Coronary heart disease (CHD) is the major cause of death in most developed countries and in many developing countries. The clinical complications of CHD lead to substantial disability and are a major source of the rising cost of health care. While CHD incidence is decreasing in western Europe, the United States, and Australia, it is steeply increasing in central and eastern Europe and, to some extent, in Asia and Africa. Worldwide, the need for more effective preventive strategies against CHD has become urgent and cannot be postponed. Much has been learned about preventive policies, both at the population and the individual level, in the past decade. The International Task Force for Prevention of CHD has developed an updated document that takes into account the results of the recent, major, lipid-lowering trials of primary and secondary prevention. Clinical and quantitative approaches are provided to assess the global risk of CHD according to classic and newly recognized risk factors and thereby to assign an appropriate level of intervention against risk factors. This targeted strategy maximizes the use of dietary methods and provides clear indications for drug treatment.

The primary importance of improving health-related behavior in the population as a whole is emphasized. In the present document, the undervalued scope for preventive care at the individual clinical level is the major theme; it is based on the selection and management of persons whose level of risk cannot adequately be reduced by presently available population measures.

Risk Factors for CHD
Age, sex, and personal and family history of cardiovascular disease are nonmodifiable risk factors for CHD. Hypercholesterolemia, hypertension, and cigarette smoking are the major modifiable risk factors. They powerfully influence risk, are common in populations, and are widely amenable to prevention and treatment. Low HDL cholesterol levels are also regarded as an important risk factor for CHD. Other modifiable determinants of risk should be taken into account in the management of CHD, such as diabetes, obesity, and physical inactivity. More recently, evidence has accumulated on a possible association of increased triglycerides, lipoprotein(a), and fibrinogen levels with an increased risk of CHD. Other variables under current investigation include coagulation factor VIIc, homocysteine, and plasminogen activator inhibitor-I. A new area of research for candidate risk factors is now directed to polymorphisms and abnormalities in several genes affecting lipoprotein and glucose metabolism and blood pressure regulation, including apolipoprotein E and the enzymes lipoprotein lipase, glucokinase, and angiotensin-converting enzyme (ACE). Inadequate protection of lipoproteins against oxidation is under current investigation as a further risk factor.

The relationship between nutrition and CHD has now been well established and is mainly based on epidemiological findings in populations and nutritional intervention trials. Stroke is also an important issue in the population at risk for CHD. Patients with CHD often suffer from stroke and vice versa. Because stroke and CHD share several risk factors, strategies aimed at reducing CHD incidence might be expected to also decrease the incidence of cerebrovascular events. There is increasing evidence that both antihypertensive treatment and lipid-lowering therapy with statins, presumably through stabilization of atherosclerotic plaques with a consequent lower frequency of embolism, reduce the
TABLE 1. CHD Risk Categories

Small increase in risk
- Presence of 1 risk factor of moderate degree; eg, in a middle-aged man, plasma total cholesterol of 200 to 300 mg/dL (5.2 to 7.8 mmol/L) with no nonlipid risk factors, OR
- Plasma cholesterol to HDL cholesterol ratio of 4 to 5, OR
- Smoking ~10 cigarettes/d, but no other risk factors, OR
- Quantitative risk estimate in the third quintile of the PROCAM algorithm (CHD event risk ~0.3% per year)

Moderate increase in risk
- Presence of 1 risk factor of severe degree; eg, smoking ~20 cigarettes/d, OR
- Presence of 2 risk factors of moderate degree, eg, a middle-aged man with a plasma cholesterol of 200 to 300 mg/dL (5.2 to 7.8 mmol/L) and HDL cholesterol <40 mg/dL (1 mmol/L) or obesity, OR
- Quantitative risk estimate in the fourth quintile of the PROCAM algorithm (CHD event risk ~0.7% per year)

High risk
- History of myocardial infarction (secondary prevention)
- Atherosclerosis of the coronary, carotid, or peripheral arteries, OR
- Presence of 3 or more moderate risk factors; eg, borderline hypertension (140/90 mm Hg to 160/95 mm Hg) and plasma cholesterol of 200 to 300 mg/dL (5.2 to 7.8 mmol/L) and smoking ~10 cigarettes/d, OR
- Presence of 2 severe risk factors; eg, plasma cholesterol >300 mg/dL (7.8 mmol/L) and smoking 20 cigarettes/d, OR
- Presence of a major genetic hyperlipidemia, eg, familial hypercholesterolemia or type III (remnant) hyperlipidemia, OR
- Presence of type 2 diabetes mellitus, OR
- Quantitative risk estimate in the fifth quintile of the PROCAM algorithm (CHD event risk ~2.3% per year)

*The Prospective Cardiovascular Münster Study (PROCAM, Münster Heart Study) is one of the largest, prospective epidemiological studies of CHD risk factors in Europe. Between 1978 and 1996 ~30 000 individuals at work in northern Germany were recruited and assessed for >30 anthropometric and laboratory parameters. Data from the 8-year follow-up of middle-aged men in PROCAM have been used to generate the CHD risk algorithm referred to in this article; for this reason, the applicability of the algorithm to men outside this age group, to women, or to other geographical regions or ethnic groups has yet to be established.

incidence of stroke. In Western countries, ischemic stroke is much more common than the hemorrhagic variety (~80% versus 20%). Nonmodifiable risk factors for ischemic stroke are age, sex, race, and inherited predisposition. Well-documented modifiable risk factors are hypertension (the single most important cause of stroke), diabetes, cardiac disease, cigarette smoking, overweight, elevated hematocrit, and increased levels of fibrinogen and tissue-type plasminogen activator inhibitor.

Global Risk of CHD

Comprehensive assessment of CHD risk is of primary importance. The concept of “global risk” emphasizes the need to include as many as possible of the known independent risk factors in the evaluation of the patient’s cardiovascular risk profile, with a view to treating each (but particularly hyperlipidemia and hypertension) in the context of overall risk.22–24 Therefore, global risk is important in determining the patient’s prognosis, the choice of appropriate therapy, and the target levels for risk factor reduction (ie, serum cholesterol levels to achieve with a given level of risk). In the context of managing elevated plasma lipid levels, this scheme provides for informed decisions regarding how stringent the diet should be, whether a drug should be used and in what dosage, and whether a drug combination is needed. For these purposes, the patient is assigned to the category of average risk or to 1 of 3 levels of increased risk (Table 1). This may be performed by clinical judgment or quantitatively by means of the algorithms derived from the Framingham Study and the PROCAM Study (Prospective Cardiovascular Münster Study) reported in detail in the full version of this document.25,26 To illustrate this concept of global risk estimation, risk calculation in sample patients in shown in Table 2.

Management of CHD Risk Factors

Hyperlipidemia

Hyperlipidemia can be primary or secondary, or both may be present. Primary hyperlipidemias are classified for clinical purposes as (1) hypercholesterolemia (polygenic or familial); (2) combined (mixed) hyperlipidemia; or (3) hypertriglyceridemia. In cases where hyperlipidemia is secondary to a treatable cause (eg, a side effect of a drug, hypothyroidism, alcohol abuse, or diabetes), this should be dealt with first. Primary hyperlipidemia is treated according to its type and severity, in the context of global risk of CHD. Whenever possible, the physician determines not only total cholesterol but also HDL cholesterol, LDL cholesterol, and triglyceride levels to evaluate the lipid-mediated risk of CHD and to permit a rational choice of drug therapy if required. Diagnosis of hyperlipidemia requires at least 2 consistent analyses.

Hyperlipidemia is managed primarily by conservative measures (correction of overweight, a lipid-lowering diet, and removal of underlying causes); drug treatment is instituted only if conservative measures fail to achieve the lipid target value. The decision for lipid-lowering drug therapy should be based on trial data wherever possible. Five major, lipid-lowering trials with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) have been completed in recent years, and they form the basis of current recommendations. The results of these trials, the Scandinavian Simvastatin Survival Study (4S),27 the West of Scotland Coronary Pre-
TABLE 2. Calculation of Global Risk by Using the Algorithm Derived From the Münster Heart Study (PROCAM)

<table>
<thead>
<tr>
<th>Multiple risk factors, elevated LDL cholesterol (180 mg/dL [4.7 mmol/L])</th>
</tr>
</thead>
<tbody>
<tr>
<td>45-Year-old man, systolic blood pressure 180 mm Hg, HDL cholesterol 30 mg/dL, triglycerides 250 mg/dL, LDL cholesterol 180 mg/dL, smoker, nondiabetic, positive family history of myocardial infarction, positive history of angina pectoris. The risk of an acute event in this man is 625/1000 in 8 years, or 8% per year; ie, he falls into the highest quintile of risk.</td>
</tr>
</tbody>
</table>

Multiple risk factors, normal LDL cholesterol (100 mg/dL [2.6 mmol/L])

| 45-Year-old man, systolic blood pressure 180 mm Hg, HDL cholesterol 30 mg/dL, triglycerides 250 mg/dL, LDL cholesterol 100 mg/dL, smoker, nondiabetic, family history of myocardial infarction, positive history of angina pectoris. The risk of an acute event in this man is 267/1000 in 8 years, or 3% per year; ie, he, too, falls into the highest quintile of risk. |

TABLE 3. Numbers of Patients That Need to Be Treated for 1 Year to Prevent 1 End-Point Event in 4 Major Prospective Trials

<table>
<thead>
<tr>
<th>Primary Prevention Trials</th>
<th>Secondary Prevention Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean baseline LDL cholesterol in mg/dL (mmol/L)</strong></td>
<td><strong>150 (3.9)</strong></td>
</tr>
<tr>
<td><strong>Definition of primary end point</strong></td>
<td>“First coronary event”</td>
</tr>
<tr>
<td><strong>Approximate number needed to treat</strong></td>
<td>244</td>
</tr>
</tbody>
</table>

Because of differences in trial design and in the definition of end points, the numbers need to treat shown in this Table should be regarded as rough estimates only.
Thrombogenic Risk Factors
Thrombogenic factors increase the risk of acute coronary occlusion and stroke and may play a causal role. Health-related behavior is important in the management of these factors and includes smoking cessation, reduction of overweight, a low intake of saturated fat, and an increased consumption of polyunsaturated fatty acids (ω-6 and ω-3). Weight reduction and some fibrate drugs lower plasma fibrinogen. Activation of platelets plays a central role in unstable angina, and antiplatelet drugs can prevent such activation. The action is maximal immediately after the ischemic event and lasts ≈36 months. The effect of antiplatelet medications is optimal when they are combined with treatment of the coexistent risk factors, such as cigarette smoking, hyperlipidemia, and hypertension. The recommended dosage of acetylsalicylic acid is 75 to 160 mg/d. Ticlopidine can be used as an alternative to acetylsalicylic acid. Data from a recent, large trial showed that 75 mg clopidogrel per day may be more effective than 300 mg acetylsalicylic acid per day in reducing the thrombotic complications of atherosclerosis.39

Cigarette Smoking
About 30% of cardiovascular deaths are due to smoking.40 Recent evidence suggests that cigars and pipe tobacco also confer an increased risk of CHD. Smoking may be an even more important source of risk in areas with a rising incidence of cardiovascular disease, such as Asia and eastern and central Europe, than it is in western Europe and the United States.

Smoking cessation reduces CHD risk and is highly cost-effective. Doctors can contribute to public health education against smoking. Smoking cessation programs include brief individual counseling and extended counseling for the persistent smoker. Nicotine replacement (skin patches with a progressively decreasing dosage) is of value in the motivated patient without CHD but must be supported by a counseling program.

Physical Exercise
Lack of exercise is predictive of high CHD risk, and this relationship is independent of other risk factors. There is strong epidemiological evidence that aerobic exercise reduces the risk of CHD. Individuals who habitually expend 2000 to 3000 kcal/wk in leisure-time activities have 2 to 3 times fewer coronary events than do those expending <500 kcal/wk. Those who exercise regularly have less body fat, a higher HDL cholesterol level, lower LDL cholesterol and triglyceride levels, greater insulin sensitivity, and lower blood glucose and blood pressure. An exercise program should be recommended to all persons with a sedentary lifestyle, with a clear
and detailed prescription to meet the parallel needs of safety, personal enjoyment, and effectiveness. Aerobic exercise is obtained by using large-muscle groups to perform a high number of repetitive movements against relatively low resistance; brisk walking is an excellent form of aerobic activity. Generally, an exercise program includes 3 phases. Warming up for 5 to 10 minutes by stretching and other gentle activity is followed by an endurance or aerobic phase of 20 minutes or longer, according to fitness level, and finally a cool-down period of progressively decreasing intensity allows cardiovascular activity and heat production to subside gradually. Persons at high CHD risk should exercise under medical supervision at least initially and should undergo an exercise ECG test before starting an appropriate program of physical activity.

**Homocysteine**

Homocysteine, a sulfur amino acid, is an intermediate product of the metabolism of methionine and cysteine. Homocystinuria, a rare homozygous defect, is associated with an up to 10-fold elevation of plasma homocysteine levels, premature atherosclerosis, and recurrent thromboses. Lesser degrees of hyperhomocysteinemia are commonly associated with CHD. However, homocysteine elevation may not be an independent CHD risk factor, because these levels are related to renal function, smoking, fibrinogen, and C-reactive protein, which are themselves associated with an increased incidence of CHD. Moreover, the risk threshold for homocysteine is unclear and has been reported to lie between 12 and 18 mmol/L. Treatment with folic acid, vitamin B6, and vitamin B12 lowers homocysteine levels, but evidence that this treatment reduces the cardiovascular event rate remains conflicting. Homocysteine levels should be measured in patients with a history of premature CHD and/or stroke in the absence of other risk factors.

**The Metabolic Syndrome**

The metabolic syndrome is a cluster of metabolic disturbances that strongly predisposes to the development and progression of atherosclerosis. Peripheral resistance to insulin seems to be the central feature of this syndrome, which is characterized by central obesity, hyperinsulinism, and 1 or more of the following abnormalities: impaired glucose tolerance, dyslipidemia, hypertension, hyperuricemia, gout, and fatty liver. The dyslipidemia of the metabolic syndrome is the “lipid triad,” consisting of high LDL cholesterol and triglyceride levels and low HDL cholesterol levels. Treatment is primarily the reduction of body weight through diet and physical exercise. This may lead to marked improvement or full correction of the other metabolic disturbances.

There is a steeply increasing incidence of CHD in postmenopausal women. The risk factors that operate in women are similar to those active in men, but women are more vulnerable to smoking and hypertriglyceridemia. Although observational data suggest that estrogen replacement reduces CHD risk, interpretation is limited by possible self-selection in such studies. In a recent controlled trial of hormone replacement therapy with estrogen and progestin in postmenopausal women, no effect on nonfatal myocardial infarction or CHD death was observed.

The high incidence of CHD in the growing segment of the population aged 60 years and over is of great importance. Although the relative risk conferred by risk factors such as elevated plasma cholesterol in this group is lower than in middle age, the absolute risk is equal or greater. Risk factor intervention may therefore be of considerable value; although controlled-trial data are yet sparse, they tend to support this view. In assessing the need for intervention, both quality of life and life expectancy are taken into account. It should be borne in mind that radical changes in lifestyle become more difficult in the elderly. Also, greater drug use in this age group increases the possibility for drug interactions.

**The Future of Risk Assessment**

It is likely that research currently under way in the areas of genetics, molecular biology, and cardiac physiology will greatly contribute to the assessment of CHD risk in the future. Such issues include (1) genetic polymorphism and abnormalities of genes affecting lipoprotein and glucose metabolism and blood pressure regulation; (2) endothelial function; (3) plaque instability and inflammation; (4) LDL oxidation; and (5) parameters of inflammation (eg, C-reactive protein, *Chlamydia pneumoniae*, etc).

**Conclusions**

Based on a large body of evidence, prevention of CHD should start with global risk assessment and proceed to suitable treatment of correctable risk factors. If the blood lipid profile is abnormal, this should be corrected. Target levels for LDL cholesterol, according to CHD risk categories, are summarized in Table 4. Weight control, a qualitatively satisfactory diet, and suitable aerobic exercise are of paramount importance. The indications for drug therapy in CHD prevention are increasingly well defined.

**References**

1824 Arterioscler Thromb Vasc Biol. August 1999


