, economic and political factors. Therefore, it would not be appropriate to define preventive cardiology as a single model of care but rather the common principles which di ering models of care should embrace. The implementation of current scientific knowledge, embodied in the recommendations of this document, depends on the organisation of care, appropriate to a particular medical setting, which can deliver e ective risk factor management over the long term.

So much of our scientific knowledge comes from randomized controlled trials which are in themselves models of care. Such care is driven by protocol and patients are usually seen by specialists, and at frequent intervals to ensure continuity of management. Compliance with therapy is carefully monitored, and those who do not attend, for whatever reason, are followed up. And this high standard of care is usually maintained over several years in the course of a clinical trial. So the result achieved in the active treatment group is not just a function of the drug used but also the context in which it was prescribed and monitored. When translating a trial result into daily clinical practice simply prescribing the drug is often not enough. It is also necessary to provide a model of care which emulates the care provided in the clinical trial. The principles of such care will be described for three clinical areas: (i) Secondary prevention and rehabilitation for patients with coronary heart disease or other atherosclerotic disease; (ii) Early detection of asymptomatic arterial disease in the general population; (iii) Screening for risk of developing coronary heart disease or other atherosclerotic disease in the healthy population.

Secondary prevention

Principles of cardiac prevention and rehabilitation

Objective
The overall objective in patients who present with symptoms of coronary heart disease — stable angina, unstable angina or acute myocardial infarction — is to slow the progression of atherosclerotic coronary artery disease, and if possible induce disease regression, and reduce the risk of superimposed thrombotic complications.

In this way the risks of a further non-fatal event, or death from coronary heart disease, will be reduced and the chances of survival improved. In addition to favourably influencing the underlying causes of the disease it is also important to help create the best physical, mental and social conditions so that patients

can lead as full and active a life as possible in society. For the patient this means a better quality of life and a longer life expectancy.

Traditionally, cardiac rehabilitation has focused on supervized exercise sessions but this has gradually evolved into comprehensive lifestyle programmes — smoking cessation, healthy food choices as well as increased physical activity — based on behavioural models of change[447]. Risk factor management in terms of controlling blood pressure, lipids and diabetes, and the use of prophylactic drug therapies such as aspirin, is also now an integral part of this approach[448]. And finally, the psychosocial and vocational support required to help patients lead as full a life as possible is also provided. This evolution in cardiac rehabilitation is reflected in the World Health Organizations most recent definition[441]:

'The rehabilitation of cardiac patients is the sum of activities required to influence favourably the underlying cause of the disease, as well as the best possible physical, mental and social conditions, so that they may, by their own e orts preserve or resume when lost, as normal a place as possible in the community. Rehabilitation cannot be regarded as an isolated form of therapy but must be integrated with the whole treatment of which it forms only one facet'.

So a central feature of the modern cardiac prevention programme is now comprehensive lifestyle change for the patient — stopping smoking, making healthier food choices and increasing physical activity — and this should also involve the patients family, household and workplace. To make these desirable lifestyle changes successfully, and sustain them over a lifetime, the social context in which patients place themselves must also be conducive to this healthy way of living. If the whole household is non-smoking and everybody makes the same healthy food choices and becomes physically active then the chances of the patient doing so are greatly increased, and any changes made are more likely to be permanent. The more e ective such lifestyle changes are the less requirement there will be for drug treatment of blood pressure, blood lipids and diabetes. The patients quality of life can also improve.

Success in making these lifestyle changes is important. The traditional educational approach, based simply on giving out information, was not e ective for many patients. Patients are central to this process and must take personal responsibility if they are to make any progress. Taking charge of one's own life and seeking out knowledge and skills which will help one to make the necessary changes to reduce the risk of coronary disease, is much more likely to be successful than playing a passive role[449]. Whilst the psychology of behavioural change is constantly evolving, and therefore the model described in these recommendations may also change in the future, the principle of a behavioural model will always be central to a cardiac prevention programme.

So the scope of cardiac rehabilitation is evolving and it is also beginning to embrace a broader group of patients with coronary disease. Initially, rehabilitation was restricted to patients recovering from a myocardial infarction and then those who had had coronary artery surgery (and other forms of cardiac surgery such as valve replacement). Now with the emphasis on favourably influencing the underlying causes of the disease patients presenting with angina, both stable and unstable, are being included in cardiac prevention and rehabilitation programmes after their initial medical or surgical management. This is entirely appropriate because such patients are at high risk of having a myocardial infarction, with all its potential complications including death. By addressing lifestyle and risk factor management in these patients, including the use of prophylactic drug therapies, the risk of myocardial infarction and coronary death will be reduced. In the disease's natural history this is particularly important because prevention of myocardial damage, and preserving ventricular function, will improve the patient's prospects of being able to lead a full life again. This is in contrast to those who progress from angina to myocardial infarction which can for some, depending on the size of infarction, render them severely disabled with breathlesness and heart failure. At such a stage cardiac prevention and rehabilitation has less to o er and thus targeting symptomatic patients before they have infarcted is much more likely to be beneficial.

As cardiac rehabilitation has evolved in the scope of its activities, and the types of patients recruited, so the need for a multidisciplinary team of healthcare professionals has been created which now embraces cardiology, nursing, dietetics, physiotherapy, occupational therapy, pharmacy, health promotion, psychology and behavioural medicine. All of these professions and disciplines have an important contribution to make to a comprehensive cardiac prevention programme.

Whilst rehabilitation programmes have traditionally been hospital based the need to roll out the programme into the community is now widely recognised[450]. This is to try and ensure that lifestyle changes are sustained and to provide continuity of risk factor management, including long-term compliance with drug treatments. Hospital remains an appropriate starting point for cardiac prevention and rehabilitation because most patients presenting with coronary disease do so through accident and emergency departments or to cardiology outpatients. Those who are seen in physicians' o ces are often referred to a hospital facility for further investigation such as coronary arteriography. So most cardiac prevention programmes are initially hospital based and this has several advantages. First, all the health professionals required for a multidisciplinary programme are also based in a hospital and with all of the resources they need on the same site e.g. an area for individual and family counselling, group work including health promotion and supervized exercise sessions. Second, the hospital programme becomes an integral part of the patient's medical assessment and management by the cardiology service. Whilst the cardiologist assesses the patient's symptoms, coronary anatomy and ventricular function, and how these are to be managed

medically and surgically, the patient's lifestyle and other coronary risk factors can also be addressed in the same setting. Third, the organisation of individual and group sessions for education, health promotion and so on is much easier for both patients and staff alike when centred on a hospital facility. So for all of these reasons a hospital focus is an appropriate and convenient starting point. However, for the programme to end there would certainly limit its impact, particularly in relation to achieving lifelong changes. So integration of the hospital programme with services in the community is essential to ensure continuity of care by physicians and other health professionals over the long term. Also by leaving the hospital environment behind the patient has a much better chance of leading as normal a life as possible in the community. Some rehabilitation programmes are entirely community based but these are disadvantaged by being divorced from the physician and service responsible for the patient's cardiac care; the role of the cardiologist is central to the patient's overall management which should be fully integrated with all aspects of cardiac prevention and rehabilitation.

Patients

Patients who develop symptoms of coronary heart disease for the first time, at any age, should be able to address all aspects of cardiac prevention and rehabilitation according to their individual needs. Patients with the following clinical manifestations of coronary heart disease should therefore all be eligible for cardiac prevention:

• Stable angina pectoris
• Acute ischaemic syndromes
  Unstable angina
  Non-Q wave myocardial infarction
  Q wave myocardial infarction

The patient's characteristics will determine timing and content of a coronary prevention programme which should always be tailored to the individual. The needs of a man presenting in his 40s with angina, and who is awaiting angioplasty, will be different to those of a woman in her 60s with compromised ventricular function following a large anterior infarction, and different again to a patient in their early 80s with a small non-Q wave myocardial infarction who is still leading an independent existence. Common to every patient's programme is reducing the risk of disease progression and its complications. How to achieve this will depend on individual circumstances.

   The timing of revascularization, and the form this takes, will also have a bearing on the programme. For some patients presentation with unstable angina may quickly lead to angioplasty and stenting, or even to emergency coronary artery surgery. Others may have revascularization electively some weeks, months or even years after their first symptomatic presentation. Wherever possible every effort should be made to

modify lifestyle, and other risk factors such as blood pressure and lipids, before revascularization. Patients who have stopped smoking, achieved their optimal weight and become physically fitter with lower blood pressure and lipid levels are less likely to suffer perioperative complications of cardiac surgery, and to survive any that do occur. Whether this is also true for angioplasty is not known but, a priori, there is every justification for making the same efforts to modify patients risk factors before they have this procedure. Following open heart surgery the physical aspects of rehabilitation will necessarily receive greater emphasis, at least for the first few weeks, but this must not be at the expense of other aspects of lifestyle and risk factor management.

Content of a cardiac prevention and rehabilitation programme

Whilst the organization of a cardiac rehabilitation and prevention and rehabilitation programme will inevitably vary between different medical settings in Europe it is possible to define the main components which should be common to such programmes as follows:

• Lifestyle and cardiovascular risk assessment.
  Assessment of smoking, dietary habits and physical activity, together with risk factors such as blood pressure and lipids is essential to shape the programme to individual needs.
• Educational
  Patients and their families are informed about the disease, its causes and how these can be modified, the use of medical and surgical treatments, and cardiopulmonary resuscitation.
• Behavioural
  Using Prochaska and DiClemente's 'stages of change' model, there are three main stages that the physician needs to work through with patients[387,388]. These include preparing and advising the patient to change (the preparation stage), assisting the patient to change (the action stage), and providing the patient with follow-up (the maintenance stage). There is no fixed period required to progress through the stages. While some patients may progress with ease, others may need to be monitored closely during each stage, and others will need to return to an earlier stage after set-backs or relapses. It is important that doctors discuss and negotiate with their patients how best to achieve change. Information needs to be tailored to the patient's needs and level of understanding. Such information should be clear, concrete, and specific. Technical terms should be avoided and, where possible, verbal advice should be supplemented with written or audiovisual materials.
• Health promotion
  Promotion of a healthy lifestyle — avoidance of tobacco[451], making healthy food choices and becoming physically active — is central to the programme.

- Family based intervention
  To achieve and sustain these lifestyle changes involvement of the patients partner and other family members sharing the same household may help[451–456]. The patient is more likely to quit smoking if the partner is a non-smoker and the whole household is tobacco free. Dietary changes are more likely to occur if the person responsible for shopping and cooking is involved in the programme and the whole family makes these changes together. Similarly, for the patient to become more physically active the role of the family in supporting leisure time exercise can also be helpful. The partner and other family members also have to make psychological adjustments to the patients disease. Sexual relationships between patient and partner is a sensitive and important issue which needs to be addressed. By including the partner in the programme it is possible for the whole family to come to terms with the illness and then together take the necessary steps to reduce the risk of recurrent disease.
- Risk factor management
  Risk factor monitoring of weight, blood pressure, lipids and blood glucose is required. Setting risk factor goals is important. Maximising lifestyle changes and, where appropriate, using drug therapies in order to achieve goals is also necessary.
- Drug therapies and compliance
  Drugs will be required in some patients to control blood pressure, lipids and blood glucose. In addition some drugs, such as aspirin, are given prophylactically. When a drug is prescribed it is important to ensure, wherever possible, that doses shown to be beneficial in the trials are also used in clinical practice and compliance is sustained over the long term[457].
- Psychology
  The emotional responses to the development of coronary heart disease and how these can be addressed is essential if the patient is to be able to take the necessary steps through lifestyle changes to reduce the risk of recurrent disease. Stress management and relaxation will be part of this process.
- Screening of first degree blood relatives
  Patients with premature coronary heart disease, men under 55 years and women under 65 years, should have their immediate blood relatives screened for cardiovascular risk factors: parents (if appropriate), siblings and o spring. For patient's children, screening of blood pressure, lipids and glucose can be deferred until their early teens unless familial hypercholesterolaemia is suspected.
- Vocational
  Professional advice and help in making the necessary preparations to return to work, or seek alternative work, is important if the patient is to resume as full a role in society as they would wish. Licensing implications for driving will also have to be considered.
- Quality assurance
  Whatever the content of a cardiac prevention programme, and inevitably this will be dictated to some extent by available skills and resources — sta ,

accommodation, funding and so on — it is essential to evaluate the process and outcome of care. Only in auditing for example, the characteristics of patients who take up and adhere to the programme compared to those who do not, or the knowledge base which informs healthy food choices, or the levels of blood pressure, cholesterol, etc, achieved by the end of the hospital phase of the programme, will it be possible to evolve a programme, based on practical experience, which achieves its stated objectives.

Resources

The following resources will be required for a cardiac prevention and rehabilitation programme and some of these will already be available in the institution where the initial hospital phase is based.

Staff
Physicians. Cardiologists and other physicians in hospital, and then in the community, have a central role to play in a cardiac prevention programme because they have a unique professional relationship with the patient and are ultimately responsible for all aspects of their care. By giving leadership to the organization of a cardiac prevention and rehabilitation programme cardiologists will ensure this becomes an integral part of the whole cardiology service, of which patients are more likely to avail themselves. The cardiologist is then not only recommending treatments to relieve symptoms and modify the anatomy of the disease but also emphasizing the importance of addressing lifestyle and other risk factors. Cardiologists may not actually direct the programme, and relatively few are actively involved in cardiac rehabilitation, but their role is crucial to a programme's success within an institution. Physicians in the community also have a central role to play in the continuing care of patients, beyond the hospital based programme.

Nurses. Specially trained cardiac nurses also have a role to play in the organization of a cardiac prevention programme. They can recruit patients, organize lifestyle assessments, risk factor screening, health promotion sessions and so on. Training in models of behavioural change, health promotion, and psychosomatic aspects of the disease is essential for these nurses, together with other skills which are not usually taught as part of conventional cardiac nurse training.

Dieticians. Diet is an important part of the patient's management and professional advice, from a qualified nutritionist or dietician, is desirable if real dietary changes are to be achieved. Diet is a complex subject and one in which most doctors and nurses have received no formal training. Dietary habits are also very di erent across Europe. Although the common objective is to reduce saturated fat how this is achieved will vary from one country to another. Where professional dietary support is not available the training of medical and

nursing sta   in key aspects of nutrition and the use of well written educational materials assumes even greater importance.

Physiotherapists. Supervised exercise is also an important part of the patients management, and assumes particular importance in the rehabilitation of post surgical patients. Physiotherapists are usually responsible for this aspect of the programme.

Pharmacists. Pharmacists have an educational role in relation to the use of drugs, their clinical indications, mode of action, side e ects and benefits. By informing patients in this way the prospects of long term compliance with drug therapies is more likely.

Psychologists. A psychologist, psychiatrist or mental health worker can inform a programme about how to address the psychological consequences of developing coronary heart disease, such as anxiety and depression. These can have a profound impact on the patient's quality of life and also make it more di cult to achieve other goals in the programme such as smoking cessation, weight loss and so on. By helping patients to understand and manage these emotions will increase their motivation to make and sustain appropriate lifestyle changes, as well as returning to a full and active role in the community.

Occupational medicine. Vocational support may be required by some patients to help them return to work or find more suitable alternative employment.

Facilities

O ce space for sta , an area for individual and family lifestyle and risk factor assessment, including the necessary privacy for counselling, and an area for group activities including education and health promotion sessions and supervised physical activity.

Early detection of arterial disease in the healthy population

As sudden cardiac collapse and death is, for many individuals, the first manifestation of coronary heart disease the impetus to detect coronary heart disease earlier in its natural history — the asymptomatic phase — is considerable. Indeed death is not the only impetus for such disease screening programmes. Some who survive their first symptomatic presentation may be rendered so disabled by a myocardial infarction that secondary prevention and rehabilitation has little to o er.

Principles of screening for asymptomatic disease

Objective
The objective of a coronary heart disease detection programme is to identify those apparently healthy indi-

viduals in the general population who have asymptomatic atherosclerotic disease in order to slow the progression of atherosclerotic disease, and if possible induce regression, and also reduce the risk of superimposed thrombotic complications. In this way the risk of a first nonfatal or fatal cardiac ischaemic event can be postponed or even prevented.

The medical technology to detect atherosclerotic arterial disease, and its clinical sequelae, is already available but its role in population screening has yet to be evaluated.

A screening test for coronary heart disease has to meet a number of criteria before it is used in the general population. These criteria include:

(1) The non-invasive technique for detecting coronary heart disease is valid, precise, easy, acceptable and cost e ective
(2) The relationship between coronary heart disease detected non-invasively and the development of symptomatic disease e.g. angina, or myocardial infarction or coronary death has been quantified
(3) There is a defined screening strategy and a defined intervention and follow-up policy
(4) Trained sta   and facilities for screening and intervention are available
(5) Screening and intervention results in a reduction in clinical events: coronary morbidity and mortality
(6) Screening has no adverse e ects
(7) Cost of screening and intervention is justified in relation to the outcome.

From the point of view of the individual who agrees to have a screening test for coronary heart disease there are three questions: (1) Will I feel any better? (2) Will my risk of developing symptomatic disease and its complications be reduced? and (3) Will I live longer? In other words will the individuals quality and quantity of life both be improved.

For coronary heart disease, magnetic resonance is able to detect and quantify proximal epicardial disease, and ultrafast CT scanning uses coronary calcification as a surrogate for coronary atheroma[458]. The consequences of coronary atheroma for the myocardium can also be objectively assessed non-invasively using a variety of techniques from radionuclide scintigraphy for myocardial perfusion defects and reversible ischaemia on exercise, through to bicycle ergometry and treadmill exercise ECG testing. However, most are surrogate measures for coronary atheroma and its sequelae and each has its limitations as a sensitive and specific test for the diagnosis of coronary heart disease in an asymptomatic individual.

Population-based autopsy studies have shown a correlation between the severity of atherosclerosis in one arterial territory and involvement of other arteries[459]. This has led to an exploration of the possibilities of detecting early atherosclerotic lesions in leg or carotid arteries, which are more easily accessible for non-invasive examination than coronary arteries, to identify healthy individuals with asymptomatic atherosclerosis

who are at increased risk of developing the clinical manifestations of atherosclerotic disease.

Asymptomatic atherosclerotic disease of the leg arteries detected by non-invasive techniques — segmental blood pressure measurements (ankle brachial pressure index) or determination of tibial artery blood flow velocity by Doppler ultrasound — is associated with an increased risk of non-fatal and cardiovascular events and to have incremental predictive value when used in combination with conventional risk factors[460,461].

Ultrasonographic evaluation of carotid artery intima-media thickness has in recent years become a popular method in clinical and epidemiological atherosclerosis research. In cross-sectional studies, carotid artery intima-media thickness has been shown to have the expected associations with cardiovascular risk factors and prevalent coronary heart disease or other clinical manifestations of atherosclerotic disease[462–464]. Studies correlating carotid intima-media thickness with the severity of coronary atherosclerosis assessed by coronary arteriography have given conflicting results, ranging from poor to rather good correlations[465–468]. Importantly, prospective studies have shown that in asymptomatic individuals carotid intima-media thickness is related to the risk of coronary death and incidence of coronary heart disease events, even after adjustment for cardiovascular risk factors[469,470]. Furthermore, several trials of cholesterol lowering with statin treatment using change of carotid intima-media thickening as an end-point have shown that this treatment retards the progression of intima-media thickening[468,471–474].

At present non-invasive methods for the detection of asymptomatic coronary artery or other atherosclerotic disease look promising, but more research is needed to evaluate their incremental value over and above conventional risk factor measurements in the assessment of absolute risk of developing coronary heart disease in healthy people. Randomized controlled trials are also required to evaluate the impact of a non-invasive screening and intervention programme for coronary artery or other atherosclerotic disease on subsequent morbidity and mortality.

Screening for risk of developing coronary heart disease, or other atherosclerotic disease, in the healthy population

Screening the healthy population for risk of developing coronary heart disease (or other atherosclerotic disease) is necessary in order to identify and target high risk individuals for lifestyle and, where appropriate, therapeutic interventions.

Objective
The overall objective of a cardiovascular screening programme is therefore to detect and treat high risk individuals in order to reduce the risk of a first non-fatal or fatal ischaemic event.

Principles of screening for risk of developing disease

Centrally organized mass screening of the whole population is not required as there are other ways through existing medical services to identify and treat such high risk individuals. Screening for risk factors can only be justified if the criteria already defined for early disease detection are met. These can be summarized as follows:

(1) There is a defined screening and intervention strategy
(2) The interventions have been shown to reduce the risk of clinical events: coronary morbidity and mortality
(3) Cost of screening and intervention is justified in relation to the outcome.

The compelling scientific evidence for unifactorial interventions summarized earlier in this document in relation to smoking, blood pressure, blood lipids and so on has laid the foundations for multifactorial screening and intervention programmes. However, the model of care must be able to bring about risk factor changes comparable to those achieved in the unifactorial trials for each risk factor, and if this is achieved there will inevitably be a reduction in clinical disease.

Screening can be undertaken systematically by inviting sections of the population, for example all middle-aged adults living in one community. Or it can be o ered opportunistically to a person who makes contact, for whatever reason, with any point of the medical system. Such an opportunity can be used to assess and act on cardiovascular risk factors, but this approach should not be seen as a simple, alternative approach to systematic screening. Whether undertaken systematically or opportunistically the act of screening implies a commitment by the health professional to give lifestyle advice, make follow-up measurements, and undertake appropriate investigations such as laboratory tests. So a decision to screen, even opportunistically, can only be justified if all the appropriate arrangements, including interventions, follow-up and referral for specialist advice, wherever necessary, are all in place.

The advantages of screening for high risk individuals are several. First, it focuses interventions which are appropriate to the individual. Second, it avoids unnecessary medical action being taken in those who are at 'low risk' as defined within a given population. However, a 'low risk individual' in a population which is at high overall risk for coronary heart disease may actually be at much greater risk than all individuals in a low risk population. Third, this approach is consistent with the medical model of care between a patient and a doctor. In this way the risk factor blood pressure, which is continuously distributed in the population, becomes

the disease called hypertension (which only some people have) and for which the doctor can then legitimately o er treatment. Finally, the benefit to risk ratio improves where the benefits of an intervention in high risk individuals are larger. By the same token it is a cost e ective use of medical resources.

However, there are also several limitations to this approach. Firstly, it represents a medicalization of prevention where the person becomes a patient. Second, screening is only palliative in that it seeks to ameliorate the consequences of being at high risk but does not address the determinants of high risk in the population. Third, the strategy is also limited in its success by the context in which it occurs. For example, a change in diet is possible as a result of screening and intervention but sustaining such changes may not be possible in a society which does not share the same healthy food choices. So as this model of care is weak there is a natural tendency for the high risk individual to revert to a lifestyle which pertained before being screened. Finally, the predictive power from screening tests for an individual is low. Although a person maybe classified as high risk only a minority in that risk category will actually develop the disease within a foreseeable future.

Which individuals to screen

All adults are potentially eligible for cardiovascular screening but the uniform application of screening tests for every adult would be inappropriate. In younger adults, under the age of 40 years, some aspects of lifestyle are particularly important: smoking, obesity, sedentary existence, alcohol consumption and for women the use of the oral contraceptive pill and its potential cardiovascular complications. Lifestyle counselling maybe all that is required at this age although a small minority will have hypertension or dyslipidaemia or diabetes. Whilst lifestyle continues to be important in the middle (40–69 years) of life the physiological and metabolic consequences, in terms of hypertension, dyslipidaemia and diabetes, will now be more common and an increasing proportion of this section of the population will therefore have individually high risk factors and a multifactorial coronary heart disease risk of $\geq 20\%$ over 10 years to justify intensive lifestyle and, where necessary, therapeutic interventions. For women a premature menopause, whether natural or surgically induced (and particularly if the latter is associated with removal of the ovaries) increases the risk of premature coronary heart disease, and so particular attention to lifestyle and other cardiovascular risk factors is important. In the older population (≥ 70 years) the largest proportion of high risk individuals will be found and systolic hypertension will be a particularly common problem. However, there is also significant co-morbidity in this group and so clinical judgement is required about whether to actually screen for cardiovascular risk factors. Many of these individuals will be at a higher absolute coronary heart disease risk than any other

section of the population and therefore are potentially more likely to benefit from risk factor reductions, particularly for systolic blood pressure, but also cholesterol. However, evidence for some risk factor interventions, particularly in the very elderly is not available and judgement is again required on what action, if any, to take.

So inevitably, screening for multifactorial risk is going to be concentrated in individuals in the middle years of life where risk factors are common and where the evidence of benefit from interventions is most secure.

Content of a cardiovascular screening and intervention programme

Whilst the organization of a cardiovascular screening programme will inevitably vary between di erent medical settings in Europe it is possible to define the main contents common to such programmes as follows:

- Lifestyle and cardiovascular risk assessment
- Behavioural change
- Educational
- Family based intervention
- Risk factor management
- Screening of first degree blood relatives

All of these subjects have been covered in the section on Management of Risk.

Evaluation of the process and outcome of lifestyle and risk factor management is essential in order to inform the physician, and the other health professionals involved, on how successful the intervention has been and how it can be improved.

Resources

Staff

The physician will be the commonest point of contact when an individual seeks advice, for whatever reason, from the medical services. So for opportunistic screening physicians — cardiologists, internal medicine, other specialities or general practice — are the key. Indeed they may take sole responsibility for all aspects of cardiovascular screening and intervention including long term follow up, whilst others may delegate this responsibility to specially trained nurses or other health professionals. However, a physician is in a powerful position to address all aspects of lifestyle and can do so with an authority which other health professionals may not enjoy to the same extent. This authority is based on the doctor/patient relationship which can become a powerful tool for change as evidenced by the impact of physician advice on smoking. Further, the physician must ultimately take responsibility for prescribing drug therapies, monitoring their e ects and ensuring long term compliance. So it is better if the physician is

coordinating all aspects of care, which may also include appropriate professional support from nurses, dieticians and so on.

Role of professional National Societies in coronary heart disease prevention

These European recommendations on coronary prevention are intended to stimulate the development and revision of national guidelines on coronary heart disease prevention by National Societies of Cardiology, Atherosclerosis and Hypertension, working in collaboration with other professional organizations and groups in every European country.

Whilst the science base which describes the origins of atherosclerosis and its clinical expression is largely common to every country[475] there are important di erences across Europe in political, economic, cultural, social and medical traditions. Therefore, the development of national guidelines on coronary prevention is essential. They will reflect not only the scientific evidence, but importantly, address the practicalities of coronary prevention at a population and a clinical level. National Societies of Cardiology, Atherosclerosis and Hypertension should take the lead in this important professional activity and, wherever appropriate, work in collaboration with other specialties such as cardiac rehabilitation, hypertension, lipids and diabetes as well as primary care physicians, other health professionals and Heart Associations and Foundations. Following the publication of the European Societies recommendations on coronary prevention in 1994 they were reproduced, with appropriate modifications, in a large number of European countries. When a National Society takes responsibility for developing, publishing and disseminating its own guidelines the members of that society are more likely to read and act on them. This is particularly so if national guidelines are then incorporated into the written guidelines of an institution or department or o ce.

A second important role for the National Societies is education and training in preventive cardiology. Physicians receive little or no education in preventive medicine at medical school and preventive cardiology is not an essential requirement in most specialist vocational training programmes for cardiology in Europe. As a consequence physicians are trained to provide acute cardiac care, specialist investigations and treatments but are less well equipped to practice preventive cardiology. Nor is there any professional incentive to train in this area because few specialist appointments in cardiology require a special interest in preventive cardiology. Therefore, there is a need for National Cardiac Societies to raise the need for undergraduate and postgraduate training in the principles of preventive medicine and their practical application to prevention of coronary heart disease and other atherosclerotic diseases.

A third important role is quality assurance of professional practice and evaluating whether the standards of care defined in guidelines are being met in ordinary clinical practice. The British Cardiac Society undertook a national survey of secondary prevention of coronary disease (ASPIRE)[46] and this was subsequently extended to nine other European countries (EUROASPIRE)[45] under the auspices of the European Society of Cardiology. The Swedish Society of Cardiology has set up a national quality assurance programme in secondary prevention of coronary heart disease and a similar initiative has been taken by the Polish Cardiac Society. When national guidelines on coronary prevention are created it is important to evaluate the current state of clinical practice as this will inform the Society of where and how improvements in the delivery of care can be made.

Finally National Cardiology, Atherosclerosis and Hypertension societies should establish a formal professional relationship with Government, Ministries of Health and other governmental organizations for the prevention of coronary heart disease and other atherosclerotic diseases. Medical scientific societies have a responsibility to make professional recommendations based on scientific evidence which are used as a guide to best practice by cardiologists, physicians in hospital and the community and other health professionals. Government representatives and organizations must then form policies to ensure that these recommendations, within the financial resources available to a society, are implemented in practice.

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APPENDIX

These recommendations are the work of the Second Joint Task Force of the European Society of Cardiology (ESC), the European Atherosclerosis Society (EAS), the European Society of Hypertension (ESH), working in collaboration with the International Society of Behavioural Medicine, the European Society of General Practice/Family Medicine, and the European Heart Network. The initiative for this second Task Force came from the ESC, the EAS and the ESH, the societies responsible for the original 1994 Task Force recommendations on coronary prevention (Chairman: Professor K Pyörälä). The new Task Force consisted of a writing group, other invited members and specialists, together with representatives of other societies and organisations as listed below.

Members of the Task Force

Chairman:

D. Wood	United Kingdom

Writing Group:

G. De Backer	Belgium
O. Faergeman	Denmark
I. Graham	Ireland
G. Mancia	Italy
K. Pyörälä	Finland

Members:

I. Bokarew	Russia
F. Cambien	France
R. Cifkova	Czech Republic
H. Gohlke	Germany
F. Gutzwiller	Switzerland
W. Klein	Austria
P. A. Poole-Wilson	United Kingdom
S. Priori	Italy

B. Angelin, Sweden
European Atherosclerosis Society

C. Brotons, Spain
European Society of General Practice/Family Medicine

K. Orth-Gomér, Sweden
International Society of Behavioural Medicine

V. Press, United Kingdom
European Heart Network

P. van Zwieten, Netherlands
European Society of Hypertension

Appendix

Table 1 Food choices for a healthy lipid-lowering diet (adapted and modified from the International Task Force for Prevention of Coronary Heart Disease[475])

1. 'Recommended foods' are generally low in fat and/or high in fibre. These should be used regularly as part of the diet. The exception is vegetable oils and nuts which are recommended because of their favourable fatty acid composition but, because of their high energy content, should be used in moderation.

2. 'Foods for use in moderation' contain unsaturated fats or smaller quantities of saturated fats. As the diet should be low in fat, these foods should be used in moderation.

3. 'Foods only for exceptional use' contain large proportions of saturated or hydrogenated fats and/or cholesterol, or sugar and therefore should be avoided wherever possible.

	Recommended foods	Foods for use in moderation	Foods only for exceptional use
Cereals	Wholegrain bread, wholegrain breakfast cereals, porridge, cereals, whole grain pasta and rice, crispbread, matzo	White pasta and rice	Croissant, brioche
Dairy products	Skimmed milk, very low-fat cheeses, e.g. cottage cheese, fat-free fromage frais or quark, fat-free yoghurt, egg white, egg substitutes	Semi-skimmed milk, fat-reduced and lower fat cheeses e.g. Camembert, Edam, feta, ricotta, low-fat yoghurt. Two whole eggs per week.	Whole milk, condensed milk, cream, imitation milk, full-fat cheeses e.g. Brie, Gouda, full-fat yoghurt
Soups	Consommes, vegetable soups	Thickened soups, cream soups	
Fish	All white and oily fish (grilled, poached, smoked). Avoid skin (e.g. on sardines or whitebait)	Fish fried in suitable oils	Roe, fish fried in unknown or unsuitable oils or fats
Shellfish	Oysters, scallops	Mussels, lobster, scampi, prawns, shrimps, calamari	
Meat	Turkey, chicken, veal, game, rabbit, spring lamb. Very lean beef, ham, bacon, lamb (once or twice a week). Veal or chicken sausage. Liver twice a month	Duck, goose, all visibly fatty meats, usual sausages, salamis, meat pies, pates, poultry skin	
Fats	Polyunsaturated oils e.g. sunflower, corn, walnut, sa ower. Monosaturated oils, (olive oil, rape-seed oil). Soft (unhydrogenated) margarines rich in monounsaturated or polyunsaturated oils, low fat spreads		Butter, suet, lard, dripping, palm oil, hard margarines, hydrogenated fats
Fruit and vegetables	All fresh and frozen vegetables, emphasis on legumes: beans, dried beans, lentils, chick peas, sweetcorn, boiled or jacket potatoes, all fresh or dried fruit, tinned fruit (unsweetened)	Roast or chipped potatoes cooked in permitted oils	Roast or chipped potatoes, vegetables or rice fried in unknown or unsuitable oils or fats, potato crisps, oven chips, salted tinned vegetables
Desserts	Sorbet, jellies, puddings based on skimmed milk, fruit salad, meringue		Ice cream, puddings, dumplings, sauces based on cream or butter
Baked foods		Pastry, biscuits prepared with unsaturated margarine or oils	Commercial pastry, biscuits, commercial pies, snacks and puddings
Confectionery	Turkish delight, nougat, boiled sweets	Marzipan, halva	Chocolate, to ees, fudge, coconut bars, butterscotch
Nuts	Walnuts, almonds, chestnuts	Brazils, cashews, peanuts, pistachios	Coconut, salted nuts
Beverages	Tea, filter or instant co ee, water, calorie free soft drinks	Alcohol, low-fat chocolate drinks	Chocolate drinks, Irish co ee, full fat malted drinks, boiled co ee, ordinary soft drinks
Dressings, flavourings	Pepper, mustard, herbs, spices	Low-fat salad dressings	Added salt, salad dressings, salad cream, mayonnaise