Primary prevention of cardiovascular diseases

Emil L. Sigurdsson1,2 and Gudmundur Thorgeirsson3

1Solvangur Health Center of Hafnarfjo¨rdur, 2Department of Family Medicine, University of Iceland, 3Department of Medicine, National University Hospital of Iceland.

One of the tasks of primary health care is the prevention of disease. Cardiovascular disease is still the leading cause of death, and there are several sets of guidelines dealing with both primary and secondary prevention. The article overviews the risk factors for cardiovascular disease and the strategies for primary prevention.

Despite favourable changes in the epidemiology of cardiovascular disease (CVD) in the Western hemisphere during the past few decades, CVD remains the leading cause of death (1–3). Changes in the mortality rate of CVD are to some extent explained by changes in the main CVD risk factors (4,5). Because of unfortunate changes in the developing countries, where the majority of CVD occurs (6), CVD is projected to double between 1990 and 2020, with the developing countries experiencing approximately 80% of the increase.

Although the main workload of the health care system has traditionally been to treat diseases, and often advanced diseases, an increasing emphasis is being put on prevention, and several guidelines have been published on both primary and secondary prevention of CVD (7–10). Organisations devoted to cardiovascular health have made resonating calls for action – and not without reason (11). Firstly, the burden of CVD is increasing globally. An almost world-wide epidemic of obesity and diabetes is predicted for the future, not the least in the densely populated countries of Asia, with consequences of an escalating incidence of CVD. Secondly, not all risk factors for CVD are known, and many of those that are known are totally or partially preventable (Table I). In the Nurse’s Health Study, women who ate a healthy diet, did not smoke, consumed a moderate amount of alcohol, exercised regularly and maintained a desirable body weight had an 84% reduced risk of CVD, but only 3% of the nurses were in that category (12). Inaction is hard to justify in the face of such data. Thirdly, a high proportion of significant preventable risk factors go undetected and/or untreated in apparently healthy young people, which emphasises the vast number of opportunities for health improvement that are not responded to in our health care system.

In this article, we focus on the evidence base for primary prevention of CVD, with a brief review of the major strategies of prevention, the high risk or clinical strategy, and the population or community-based strategy. Our emphasis is on the role of health care providers in implementing current guidelines and in participating in decision-making on where and how to approach the general population with lifestyle interventions.

Strategies of primary prevention

For people at extraordinarily high risk, an individualised, patient-based approach is both a rational and effective strategy. This is the clinical or high-risk strategy. Because of so-called clustering of risk factors, i.e. the tendency of two or more risk factors to simultaneously affect the same person, high-risk individuals can be identified and targeted for effective intervention. In the Framingham study, hypertension was found to occur in isolation only about 20% of the time, but frequently coexisted with risk factors such as diabetes, obesity or dyslipidaemia. Although each risk factor is a public health problem in itself, they interact – synergistically damaging the vasculature – and have a tendency to cluster. Risk profiling, i.e. calculating the total risk rather than focusing only on blood pressure, blood sugar or cholesterol, is another logical part of this strategy and widely accepted as a sound basis for drug treatment that has disease prevention as its main therapeutic goal. Obvious examples are blood

Table I. Cardiovascular risk factors.

<table>
<thead>
<tr>
<th>Modifiable</th>
<th>Non-modifiable</th>
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<tbody>
<tr>
<td>Smoking</td>
<td>Age</td>
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<tr>
<td>Hypertension</td>
<td>Sex</td>
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<tr>
<td>Hypercholesterolaemia</td>
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<td>Physical inactivity</td>
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<td>Obesity</td>
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<td>Diabetes</td>
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pressure lowering or statin treatment for cholesterol lowering, as further discussed in subsequent sections.

The population strategy is designed to lower the risk in the whole population through adoption of a healthy lifestyle, i.e. increased physical activity, healthy diet, weight control and abstinence from tobacco. The goal is to reduce the risk for most members of the population, not just those at highest risk. What is the rationale for such wide-ranging interference with everyone’s lives? Firstly, the risk relations are continuous. Those at the lower end of the risk relation will benefit and their risk will decrease, although less in absolute terms than the risk of those at the upper end. Secondly, the fundamental aspect of risk reduction is change in life habits or behaviour. Behavioural change will be best accomplished by influencing the community (13). Finally, the majority of future cases will have an intermediate risk, but because they are so many they will provide more cases in absolute terms, although proportionally fewer, than the high-risk segment of the population. Because of the large number of people near the middle of the distribution, the most effective intervention by which to reduce the incidence of CVD is to shift the population distribution curve as a whole towards lower risk (Fig. 1). Examples of successful population projects are the North Karelia Project in Finland (14), the Stanford Three Community Study (15) and “Live for Life” health promotion programme in Sweden (16).

The high-risk and population-based strategies are far from being mutually exclusive. On the contrary, they are mutually supportive. Individualised high-risk interventions are more likely to be successful in an environment where healthy lifestyle habits are widely practised. And those who practice high-risk interventions are important champions and educators of the healthy lifestyles that are the basis of the population strategy.

CVD risk factors

The major risk factors for CVD are age, cigarette smoking, hypertension, high serum cholesterol, low levels of high-density lipoprotein (HDL), diabetes mellitus and obesity (17–20). Other risk factors may also be involved in the developing of CVD, either independently or via the major risk factors, i.e. increased serum homocysteine, abnormalities in coagulation factors, hypertriglyceridaemia, family history of premature coronary heart disease (CHD), small dense low-density lipoprotein (LDL) particles, inflammatory factors and physical inactivity. Primary prevention refers to both preventing the development of disease as well as its risk factors, and primary prevention of CVD is aimed at those with known risk factors and also those who have not yet developed detectable risk factors and have no manifestations of CVD.

Smoking. Smoking, both passive and active, remains one of the most powerful risk factors for CVD and has a dose-dependent effect on risk. It is also a risk factor for various malignant diseases and chronic lung disease (21). Although this is common knowledge, the important role of physicians and other health care providers in helping people to stop smoking is less appreciated but repeatedly demonstrated. The simple advice from a physician to stop smoking has been shown to double the spontaneous rates of quitting in a variety of clinical settings (22). As many opportunities as possible in the varied encounters between patients and the health care system should be used to ask about smoking habits and to offer assistance to those who are ready to fight the habit. It should, however, be kept in mind that it is an uphill struggle to give up smoking and there are strong commercial and social forces that promote smoking, especially among the young. Since smoking is currently the primary preventable cause of death, and smoking cessation rapidly reduces the risk for CVD (23), it is an obvious public health priority to fight this health hazard. In some countries a positive change has been noted with the prevalence of smoking decreasing (5,16).

Hypertension. Elevated blood pressure is a well-established preventable risk factor for the development of all manifestations of atherosclerosis, coronary heart disease, stroke, peripheral artery disease and heart failure. Epidemiologic studies have shown that systolic blood pressure is an equally strong risk factor as elevated diastolic blood pressure, and isolated systolic hypertension has been shown to be distinctly hazar-
dous at all ages, including the elderly. Robust trial evidence has shown that reduction of blood pressure by drugs reduces risk, although treatment does not remove all of the CHD risk accompanying elevated blood pressure (24,25). The current European recommendations emphasise the importance of repetitive measurements of blood pressure, sometimes over a period of several months, for the accurate assessment of blood pressure – which is needed for the decision whether to treat or not to treat (1).

Fundamental to that decision is the assessment of the patient’s overall cardiovascular risk profile, because the detrimental impact of blood pressure is determined by the presence or absence of other risk factors that act synergistically to damage both the macro- and the microvasculature. These recommendations acknowledge that the optimal is diastolic blood pressure < 85 and systolic < 120 mmHg, and the goal of treatment is to get the blood pressure below 140/90 and even lower among those with diabetes. Lifestyle interventions are important and in some cases can be sufficient for adequate control. These recommendations should be given to all patients considered to have hypertension. Weight control, reduction in the use of sodium and alcohol as well as regular physical activity are the bases of these lifestyle recommendations. Drug treatment is recommended if the systolic blood pressure is ≥ 160 and/or diastolic pressure ≥ 100 mmHg, despite lifestyle interventions. Drug treatment is also often required when the systolic pressure is 150–160 and/or diastolic pressure between 95 and 99 mmHg. The decision to use blood pressure lowering drugs in patients with mild hypertension, i.e. systolic pressure 140–150 and/or DBP 90–94, depends on whether other risk factors are present and/or there is target organ damage (1,7).

**Serum cholesterol.** Serum total cholesterol increases the risk of CHD over a broad range of levels. Comparative studies between different countries and different populations find that CHD is uncommon in cultures with low levels of serum cholesterol even when smoking is common (26,27). A strong connection exists between habitual consumption of diets rich in saturated fats and cholesterol in a given population and the usual levels of serum cholesterol in that population and thus the burden of CHD (26,28). A population strategy of dietary changes for the benefit of whole populations has therefore been recommended (29) and successfully implemented (6,14). As previously discussed, a population strategy should be augmented by the individualised clinical approach of physicians identifying those who need urgent and aggressive risk factor modification, including drug treatment and family screening.

Although recommendations from the National Cholesterol Educational Program (NCEP) in the USA make use of LDL cholesterol as the primary target (30), the European guidelines recommend using the total cholesterol in the risk assessment (7). Both sets of guidelines emphasise that recommendations must be based not only on lipid measurements but also on assessment of the absolute coronary risk projected by a total risk profile. A cholesterol level of 5–6 mmol/L may require cholesterol-lowering drug treatment in a patient with high overall coronary risk, whereas a serum cholesterol level of 7–8 mmol/L may be left untreated, except for lifestyle advice, in an individual with low absolute risk (7). The first objective is therefore to assess total CVD risk and to identify the risk factors that can be modified. The expert panels authoring the European and American guidelines have come to the consensus that 10-year absolute risk over 20% of developing manifestations of CVD calls for lifestyle recommendations for a period of a few months, and if risk reduction is insufficient drug treatment should be considered. The safety and efficacy of statin therapy in the primary prevention setting is based on robust trial evidence (31). Total cholesterol less than 5 mmol/L with LDL (calculated) below 3 mmol/L is ideal for the whole population and a worthwhile public health goal is to achieve these levels with appropriate diet and regular physical activity.

**Diabetes.** Diabetes, both type I and type II, is associated with a striking increase in risk of CVD (32). It has been estimated that type 2 diabetes confers a similar mortality risk as previous myocardial infarction (MI) (33), and as a risk factor it is a coronary disease equivalent. Studies have revealed that approximately 20% of patients with clinically manifest CHD have diabetes (34) and as the prevalence of diabetes is increasing its contribution to the global burden of CVD is attaining ever-increasing importance. The well-known risk factors for CVD have the same impact in diabetic patients as in non-diabetic, but the diabetic patient is at a much higher absolute risk of CVD events than the non-diabetic. Risk factor management in this patient group is extremely important. In the UK Prospective Diabetes Study (UKPDS), a decrease by 10 mmHg in mean systolic BP was associated with a 12% risk reduction for any diabetes complication, 15% for deaths related to diabetes and 11% for MI (35,36). Consequently, in newly published recommendations from the American Diabetes Association, the target goal for hypertensive treatment among diabetes patients is set at < 130/80 mmHg, and it is recommended that this should be achieved with drug treatment if non-pharmacological...
interventions, which by themselves have a positive effect on glucose control, do not result in adequate blood pressure control (37,38). Most recently, the Steno-2 study from Denmark (39) has demonstrated that intensified intervention against multiple risk factors in patients with type 2 diabetes and microalbuminuria reduced cardiovascular and microvascular events by about 50%. The intensive treatment involved stepwise introduction of lifestyle and pharmacological interventions to maintain glycosylated haemoglobin below 6.5%, blood pressure below 130/80 mmHg, cholesterol below 4.5 mmol/L and triglycerides below 1.7 mmol/L. The lifestyle interventions included reduced intake of dietary fat, regular participation in light or moderate exercise and abstinence from smoking. Based on these results, five patients needed to be treated for 7.8 years to prevent one cardiovascular event. The design of the study did not reveal which component of the treatment was the most important in reducing the incidence of diabetic complications, but benefits had previously been shown for several components of this approach – blood pressure control, statin therapy for cholesterol lowering (40) and strict glycaemic control for prevention of microangiopathy.

**Obesity-physical inactivity.** Epidemiological studies have shown that the relationship between body weight and mortality rate is J-shaped, the lowest mortality rate being among those with “normal” weight, expressed as body mass index (BMI, weight (kg)/height (m²)) (41). Those with a BMI about 22–25 have the best prognosis, but the risk of CHD begins to increase with only moderate weight gain (42,43). In a recently published analysis from the Framingham Heart Study (44) it was concluded that obesity in adulthood is associated with a decrease in life expectancy of about 7 years in both men and women. The impact was similar to that of smoking. Increased intra-abdominal fat mass, i.e. central obesity, is a marker of increased CHD risk, and when assessed with waist to hip circumference ratio this fat distribution indicates greater risk than general adiposity defined by BMI (43). Apart from being an independent risk factor for CVD, obesity has a detrimental effect on other CVD risk factors, including blood pressure, plasma LDL cholesterol, HDL, triglycerides and glucose tolerance. In light of the positive progress in the fight against some of the CVD risk factors such as smoking, elevated blood pressure, hypercholesterolaemia (4,45) and increasing prevalence of obesity, especially in young adults is threatening to nullify the positive gains of recent decades. This new epidemic may turn into another public health disaster (46). Since obesity is at least potentially preventable, reducing weight among those who are overweight and preventing obesity among the general population, beginning in childhood, should be one of the most important health priorities for the years to come. The fight against obesity usually includes a battle against physical inactivity, which is another independent although interacting risk factor of CVD with a similar relative risk as smoking, hypercholesterolaemia or hypertension (47). Conversely, physical activity has been reported to lower LDL and triglycerides, raise HDL, improve insulin sensitivity, lower blood pressure and reduce the risk of coronary heart disease and stroke (48,49). Part of its complex effect may be mediated through enhanced fibrinolytic potential and reduced platelet adhesiveness and thus reduced thrombotic potential. Increased physical activity in accordance with everyone’s state of health is therefore a general public health recommendation as well as part of most individualised lifestyle modification programmes aimed at CVD prevention (10).

**Pills to prevent**
The use of drugs in preventing CVD has been investigated in several studies (50–53). Aspirin is used to some degree in the primary prevention of CVD, but this utilisation is a double-edged sword and even in small doses aspirin can do more harm than good (54–56). Although the reduction in relative risk may be similar in both primary and secondary prevention, i.e. 30% (57), the absolute risk is very different, as is the number needed to treat. In secondary prevention, 50 patients have to be treated for 2 years and in primary prevention 200 patients need to be treated for 5 years to prevent one non-fatal MI (58). Because of this, one should be very careful to use drugs as a general mean of prevention unless the benefits have been proven in well-conducted clinical trials.

Several observational studies have suggested that postmenopausal oestrogen replacement therapy is associated with reduced cardiovascular morbidity and mortality. The possible protective effects have been put to the test in several therapeutic trials, the largest and most important being the Heart and Estrogen/Progestin Replacement Study (HERS) (59) in secondary prevention and the Women’s Health Initiative (WHI) (60) in primary prevention. HERS found no difference in cardiac events after 5 years between postmenopausal women with established coronary heart disease randomised to receive conjugated oestrogen plus progesterin and those randomised to placebo and found an increase in risk among the treated group during the first year of the study. The WHI randomly assigned 16 608 healthy postmenopausal women to receive either a combination of con-
jugated equine oestrogen and medroxyprogesterone-acetate or placebo. After 5.2 years the trial was stopped because of an increased hazard ratio for both cardiovascular disease (hazard ratio (HR): 1.29) and stroke (HR: 1.41).

The results from the clinical trials strongly contradict results from previous observational studies. Today, it is generally accepted that oestrogen alone or in combination with progestin has no role in the primary or secondary prevention of cardiovascular disease.

**Priorities in prevention**

Because primary prevention of CVD is a huge task and the workload that is put on health professionals is often overwhelming, some priorities are inevitable. The two key concepts to be emphasised in this regard are evidence-based approach and global risk assessment. The recent negative or neutral trial results with oestrogen and vitamins (40), in both cases overturning conclusions from observational studies, demonstrate that in the field of prevention as in therapeutics we are bound by the rules of evidence-based medicine.

A fundamental aspect of risk profiling is that the atherogenicity of LDL, the presumed key player in atherogenesis, varies greatly depending on the company it keeps, the presence of subclinical atherosclerosis, other risk factors and the lipid profile (triglycerides, lipid remnants, small dense LDL-particles, low HDL). The so-called metabolic syndrome (Table II) increases the risk of CVD at any level of LDL. The syndrome comprises abdominal obesity, atherogenic dyslipidaemia (elevated triglycerides, lipid remnants, small dense LDL-particles, low HDL). The so-called metabolic syndrome (Table II) increases the risk of CVD at any level of LDL. The syndrome comprises abdominal obesity, atherogenic dyslipidaemia (elevated triglycerides, lipid remnants, small dense LDL-particles, low HDL). The so-called metabolic syndrome (Table II) increases the risk of CVD at any level of LDL. The syndrome comprises abdominal obesity, atherogenic dyslipidaemia (elevated triglycerides, lipid remnants, small dense LDL-particles, low HDL). The so-called metabolic syndrome (Table II) increases the risk of CVD at any level of LDL. The syndrome comprises abdominal obesity, atherogenic dyslipidaemia (elevated triglycerides, lipid remnants, small dense LDL-particles, low HDL). The so-called metabolic syndrome (Table II) increases the risk of CVD at any level of LDL. The syndrome comprises abdominal obesity, atherogenic dyslipidaemia (elevated triglycerides, lipid remnants, small dense LDL-particles, low HDL). The so-called metabolic syndrome (Table II) increases the risk of CVD at any level of LDL. The syndrome comprises abdominal obesity, atherogenic dyslipidaemia (elevated triglycerides, lipid remnants, small dense LDL-particles, low HDL). The so-called metabolic syndrome (Table II) increases the risk of CVD at any level of LDL. The syndrome comprises abdominal obesity, atherogenic dyslipidaemia (elevated triglycerides, lipid remnants, small dense LDL-particles, low HDL). The so-called metabolic syndrome (Table II) increases the risk of CVD at any level of LDL. The syndrome comprises abdominal obesity, atherogenic dyslipidaemia (elevated triglycerides, lipid remnants, small dense LDL-particles, low HDL). The so-called metabolic syndrome (Table II) increases the risk of CVD at any level of LDL. The syndrome comprises abdominal obesity, atherogenic dyslipidaemia (elevated triglycerides, lipid remnants, small dense LDL-particles, low HDL).

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