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Cardiovascular Disease Prevention

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Over the past century, life expectancy has increased by approximately 8 years. Although this is a remarkable achievement, it is also a mixed blessing, and there is a distinct downside to this success, chief among which is the dramatic inversion of the population pyramid that is projected to take place in the not-too-distant future, made all the more acute by the drop in birth rates in Western societies. This change in demographics is likely to have major consequences.

To start with, the post–baby boom population aging means that there will not be enough young people to ensure the sustainability of the funding of health care and pension benefits for the elderly. This will have dire socioeconomic consequences, which we are already starting to have to come to grips with in the Western world.

Furthermore, lifestyle, too, is undergoing sweeping changes. Major social milestones are being crossed increasingly later in life, such as getting married, starting a family, and assuming greater work responsibilities. No longer is it common to lose our parents or even grandparents while we are young, and when this happens, we are unprepared to cope with it.

But let’s not be spoilsports, we should give praise where praise is due. Much to our pride, cardiologists can take credit for the lion’s share of extended life expectancy, with 6 of those 8 years, while all the other specialists taken together account for only 2 years: oncologists, for example, can lay claim to only 2.4 months!

Yet although we as cardiologists may justifiably bask in our success, we should take care not to drop our guard. Cardiovascular disease (CVD) is expected to continue being the number one killer in the Western world for the next 20 years: we still have plenty of work ahead of us.

Our potential scope of action is enormous. We have already proven that we can treat and prevent CVD. Prevention is obviously better than treatment. However, whereas
treatment rests entirely in the hands of the cardiologist, prevention, quite rightly, does not and should not. And this leads us directly to the question posed in this issue of *Dialogues in Cardiovascular Medicine*: who among doctors, cardiac societies, or politicians, should be spearheading the prevention of CVD?

But what exactly is CVD prevention about? In CVD, the archenemy is atherosclerosis and its clinical manifestations such as angina pectoris, myocardial infarction, transient ischemic attacks, and ischemic stroke. However, since the ultimate cause of atherosclerosis is still cloaked in mystery, all our attention is directed toward addressing modifiable risk factors such as smoking, sedentary behavior, nutritional imbalance, impaired glucose tolerance and diabetes, hypertension, dyslipidemia, overweight and abdominal adiposity, heart rate, socioeconomic status, etc.

Clearly, all of this is too much and too important to be left in the hands of the cardiologist or of the general practitioner alone. Firstly, because they simply do not have the time, an, secondly, because they do not have the know-how to deal with such a complex issue on their own.

It is all very well and easy to tell patients to “change their lifestyle” and draw up a list of do’s and don’ts, of pleasures forbidden and burdens imposed. Taken to the extreme, the issue becomes a philosophical one, in the sense that if we are really in earnest about preventing CVD, the majority (if not all) aspects of Western civilization will have to be altered dramatically.

Of course, this is a pipe dream. Probably the most we can hope for is that the combined efforts of politicians, policymakers, health authorities, insurance companies, scientific societies, doctors, and allied professionals may be able to increase awareness among populations and help countries in transition avoid making the same mistakes as the more industrialized countries did in the past.

Changing the lifestyle of a population for the better is no easy task—ironically, getting it to deteriorate is easily done enough: the negative influence of subliminal messages from consumer society (TV, movies, Internet) is pervasive to the extent that even in Italy, children now prefer burgers and chips to the traditional plate of spaghetti with tomato and basil, which of course is the healthier option! Changing the lifestyle of a population means challenging important vested economic interests—such as the tobacco industry, to name but one. The introduction of legislation banning smoking in public places in Italy has been effective in reducing tobacco consumption, and good results in terms of reduction of CVD mortality are already noticeable. Amazingly, the ban went down quite well in Italy, raising the hope that decisions of this type may increasingly be understood by the population as being made for their own good and that of
their loved ones. Similar legislation is now needed on many other fronts: reduction of salt (and sugar) in bread and processed foods, use of more fibers, less fat, etc. This means of course that the food industry will have to completely change its outlook.

The isolated cardiologist can only suggest some or all of these measures to his/her patients, with more or less immediate short-term success. As for the long term, however, National Cardiological Societies are far more effective in getting governments to actively promote the prevention of CVD. Thus, one of the major goals of the European Society of Cardiology (ESC) is to influence European politicians, and this is exactly what has been achieved over the past 5 years with the call to action by the European Summit on CVD Prevention to develop a heart-friendly environment in Europe. The Summit hopes to ensure the implementation of the 12 July 2007 resolution of the European Parliament on tackling CVD, as well as that of the European Heart Health Charter, officially launched in June 2007 in Brussels, and which has gained the support so far of 14 European health promotion organizations.

By now it should be clear that in the battle to prevent CVD no-one is superfluous, all are needed: we must abide by the motto of Churchill’s famed Commandos: “United we conquer.”

And what can Dialogues in Cardiovascular Medicine and its two editors in chief contribute? Food for thought with this “Cardiovascular Disease Prevention” issue, which raises relevant questions and provides a few leads.
Should cardiovascular disease prevention be undertaken by doctors or policymakers and politicians?

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The World Health Organization (WHO) report on Prevention of Cardiovascular Disease (CVD) describes three strategies for prevention: a population strategy, a high-risk strategy, and a secondary prevention strategy. The population strategy is paramount because it addresses the whole population, whereas the high-risk and secondary prevention strategies only address a minority of the population, namely, high-risk and sick individuals. The 61st World Health Assembly of the WHO on May 24th, 2008, stated its implementation strategy for prevention and control of noncommunicable diseases, of which CVD is the most common. The foundation for this action plan is the global strategy for the prevention and control of noncommunicable diseases reaffirmed by the Health Assembly in 2000, the WHO Framework Convention on Tobacco Control in 2003, and the Global Strategy on Diet, Physical Activity, and Health in 2004. The plan is intended to support coordinated, comprehensive, and integrated implementation of strategies and evidence-based interventions across individual diseases and risk factors, especially at the national level. A societal approach—health in all policies—by policymakers and politicians is paramount to preventing CVD.
identifies those asymptomatic individuals who are apparently well, but at high multifactorial risk of developing CVD, with the object of reducing their total CVD risk through lifestyle, risk factor, and therapeutic management. However, its overall impact on the burden of disease is limited because it only targets high-risk individuals, who are a minority of the population. The secondary prevention strategy addresses those who’ve survived the development of symptomatic atherosclerotic disease—acute coronary syndromes, angina, stroke, transient cerebral ischemia, peripheral arterial disease—with the object of reducing the risk of recurrent cardiovascular events and improving quality of life and life expectancy. However, it also targets only a minority of sick individuals and is necessarily limited to survivors. For some, the first manifestation of CVD is sudden collapse and death from acute myocardial ischemia inducing fatal ventricular arrhythmias or massive cerebral infarction or ruptured aortic aneurism. In addition, among those who survive the initial ischemic insult, consequent tissue damage may be so great that secondary prevention offers little gain. Prognosis is largely determined by the scale of myocardial or cerebral damage.

So a population strategy tackling the major social, economic, and cultural determinants of CVD at a societal level is paramount, and without such a strategy these diseases will remain a major cause of ill health and premature death, regardless of the evidence that high-risk and secondary prevention strategies directed at individuals do reduce cardiovascular morbidity and mortality.

**POPULATION STRATEGY**

The 61st World Health Assembly of the WHO announced on May 24th, 2008, its implementation strategy for prevention and control of noncommunicable diseases—CVD, cancer, chronic obstructive pulmonary disease, and diabetes—of which CVD is the most common. The report noted the rapid rise of noncommunicable diseases, which represents one of the major health challenges to global development, threatening economic and social development and the lives and health of millions of people. Using current trends, it estimates that by 2020 these diseases will account for 73% of deaths, and 60% of the disease burden worldwide. Low- and middle-income countries will suffer the greatest impact of noncommunicable diseases, and the rapid increase is seen disproportionately in poor and disadvantaged populations and is contributing to widening health gaps within and between countries. However, the major causes of these diseases are tobacco use, unhealthy diet, and physical inactivity, which in turn impact adversely on body weight and its distribution, blood pressure, lipids, and diabetes. The major causes of CVD are preventable.

The foundation for this action plan is the global strategy for the prevention and control of noncommunicable diseases reaffirmed by the Health Assembly in 2000. It also builds on the WHO Framework Convention on Tobacco Control adopted by the Health Assembly in 2003 and the Global Strategy on Diet, Physical Activity, and Health, endorsed by the Health Assembly in 2004 and the strategies to reduce public health problems caused by harmful use of alcohol. The plan is intended to support coordinated, comprehensive, and integrated implementation of strategies and evidence-based interventions across individual diseases and risk factors, especially at the national level. The plan has six objectives:

1. **To raise the priority accorded to noncommunicable disease, and to integrate prevention and control of such diseases into policies across all government departments.** Raising the priority is justified by the fact that noncommunicable diseases are closely linked to global social and economic development, and national policies in sectors other than health—treasury, environment, agriculture, education, etc—have a major bearing on the risk factors for noncommunicable diseases. So health in all policies is an important principle. In addition, inequalities in access to protection, exposure to risk, and access of care are the cause of major inequalities in the occurrence and outcomes of noncommunicable diseases.

2. **To establish and strengthen national policies and plans for the prevention and control of noncommunicable diseases.** Countries need to establish or strengthen existing policies and plans for prevention and control of noncommunicable diseases as an integral part of their national health policy. The three components are: (i) development of a national multisectoral framework for prevention and control; (ii) integration of prevention and control of noncommunicable diseases into a national health development plan; and (iii) reorientating and strengthening health systems to enable them to respond more effectively and equitably to the health care needs of people with chronic diseases.

3. **To promote interventions to reduce the main shared modifiable risk factors for noncommunicable diseases: tobacco use, unhealthy diets, physical inactivity, and**
harmful use of alcohol. As the underlying determinants of noncommunicable diseases often lie outside the health sector, strategies need the involvement of public and private actors in multiple sectors: agriculture, finance, trade, transport, urban planning, education, and sport.

4. To promote research for prevention and control of noncommunicable diseases. Priority areas include analytical, health system, operational, economic, and behavioral research required for program implementation and evaluation.

5. To promote partnerships for the prevention and control of noncommunicable diseases. Strong international and national partnerships are required to provide effective public health responses to the threat posed by noncommunicable diseases. Collaborative work should be fostered among United Nations agencies, other international institutions, academia, research centers, nongovernmental organizations, consumer groups, and the business community.

6. To monitor noncommunicable diseases and their determinants and evaluate progress at the national, regional, and global levels. Monitoring noncommunicable diseases and their determinants provides the foundation for advocacy, policy development, and global action. Monitoring should include time trends in prevalence of risk factors and mortality rates in populations, and also evaluating the effectiveness and impact of interventions and progress made.

This international WHO strategy for prevention of noncommunicable diseases is complemented by the European Society of Cardiology (ESC) initiative, working in partnership with the European Heart Network and WHO Regional Office for Europe, to engage the European Union (EU) in a coordinated approach to prevention of CVD across Europe. A conference of these three partners was facilitated by the Irish Ministry of Health in February 2004 in Cork. This informed the conclusions of the EU Council on Employment, Social Policy, Health, and Consumer Affairs in June 2004, and an EU Heart Health Conference in 2005, which resulted in the Luxembourg Declaration. This declaration defined the characteristics that are associated with cardiovascular health as:

- Avoidance of tobacco.
- Adequate physical activity (at least 30 minutes per day).
- Healthy food choices.
- Avoiding overweight.
- Blood pressure below 140/90 mm Hg in patients without diabetes or target-organ damage or multiple risk factors.
- Total blood cholesterol below 5 mmol/L (approx 200 mg/dL).

To achieve these healthy characteristics for the population as a whole requires a population strategy because it addresses the societal determinants of CVD in populations through national policies aimed at eliminating tobacco consumption, providing and promoting healthy food choices, and the opportunities to be physically active. A combination of a healthy diet and regular physical activity will keep a healthy weight and shape. It will also favorably impact on the prevalence of physiological and biochemical risk factors, eg, lipids, in the population. This all-encompassing strategy shifts the whole distribution of risk factors in the population toward more favorable levels without the need to medically examine individuals.

**CLINICAL STRATEGIES: PRIMARY AND SECONDARY PREVENTION**

In contrast, the high-risk primary prevention strategy identifies those individuals among the apparently healthy population with a high multifactorial risk of developing CVD, and the secondary prevention strategy addresses individuals who have developed symptomatic CVD. The primary prevention strategy requires some form of screening of the adult population to identify those at high CVD risk. The secondary prevention strategy does not require screening because patients present with symptomatic disease and are medically diagnosed. However, these two strategies share a common aim that is to reduce total cardiovascular risk through lifestyle interventions, management of other risk factors, and use of cardioprotective drug therapies. The distinction between primary and secondary prevention is to some extent artificial since risk is a continuum in the population, and many asymptomatic high-risk people have evidence of asymptomatic atherosclerosis.

**Primary prevention**

Primary prevention of CVD in individuals has traditionally focused on single risk factors such as "hypertension" rather than multiple risk factors—or the total risk approach—and as a consequence the much larger benefits of total CVD risk reduction have not been achieved. Although there is a continuous relationship between blood pressure and the risk of developing...
CVD prevention: by doctors or policymakers and politicians? - Wood and Kotseva

CVD, the higher the blood pressure the higher the risk, the term “hypertension” dichotomizes this distribution into those with a blood pressure consistently greater than a specified level, eg, 140/90 mm Hg, and those with a blood pressure less than this level, which is deemed “normal.” The level of blood pressure defining “hypertension” is not based on the epidemiology of blood pressure and cardiovascular risk, but is rather deduced from randomized controlled trials which have shown evidence of benefit through reducing blood pressure in those with levels above say 140/90 mm Hg. The consequence of this approach is that someone with a blood pressure of 142/92 mm Hg is considered to be “normotensive,” and therefore requiring no treatment. Yet the risk of developing CVD is very similar for these two levels of blood pressure. More importantly, the total risk of developing CVD is not just a function of a single risk factor such as blood pressure, but of all the cardiovascular risk factors taken together. This is called total cardiovascular risk. This term is used to describe the probability of a person developing an atherosclerotic cardiovascular event, based on an assessment of all their risk factors, over a defined period of time.

The importance of estimating total CVD risk before a decision to intervene medically is made is illustrated in Figure 1 and Table I. The figure illustrates that in a middle-aged man who is a nonsmoker with a blood pressure 120 mm Hg the absolute risk of developing fatal CVD progressively increases as the total cholesterol to high-density lipoprotein (HDL) cholesterol ratio rises. However, at every level of this lipid ratio, the absolute risk for a man of the same age who smokes cigarettes and has raised blood pressure is substantially higher. In fact, the absolute CVD risk of a ratio of 3.0 is actually higher in such a man than a ratio of 7.0 in a nonsmoking man with lower blood pressure. Although women are usually, age for age, at lower absolute risk of CVD than men, this advantage is lost at any level of the lipid ratio if the woman is a smoker with raised blood pressure. Another way of illustrating the same principle is Table I. Which person should receive lipid-lowering therapy? In the single risk factor paradigm the person with the highest cholesterol is the one most likely to be treated. But in the total risk paradigm it is the person at highest CVD risk, namely, the patient with the lowest cholesterol of 5.0 mmol/L, but with a total risk of 21%, who should receive lipid-lowering therapy.

The concept of total CVD risk assessment and management was first advanced by Jackson in 1993 in the context of treating “hypertension.” This was followed by the Joint European Societies recommendations in 1994, which applied this principle to the management of all risk factors, including diabetes. The European coronary heart disease (CHD) risk chart developed by Graham was based on an original concept pioneered by Anderson and used age, sex, smoking status, blood cholesterol, and systolic blood pressure to estimate the 10-year risk of a first fatal or nonfatal CHD event. There were separate charts for those with and without diabetes. A CHD risk of 20% was defined as sufficiently high to justify a more intensive lifestyle intervention and the use of drug therapies to lower blood pressure and cholesterol, and treatment targets for these risk factors.
In the 1998 Joint European Societies guidelines, however, these charts had several limitations. First, they were derived from American data from the Framingham community study and the applicability of this prospective cohort study of white middle-aged men and women to all European populations was uncertain. Second, the size of the cohort, just over 5000 individuals, was fairly small for an epidemiological study. Third, the definitions of nonfatal CHD events differed from those used in many other epidemiological studies making it difficult to validate the chart. Finally, estimating the risk of other manifestations of atherosclerosis such as stroke or aneurysm of the abdominal aorta was not possible.

The third edition of the Joint European Societies Guidelines published in 200313 used a new system for cardiovascular risk estimation called SCORE (Systematic Coronary Risk Estimation), based on data from 12 European prospective cohort studies: 205178 subjects with 2.7 million years of follow-up and 7934 cardiovascular deaths.14 Two charts were produced: one for high-risk regions, and the other for low-risk regions (Figure 2, and Figure 3 page 88).13 SCORE estimates the 10-year risk of a first fatal atherosclerotic event, whether heart attack, stroke, aneurysm of the aorta, or other fatal manifestation of atherosclerotic disease. All ICD (International Classification of Diseases) codes that could reasonably be assumed to be atherosclerotic are included.

CVD mortality was used rather than total CVD (fatal + nonfatal) events because the definition and ascertainment of nonfatal events was not the same in the different cohort studies that make up SCORE. However, the use of mortality has the advantage that recalibration of the charts is possible in relation to changing time trends in CVD mortality. Any risk model will overpredict in countries in which mortality has fallen and underpredict in those in which it has risen. Recalibration of SCORE to allow for these secular changes in the population of a given country can be undertaken if good quality up-to-date mortality and risk factor prevalence data are available. The SCORE CVD mortality charts have been recalibrated for a number of European countries: Germany, Greece, Poland, Spain, Sweden, Cyprus, Bosnia and Herzegovina, and Russia. In the 2003 Joint European Societies guidelines, a 10-year risk of CVD of 5% or more for fatal events was defined as high risk, and people at this level of risk should receive a professional lifestyle intervention and, if appropriate, drug therapies to reduce total CVD risk. The choice of a 5% level was arbitrary as risk is a continuum in the population and there are no randomized controlled trial data that define the level of risk at which it is appropriate to intervene. However, there is evidence of benefit from trials of single risk factor reduction, which show benefit for individuals at levels of total risk below 5%. So a 5% CVD risk threshold for intervention is conservative. However, there are other more important factors to take into account when de-

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**Figure 2. 2003 SCORE Chart for high-risk regions.**
10-Year risk of fatal cardiovascular disease (CVD) in populations at high CVD risk based on the following risk factors: age, gender, smoking, systolic blood pressure, total cholesterol.
deciding on a risk threshold for treatment at a national level, including the prevalence of high-risk individuals to be targeted and the practicalities and costs to the health care system of providing appropriate management. In the 2007 Joint European Societies guideline, the threshold of a 5% risk of cardiovascular death over 10 years was reaffirmed, but these patients were described as being at “increased risk,” in order to emphasize the continuum of risk in the population, rather than an arbitrary threshold for automatic intervention with drugs. The treatment of an individual should be guided by their level of total CVD risk, but the physician also needs to take account of many other factors before committing a patient to life-long therapies.

Younger people, say below the age of 40 years, pose a different challenge in the context of total CVD risk. The charts show that at younger ages it is almost impossible to achieve the 5% CVD risk threshold, however high their risk factors are. But they will be at very high relative risk to people of the same age and sex, despite their low absolute risk. In the 2003 Guidelines, the recommendation was to extrapolate risk to age 60 years to illustrate the high-risk track of an individual if preventive action was not taken. It was not intended that young people should necessarily be treated as if they were 60 years old, as this could lead to excessive drug treatment in these age groups. The purpose of the extrapolation was to alert both the patient and their physician to the need for lifestyle change, and to signal the need for a lower threshold for intervention as they get older. In the most recent Joint European Societies guidelines published in 2007, a relative risk chart (Figure 4) has been created so that younger persons at low absolute risk can be shown their risk relative to their peers.

At the other end of the spectrum, the vast majority of older people, especially men, will have an estimated risk of CV death over 10 years that exceeds the 5% threshold for intervention, based on age (and gender) alone, even when other CV risk factor levels are relatively low. So as for younger people, clinical judgment is required in deciding who is most likely to benefit from lifestyle and therapeutic interventions by taking account of lifestyle, comorbidity, the levels of individual risk factors, and target-organ damage. A CVD risk

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of 5% or higher in the older population is not an automatic indication for drug therapies. Separate charts are available for both total cholesterol alone, and the total cholesterol/HDL cholesterol ratio (Figures 2, 3, 5, and 6). Ideally, the risk chart based on the lipid ratio is preferred because HDL cholesterol makes an independent contribution to CVD risk, especially for women and those in the middle years of life. However, measurement of HDL cholesterol is not routine in many parts of Europe and so total cholesterol can be used instead. The electronic, interactive version of SCORE, called HeartScore, is available from the ESC (http://www.heartscore.org/Pages/welcome.aspx). By using the SCORE risk charts it is possible to identify
from the apparently healthy population those individuals who are at high risk of dying from CVD, ie, a 5% or higher risk of fatal CVD over 10 years. The advantages of using the SCORE CVD risk charts are summarized in Table II.

There is no separate SCORE chart for people with diabetes because in the 2007 Joint European Societies guidelines they are now automatically classified as high CVD risk and treated accordingly. There are two reasons for classifying people with diabetes as high risk. Firstly, individuals diagnosed with diabetes tend to already have a clustering of other risk factors—obesity and central obesity, elevated blood pressure, low HDL cholesterol, raised triglycerides—which puts them at high multifactorial risk of developing CVD. Secondly, people with diabetes presenting with symptomatic CVD have a higher case fatality compared with people without diabetes. Overall, the impact of diabetes on CVD risk in SCORE appears to be greater than that for diabetes in the Framingham study, with relative risks of approximately 3 in men and 5 in women.

Although the principle of total CVD risk assessment is now widely accepted as the most appropriate way of identifying those asymptomatic individuals requiring lifestyle and therapeutic intervention, the evidence for multifactorial intervention is less compelling. In a systematic review of 10 trials with disease outcome data, there was no significant effect on total or coronary mortality, but a small and potentially important 10% reduction in CHD mortality may have been missed. This apparent lack of effect on coronary mortality reflects a modest reduction in smoking and small changes in blood pressure and lipids, the latter due to limited drug treatment, in these trials. In contrast, numerous single risk factor trials using drug therapies to lower blood pressure and lipids have shown comparable reductions in CVD risk that would be predicted from the epidemiological relationships. Therefore, if multifactorial interventions achieve the same treatment effects as those in unifactorial trials, this will achieve a substantial cumulative reduction in total CVD risk. The challenge is to achieve such risk reductions through a combination of lifestyle and, where appropriate, drug therapies.

Secondary prevention

All patients with atherosclerotic CVD—coronary artery disease, cerebral artery disease, peripheral arterial disease—are eligible for secondary prevention. However, the focus of secondary prevention has been on patients with coronary disease, and particularly those who’ve had a myocardial infarction or been revascularized. Exercise-based cardiac rehabilitation of coronary patients reduces both cardiac and total mortality. This meta-analysis showed no difference in mortality effect between exercise-only cardiac rehabilitation and comprehensive cardiac rehabilitation. Importantly, the effect of cardiac rehabilitation on total mortality was independent of CHD diagnosis, type of cardiac rehabilitation, dose of exercise intervention, or duration of follow-up. The contribution of secondary prevention programs with or without exercise was evaluated in a separate meta-analysis. The effects on mortality and myocardial infarction were similar for programs that included both exercise and risk factor education, or risk factor education without exercise, or for exercise alone. In a systematic review of trials of secondary prevention, multidisciplinary disease management programs led to a reduction in admissions to hospital and recurrent myocardial infarction. However, this distinction between cardiac rehabilitation and secondary prevention is artificial and these meta-analyses demonstrate, from different perspectives, the benefits of a comprehensive approach to reducing total cardiovascular risk. This comprehensive approach through smoking cessation, diet, and physical activity, and supplemented with control of blood pressure, lipids and glucose, and the use of cardioprotective drug therapies, should be available to all patients with atherosclerotic CVD, whatever arterial territory is affected.

CLINICAL PRIORITIES, TOTAL CVD RISK ESTIMATION, AND OBJECTIVES

Priorities

The following priorities are recommended for CVD prevention in clinical practice in the 2007 Joint European Societies guidelines based on the principle that individuals at the highest levels of CVD risk gain most from risk factor management:

- Patients with established atherosclerotic CVD, whether of the coronary, peripheral, cerebral vessels or of the aorta, even if asymptomatic.
- Asymptomatic individuals who are at high total risk of developing symptomatic CVD because of:
  - Multiple risk factors resulting in a markedly raised total CVD risk
  - Markedly raised levels of single risk factors: cholesterol ≥6 mmol/L (309 mg/dL), low-density lipoprotein (LDL) cholesterol ≥6 mmol/L (232 mg/dL), blood pressure ≥180/110 mm Hg
  - Type 2 diabetes and type 1 diabetes with microalbuminuria
• Close relatives of persons with early-onset atherosclerotic CVD (typically before age 60), or at particularly high CVD risk.

As a general guide, a middle-aged person with a 10-year risk of CVD death of 5% or more, is regarded as being at sufficiently high risk to justify professional lifestyle intervention and, where appropriate, drug therapies to reduce that risk. As the total risk increases, so does the likelihood of requiring medication to lower blood pressure, modify blood lipids, and control glucose levels. In addition, aspirin or other antiplatelet therapies may be required.

Total CVD risk estimation

Patients who have a clinical event such as an acute coronary syndrome or stroke have already declared themselves to be at high risk of a further cardiovascular event and automatically qualify for intensive lifestyle intervention and, where appropriate, drug therapies to reduce that risk. As the total risk increases, so does the likelihood of requiring medication to lower blood pressure, modify blood lipids, and control glucose levels. In addition, aspirin or other antiplatelet therapies may be required.

Advantages of SCORE risk chart

• Intuitive, easy to use tool
• Takes account of the multifactorial nature of CVD
• Allows flexibility in management—if an ideal risk factor level cannot be achieved, total risk can still be reduced by reducing other risk factors
• Allows a more objective assessment of risk over time
• Establishes a common language of risk for clinicians
• Shows how risk increases with age
• The new relative risk chart helps to illustrate how a young person with a low absolute risk may be at a substantially high and reducible relative risk

Table II. Advantages of using the Systematic Coronary Risk Estimation (SCORE) risk chart.

• Low-risk persons should be offered advice to maintain their low-risk status. While no threshold is universally applicable, the intensity of advice should increase with increasing risk. In general, those with a risk of CVD death of 5% or more qualify for intensive advice, and may benefit from drug treatment. At risk levels over 10%, drug treatment is more frequently required. In persons older than 60, these thresholds should be interpreted more leniently, because their age-specific risk is normally around these levels, even when other CV risk factor levels are “normal.” Therefore, uncritical initiation of drug treatments in the elderly should be discouraged.
• Relative risks may be unexpectedly high in young persons, even if absolute risk levels are low. The relative risk chart may be helpful in identifying and counseling such persons.
• The charts may be used to give some indication of the effects of reducing risk factors, although with the caveat that there will be a time lag before risk is reduced to these lower levels. For example, those who stop smoking in general halve their risk, but this occurs over several years.

Qualifiers

• The charts can assist in CVD risk assessment and management, but must be interpreted in the light of the clinician’s knowledge and experience, especially with regard to local conditions.
• Risk will be overestimated in countries with a falling CVD mortality, and underestimated in countries in which mortality is increasing.
• At any given age, risk estimates are lower for women than men. This may be misleading, since, eventually, at least as many women as men die of CVD. The charts illustrate that risk is merely deferred in women, with a 60-year-old woman resembling a 50-year-old man in terms of total CVD risk.

Risk will also be higher than indicated in the charts in:

• Sedentary subjects and those with central obesity; these characteristics determine many of the other aspects of risk listed below.
A relative risk chart (Figure 4) has been developed to inform younger patients of their risk relative to some one of the same age and sex with no risk factors for CVD. So a younger person whose total risk is low can be up to 12 times more likely to develop CVD than a person of a similar age and sex who does not smoke and has low blood pressure and lipid levels. Clinical judgment is then required to decide, beyond lifestyle, if there is a need to start drug therapies.

Objectives of CVD prevention

In the most recent Joint European Societies guidelines, a new emphasis is given to assist those at low risk of CVD to maintain this state lifelong.

The desirable characteristics of low total risk include:
• No smoking
• Healthy food choices
• Physical activity; 30 minutes of moderate exercise a day
• Body mass index of <25 kg/m² to avoid central obesity
• Blood pressure of <140/90 mm Hg
• Total cholesterol <5 mmol/L (190 mg/dL)
• LDL-cholesterol <3 mmol/L (115 mg/dL)
• Glucose < 6.0 mmol/L (110 mg/dL)

In those with established atherosclerotic CVD or diabetes or at high multifactorial risk of developing CVD, the objective is to lower their total risk in order to reduce cardiovascular mortality and morbidity. In addition to a healthy lifestyle, more rigorous control of other risk factors is recommended:
• Rigorous blood pressure and lipid control is desirable in the highest-risk subjects and particularly those with established atherosclerotic CVD or diabetes:
  – Blood pressure <130/80 mm Hg if feasible
  – Total cholesterol <4.5 mmol/L (175 mg/dL), with an option of <4 mmol/L (155 mg/dL) if feasible
  – LDL-cholesterol of <2.5 mmol/L (100 mg/dL), with an option of <2.0 mmol/L (77 mg/dL) if feasible
  – Glucose < 6.0 mmol/L (110 mg/dL)

• Prescribing cardioprotective drug therapies—anti-platelet therapies, β-blockers, angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs), statins, anticoagulants—in particular groups, especially those with established atherosclerotic CVD.

IMPLEMENTATION OF CVD PREVENTION IN CLINICAL PRACTICE

Although the Joint European Societies guidelines on prevention of CVD in clinical practice published in 1994, 1998, 2003, and 2007 have made recommendations for a healthier lifestyle and set goals for blood pressure, lipid and glucose management, and the use of cardioprotective drugs, there is a gap between these standards of care for all priority groups of patients and the reality of clinical practice.

Surveys of clinical practice such as EUROASPIRE I, II, and III (EUROpean Action on Secondary and Primary prevention by Intervention to Reduce Events), which have monitored the trends of preventive cardiology practice in Europe over the last decade, have shown that integration of CVD prevention into daily clinical practice is inadequate. The first EUROASPIRE survey was carried out in 1995/96 in nine European countries: Czech Republic, Finland, France, Germany, Hungary, Italy, the Netherlands, Slovenia, and Spain. The second EUROASPIRE survey was undertaken in 1999/2000 in 15 European countries including those countries which participated in the first survey, and Belgium, Greece, Ireland, Poland, Sweden, and the UK. One of the objectives of the second survey was to see if the practice of preventive cardiology in coronary patients had improved in those countries and centers that took part in EUROASPIRE II. This comparison of results from the two surveys should be a cause for considerable concern to all cardiologists, physicians, and others responsible for the care of coronary patients in hospital and the community. The adverse lifestyle trends, particularly the increase in smoking in younger female patients, and the substantial increase in obesity and central obesity in every country, makes a compelling case for more effective lifestyle programs.

About one fifth of coronary patients still continued to smoke cigarettes, with a significant increase in smoking among women patients, despite increasing availability of new and effective treatments to help patients stop smoking. The physician’s advice to stop smoking is the most important first step in the smoking cessation process, but this advice should be reiterated and rein-
forced by all health professionals. Body weight continued to increase dramatically: 4 out of 5 patients in the second survey had a body mass index (BMI) ≥25 kg/m² and one third were obese (BMI ≥30 kg/m²)—an increase from one quarter in the first to one third of all patients in the second survey. Waistlines also increased, with more than half of all patients being centrally obese (waist circumference ≥102 cm men and ≥88 cm women) in the second survey. Weight reduction interventions include dietary modification, increased physical activity, and some drug treatments such as inhibitors of intestinal fat absorptions and drugs acting on the central nervous system to suppress appetite. These adverse trends in body weight and distribution reflect the same trends in the general population, and contribute to a worsening of other risk factors such as rising blood pressure, dyslipidemia, and diabetes.

Blood pressure management showed no improvement over the two surveys. More than half of all patients still had blood pressures above the recommended target (<140/90 mm Hg), which increases their risk of recurrent coronary disease, stroke, kidney disease, and heart failure. Therapeutic control in patients using blood pressure-lowering medication remains unchanged across the two surveys, which leaves more than half of all patients not reaching the blood pressure goal in the second survey. This failure to improve management of blood pressure more effectively was despite large increases in prescriptions for all classes of antihypertensive medications.

In contrast to blood pressure, the management of blood lipids improved dramatically across the two surveys, largely because of the increasing use of statins. The proportion achieving the total cholesterol target of <5.0 mmol/L increased from 14% to 41%, nearly threefold. Therapeutic control of total cholesterol in those using lipid-lowering medication improved more than twofold. However, this still leaves nearly half of patients who did not achieve the total cholesterol target. The new Joint European Societies Guidelines (2007) have set lower cholesterol targets of <4.0 mmol/L for total cholesterol and <2.0 mmol/L for LDL cholesterol where feasible, and these will be an even tougher challenge.

Comparison between the two EUROASPIRE surveys shows that the prevalence of diabetes continued to increase, from 18% in the first to 22% in the second survey, reflecting the rise in obesity and central obesity. It is of particular concern that the prevalence of undetected diabetes increased nearly fourfold, from 4% in the first to 15% in the second survey. Therapeutic control of self-reported diabetes remained poor, with only one fourth of patients with a history of diabetes having a fasting glucose <6.1 mmol/L in the second survey.

The use of cardioprotective drug therapies has been shown to reduce cardiovascular and total mortality and the risk of recurrent coronary events in patients with CHD: aspirin or other platelet-modifying drugs, β-blockers, in people with myocardial infarction; ACE inhibitors in people with left ventricular dysfunction; and anticoagulants in post-myocardial infarction patients with increased risk of thromboembolism. In EUROASPIRE, prescriptions for cardioprotective medications increased across the two surveys for antiplatelet therapies (81% to 84%), β-blockers (54% to 66%), ACE inhibitors (29% to 43%), and statins (18% to 58%). However, despite the impressive increase in prescriptions for all these drug classes, the majority of coronary patients in Europe had still not achieved the blood pressure and total cholesterol targets as defined in the 1998 Joint European Societies guidelines on prevention of CHD.

The comparison between these two EUROASPIRE surveys demonstrates a substantial gap between the standards set in the CVD prevention guidelines and clinical practice. These surveys, uniquely spanning 5 years of European clinical practice, show that lifestyle trends in patients with CHD are a growing cause for concern. Other surveys have also reported inadequate risk factor management and underuse of prophylactic drug therapies in patients with CHD in Spain (PREVENCIÓN Secundaria del Infarto de Miocardio en España [PREVESE] I and II, in 1994 and 1998), France (PREVENIR, 1998 and 1999, Usik 1998 and 2000), and Croatia (TASPIC-CRO [Treatment And Secondary Prevention of Ischemic Coronary Events in Croatia], in 1998 and 2003). The EUROASPIRE III survey in 22 countries was undertaken in 2006/2007 in 22 countries, including 14 of those countries that participated in EUROASPIRE II, and the principal results on coronary patients in hospital and high-risk patients in primary care have been presented on the ESC Web site (www.escardio.org/euroaspire).

What is abundantly clear from these European surveys is that drug therapies are simply not sufficient and they have to be combined with a professional lifestyle intervention. Patients need professional support to make lifestyle changes and also manage their risk factors more effectively. Simply giving a drug prescription is not enough. Patients need to understand the nature of their disease and how to manage it through achieving
a healthy lifestyle as well as adhering to cardioprotective drug therapies over the long term. Most importantly of all, the adverse lifestyle trends in coronary patients reflect the same unfortunate trends in the general populations of these countries, which makes a compelling case for a societal strategy for CVD prevention. They illustrate how difficult it is for individual patients to change their behavior, despite the development of life-threatening disease, given that their unhealthy lifestyles are shared by an ever-increasing proportion of the adult population. To help patients to quit smoking, adopt a healthy diet, and increase physical activity requires sustained professional support. Yet only a third of patients with coronary disease access cardiac rehabilitation programs in Europe.27 All patients with coronary disease as well as those at high risk of developing CVD should be able to access preventive cardiology programs.

At present, the health care systems in Europe are predominantly focused on acute salvage of ischemic tissues through medical interventions, devices, and pharmacological treatments; and not on addressing the underlying causes of the disease to prevent further morbidity and mortality. However, patients require professional support to make lifestyle changes and to have their other risk factors monitored and managed according to the standards defined in the guidelines.15 We made no distinction between symptomatic coronary disease (secondary prevention) and those at high risk (primary prevention). All these patients are at high risk of CVD and need professional support to achieve the same lifestyle and risk factor targets. EUROACTION was a family-centered program and actively involved patients’ partners and other family members. A family intervention is appropriate because married couples show concordance for lifestyle, and concordance for change.30,31

The EUROACTION program incorporated several important principles. It was intentionally set up in busy general hospitals and general practices, outside specialist cardiac rehabilitation centers, to provide a service for all coronary and high-risk patients in routine clinical practice. Integration of the diagnosis and management of patients with continued preventive care in the same medical facility is likely to result in increased and sustained participation. In the EUROASPIRE survey, only a third of coronary patients attended cardiac rehabilitation,27 whereas two thirds joined the EUROACTION program. Recruitment was even better in primary care, with 9 out of 10 patients joining the program. EUROACTION was inclusive because it addressed all the high-priority patient groups as defined in the guidelines.15 We made no distinction between symptomatic coronary disease (secondary prevention) and those at high risk (primary prevention). All these patients are at high risk of CVD and need professional support to achieve the same lifestyle and risk factor targets. EUROACTION was a family-centered program and actively involved patients’ partners and other family members. A family intervention is appropriate because married couples show concordance for lifestyle, and concordance for change.30,31

The EUROACTION preventive cardiology program reduced the risk of CVD compared with usual care mainly through lifestyle changes by families, who together made healthier food choices and became more physically active (Figures 7 and 8).29 This change led to some weight loss and, for high-risk patients, a signifi-
cant reduction in central obesity. Blood pressure control was significantly improved in both coronary and high-risk patients, and for patients with coronary disease this was achieved without the use of additional antihypertensive drugs. Control of blood cholesterol concentrations in coronary patients was improved in both the intervention and usual-care groups; and for high-risk patients changes over 1 year showed a significant improvement in the proportion achieving the total and LDL-cholesterol targets because of increased use of statins. Cardioprotective drugs—aspiren, β-blockers, ACE inhibitors, and statins—were commonly prescribed for coronary patients in both the intervention and usual care groups. However, the use of all cardio-

protective drugs was substantially lower in primary care, but in intervention there was a significantly increased use of ACE inhibitors and statins compared with usual care. Although these results are encouraging there is scope for further improvement. The smoking cessation intervention based on advice reduced relapse in patients with CHD, but had no effect on the prevalence of smoking in high-risk patients. Even though the protocol recommended the use of smoking cessation therapies, these were not used because of cost. Although the same protocol for risk-factor management was used in hospital and general practice, use of blood pressure and lipid-lowering drugs was much more conservative in general practice. As a consequence, most of the high-risk patients did not achieve lipid targets. Diabetes care could have been further improved if the intervention nurses had taken personal responsibility for diabetes management.

In summary, the EUROACTION demonstration project in preventive cardiology showed that standards of preventive care in general hospitals and general practices across Europe can be improved. This nurse-coordinated, multidisciplinary, family-based, ambulatory program achieved healthier lifestyle changes and improvements in other risk factors for patients with CHD and those at high risk of CVD, and also their partners, compared with usual care. EUROACTION
is a model of preventive cardiology, which has been successfully implemented and assessed, and can be used in routine clinical practice. To achieve the effects of EURO-ACTION, we need to go beyond specialized cardiac rehabilitation services and provide local preventive cardiology programs, appropriately adapted to the medical, cultural, and economic setting of a country.

CONCLUSIONS

However good our clinical prevention programs are, ultimately it is very difficult for patients to quit smoking, eat healthily, and be physically active for the rest of their lives if the society in which they live is not conducive to a healthy lifestyle. A preventive clinical strategy will reduce disability and save the lives of some individuals, but its impact on the overall burden of disease is necessarily limited. This is because most deaths in a population come from those at lower levels of CVD risk, simply because they are more numerous compared with high-risk individuals who, paradoxically, develop fewer events in absolute terms—the Rose Paradox (Figure 9).32,33 So a societal approach—health in all policies—by policymakers and politicians is the paramount strategy for the prevention of CVD.

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Cardiovascular Disease Prevention

Expert Answers to Three Key Questions

1

Should coronary artery disease prevention be undertaken by doctors or by allied professionals?

G. G. De Backer

2

Should cardiovascular disease prevention be undertaken by national cardiac societies?

G. Kamensky, J. Murin

3

Should cardiovascular disease prevention be undertaken by politicians?

D. Greco, G. Laurendi
CAD PREVENTION: WHAT’S IN A WORD?

From the lead article in this issue of *Dialogues in Cardiovascular Medicine*, it is clear that a comprehensive coronary artery disease (CAD) prevention program should include different strategies - a population strategy, a high-risk strategy, and a secondary prevention strategy. Of these, the population strategy is paramount. The importance of this cannot be overemphasized. Policymakers and health economists may be tempted to oppose these strategies. This is wrong; on the contrary, all these approaches complement each other to the extent that the harmonious development of all strategies can achieve more than the sum of each separately: the different approaches are interactive and mutually supportive. However one should also accept that nowadays, in most countries, the health budgets have risen to levels that require resetting priorities. The limited resources for preventive medicine should be used as efficiently as possible. It is therefore logical that questions are asked as to what are the most efficient approaches, with the greatest return, and at the lowest cost.

PARAMOUNT ROLE OF POPULATION STRATEGY

A population strategy requires a multidisciplinary and integrated approach involving policymakers responsible for such diverse fields as education, transport, agriculture, economy, urbanization, finances, and public health. The experience from the North Karelia project in Finland1 is a good example of how an epidemic of CAD was reversed thanks to successful implementation of a population-based preventive program.

CAD prevention can also be subdivided into primordial, primary, and secondary prevention. Primordial prevention aims at avoiding the occurrence of risk factors in the community; this can only be achieved through reducing lifelong exposure to environmental and lifestyle-related risk factors.

In developing countries, the challenge is to avoid the occurrence of an epidemic in CAD, such as took place in the fifties and sixties in Western Europe. This can only be achieved by a public health approach in which both medical doctors and other health professionals have a role to play, as a team, and...
within the broader context of collaboration with policymakers. This involves the promotion of healthy lifestyles and avoiding the mistakes that were made in industrialized countries during the previous century.

This does not mean that the high-risk strategy should not be pursued; it only means that prevention of CAD is more than the care for high-risk individuals and patients; it calls for a broader action by health professionals, policymakers, politicians, and all of society. These aspects are covered elsewhere in this issue of Dialogues.

**COMPLEMENTARY ROLE OF HIGH-RISK AND SECONDARY PREVENTION STRATEGIES**

In this paper, we examine the high-risk and secondary prevention strategies, keeping in mind that they should be considered as a “rescue operation” offering little toward the fundamental solution to the problem posed by the current CAD epidemic. Nevertheless, since the underlying condition responsible for the development of clinical CAD—atherosclerosis of the arterial wall—is present in a large majority of adults in most European countries, the high-risk approach is certainly needed.

**Figure 1** shows findings from a recent population study carried out in a rural community in Belgium involving a large cohort of asymptomatic apparently healthy subjects aged 35 to 55 years. It gives the prevalence of intima/media thickening or plaques as observed in the carotid and femoral arteries by age and gender. In men aged 45 to 55 years, the prevalence of abnormalities was as high as 81%.

Thus, in most communities in Europe, the high-risk strategy of CAD prevention is a prime requirement. However, one should bear in mind the fact that this strategy is applied when the disease process is already advanced, and consequently that it can only aim to delay clinical events for as long as possible rather than achieve complete avoidance.

Nevertheless, this in itself is already a major achievement. At the present time, 38% and 42% of all premature deaths in men and women, respectively, in Europe are due to cardiovascular diseases (CVD). In Belgium, CVD is the third major cause of long-term work incapacity. Therefore, the high-risk strategy is anticipated to prevent a substantial number of early deaths and achieve an increase in life expectancy in the current Belgian CAD population.

Secondary prevention of recurrent CAD events in patients with established CAD speaks for itself particularly in patients who have developed the disease at an early age. This, however could well lead to an increase in total CVD mortality since in the very old, when death becomes unavoidable, CVD is by far the commonest cause of death. So if one can postpone the first CAD event or delay recurrent events in patients with established disease one shouldn’t be surprised that at the end more people die from CAD, but having lived longer in good health.

The Lead Article by David A. Wood and Kornelia Kotseva in this issue of Dialogues clearly shows, based on findings from the EUROASPIRE studies (EUROpean Action on Secondary Prevention through Intervention to Reduce Events) and other surveys, that guidelines on CVD prevention are poorly implemented in daily practice, and that the gap between what is recommended by evidence-based guidelines and what is achieved in daily practice remains unacceptably large.
Table I summarizes the findings from the hospital arm of EUROASPIRE III, with, on the left, the recommendations from the guidelines of the Third Joint Task Force published in 20035 and, on the right, the results from EUROASPIRE III illustrating the situation in 2006-2007.6 Ideally, one should come up with 100% implementation for each parameter.

The results tell a very different story, ranging from a low of 12% (waist circumference <80 cm in women) to the “highest” percentage of achievement observed (55%, LDL cholesterol <2.5 mmol/L).

There is thus considerable potential in CAD patients throughout Europe for raising the standard of preventive cardiology through increased lifestyle interventions, control of risk factors, and optimal use of prophylactic drug therapies.

Table II gives a summary of what could help make CAD prevention easier in practice. Clinicians, and particularly general practitioners (GPs), are overwhelmed with guidelines; they generally feel that the guidelines are too complex and therefore difficult to apply in daily practice. Recent Joint European Task Forces have made every effort to draft simple, straightforward, clear, and credible guidelines. Given the diversity that still exists among guidelines from different expert committees, one should aim at a better harmonization with more focus on areas of consensus rather than on “state-of-the-art” science.

Guidelines should therefore be summarized in short, self-explanatory, simple figures and tables; this was done with the latest Joint Task Force guidelines7; pocket versions became immediately available as well as other aids to help practitioners in their daily practice. Clinicians may also be helped by management tools such as the Heart Score model that has now become available on CD-ROM.8

Furthermore, the European guidelines should not be considered as something carved in stone to be imposed on clinicians. On the contrary, it is strongly recommended that local Task Forces interact with national societies to adopt/adapt these guidelines, taking into consideration local, socioeconomic, and cultural issues. Europe is extremely diversified in terms of cultures and languages, which makes implementation a real challenge.

Some have criticized the guidelines inasmuch as clinicians may not feel committed because they are not part of the creation of the guidelines. This has not been the case in Europe within the 4th Joint Task Force, where GPs, specialists, and other health professionals were well represented. This should be repeated at national level within national Joint Alliances, letting all health professionals be involved in drafting the prevention program.

GPs and other health professionals should have sufficient time to spend on preventive medicine. As time is money, insurance systems should budget for reimbursement of preventive actions. Government policies should more actively promote CAD prevention. More attention should go into adherence to lifestyle changes and long-term drug therapies, including educational programs addressed at patients and their families as well as at health professionals.
WHAT IS THE ROLE OF DOCTORS VERSUS OTHER HEALTH PROFESSIONALS?

Who is best qualified to implement CAD prevention in daily practice? Probably no single professional group is capable of ensuring CAD prevention on its own. Doctors are trained to diagnose and treat CAD. When they are asked about their role in health care, they tend to emphasize the care of the individual patient precisely because this is what they have been always taught to do. Teaching in most medical universities focuses on the approach to the individual patient with only poor coverage of preventive- or community-oriented public health strategies. This is unfortunate, because doctors can play a major role in CAD prevention by providing advice to persons at high risk and patients with established CAD. The consultation with the doctor provides and ideal opportunity to discuss risk factor management, changes in lifestyle, and compliance with drug therapies. The medical consultation can also be considered as the most appropriate setting to adapt the level of prevention to the patient's total cardiovascular risk. It is unfortunate that many medical consultations are still exclusively dominated by concern with short-term immediate issues, at the expense of the future. Lack of time and money is a problem, but the question can be asked whether reallocating some time from treatment to prevention would not be worthwhile.

GPs are also in best position to involve the patient's family, which is of great importance in securing adherence to lifestyle changes and compliance. If GPs are to take up the challenge of CAD prevention effectively, they will need appropriate training in the following aspects:

- Patient-centered methods in the consultation process.
- Motivation for change: how to support and strengthen the patients' decision to implement healthy habits.
- Evaluation of multifactorial risk and use of risk charts.
- Communication on the outcomes and risks of interventions.
- Definition of treatment goals and implementation of follow-up.

Identical requirements apply to cardiologists or other specialists involved in high-risk or secondary prevention programs. The alternative is to share these above-described tasks with trained nurses or other health professionals. Controlled studies have shown that nurse-managed programs are able to improve lifestyle, risk factor control, appropriate use of cardioprotective drugs, and quality of life. Nurses are trained in how to manage patients treatments, but may lack specific knowledge about diet, exercise, and behavior changes, although specialized nurses may be able to fill that gap.

Dietitians may be of great help in achieving dietary goals, but they often have very little training in exercise prescription or behavioral change. Exercise physiologists are knowledgeable about physical activity requirements, but less so of the psychological aspects involved. Psychologists, for their part often lack physiological knowledge.

How can all this be improved? University courses are now increasingly being tailored to fill this gap by providing the scientific bases to develop behavioral models for achieving lifestyle changes through interventions on diet, exercise and smoking, as well as weight, blood pressure, and lipid and blood glucose abnormalities.

However, it is unlikely that in the near future any one professional will be able to provide the comprehensive, multifactorial, and multidisciplinary package that is needed in the high-risk strategy of CAD prevention. Most high-risk subjects and patients with established CAD continue to rely on GPs and cardiologists for implementing primary and secondary prevention, and various studies have clearly demonstrated the gap between evidence-based guidelines and what is achieved in daily practice. All indications show that this is best addressed by aiming at structural changes for CAD prevention programs to be carried out by a teams of health professionals with the doctor—very often the GP—as coordinator. These teams should provide easily understandable information, empathic emotional support, allow patients to ask questions, and develop strategies to assess adherence.

Large differences exist between European countries in terms of availability of GPs, specialists, nurses, and other health professionals. In some countries, this may influence the decision as to what role doctors or other professionals have in CAD prevention.

WHAT ROLE DOES THE PATIENT HAVE?

In addition to doctors and other health professionals, there is a third player who should not be left out of this discussion, namely, the patient or the high-risk subject. All CAD prevention strategies should be based on a patient-centered approach. Doctors and other health professionals should always be careful to appraise and take into account the patient's concerns, beliefs, and values, and respect the patient's choices even if they differ from the health professional's personal views.
The responsibility of the health professional is to offer a correct and balanced account of the scientific and technical issues related to CAD prevention so that the high-risk subject and the patient can be as well informed as possible.

Adherence to lifestyle management and lifelong drug therapies can only be achieved if patients make this their own decision. Lifestyle management and drug treatment goals should be set in collaboration with the patients, taking into account their values and priorities. One should also realize that behavioral change is part of the self-management of health in general. Self-management is defined as a person's ability to manage symptoms, treatment, and lifestyle in order to adapt to chronic conditions such as established CAD. Self-management can be learned and optimized by patient-centered self-management interventions based on the theory of self-efficacy promotion[10], but at the end of the day, the decision to take action rests with the patient.

ORGANIZATIONAL ASPECTS

There is more to consider in CAD prevention beyond the patient and doctors or other health professionals, and that is the organizational context in which primary or secondary prevention of CAD is developed.

One of the most frequently heard complaints of doctors when it comes to CAD prevention is that they lack time. This has much to do with the organizational structure of primary care settings and of specific sections for preventive cardiology in hospitals. CAD prevention can be improved when quality assurance is introduced into daily practice on the basis of registration and planned follow up. Setting up a patient registry is of great importance to guarantee attendance of follow up visits. All this is more easily achieved in settings where doctors are assisted by other health professionals. Follow up by nurses has been shown to be as effective or even more effective than by doctors. This applies both to primary care and preventive cardiology in all hospitals where cardiac patients are taken care of.

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Cardiovascular disease, mainly through coronary artery disease (CAD), is the number one killer in men and women in Europe even though most deaths and disabilities from CAD could be avoided by adopting healthy lifestyles. Because most CAD risk factors usually have no warning signs, continuous and intensive education on a healthy lifestyle at a population level is of enormous importance. The European Society of Cardiology (ESC), together with its National Cardiac Societies and the support of the European Union and other professional organizations, initiated the pan-European EuroHeart prevention project, with the aim of reducing the burden of CAD in Europe. The first year of the project clearly established the undisputable role of National Cardiac Societies in CAD prevention.

Cardiovascular disease (CVD) causes more than half the deaths in Europe (52%) and in the European Union (EU) (42%). Coronary artery disease (CAD) is the leading cause of mortality in men over 45 years, and in women over 65 years throughout Europe, and 51% of patients had premature CAD at the time of their first clinical manifestation of CAD. In addition, while CVD mortality, incidence, and fatalities are falling in most Western European countries, they are either not falling as fast, or are even rising, in Central and Eastern European countries. The reason is simple: in spite of the well-known fact that most CAD is eminently preventable, the most important risk factors are frequently not only not under control, but they are even increasing particularly in countries with relatively less-developed economies.

**FIRST WAS THE INITIATIVE OF THE EUROPEAN SOCIETY OF CARDIOLOGY**

Michael Tendera, during his presidency of the European Society of Cardiology (ESC), in 2004 in his *Concise Guide in Influencing Health Policy in Europe* correctly emphasized that “Cardiologists alone cannot handle the problem of cardiovascular disease. Therefore, there is a strong need to further develop external relations on the political level, with industry, other professional organizations and the press.” In the same year a most important conference the Cork Conference, held on 24-26 February, 2004, in Cork, Ireland, was organized by the EU Commission, the ESC, the European Heart Network, and EU members states. This conference prepared an important document, *Promoting Heart Health—A European Consensus*. This document emphasized not only the great burden of cardiovascular diseases on the EU population, which can be considerably prevented, but it also mentioned the importance of maximal collaboration at every state level, where the National Cardiac Societies (NCSs) should play an important and leading role. This idea was supported by the Luxembourg Declaration, which was prepared during the Heart Health Conference in Luxembourg on 29 June, 2005 (http://www.noellmobilesystems.com/en/luxembourg-declaration.132.html).

**THE EUROHEART PROJECT**

Many discussions of, and arguments by, the ESC finally helped to persuade the EU to support a cardiovascular prevention project in Europe. The resultant EuroHeart is a 3-year project co-funded by the European Commission Public Health Program 2003-2008.

**Keywords:** cardiovascular disease; coronary artery disease; mortality; epidemiology; EuroHeart project; European Heart Health Charter; cardiac societies

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cross-sector cooperation, it has been developed by the ESC along with the European Heart Network, and brings together 33 partners in 22 European countries (among which 18 heart foundations and 11 NCSs) as it also includes associated partners who will act as experts in one or more work packages. The project started in April 2007 and will finish in March 2010.

The general objectives are to address the significant burden of CVD in Europe and to determine specific areas of policies and public health interventions that can contribute to preventing avoidable deaths and disability. The strategic objectives of EuroHeart Project are to:

- Strengthen cross-sector cooperation through the launch of a European Heart Health Charter through mobilizing support for cardiovascular health promotion and CVD prevention. The aim of the Charter is to substantially reduce the burden of CVD in the European Union and the World Health Organization (WHO) European Region and to reduce inequalities/inequities in the disease burden within and between countries.
- Obtain comprehensive and comparable information on policies and measures impacting on cardiovascular health promotion and CVD prevention through the mapping and analyzing of national plans, policies, and measures across Europe.
- Improve the awareness, diagnosis, and treatment of CVD in women through investigating issues concerning CVD in women.
- Promote best practice in prevention and treatment of cardiovascular conditions through the implementation and adaptation to national situations of European guidelines on CVD prevention in those countries where there is a gap.
- Improve prevention practices at primary care level by developing local-language versions of the Web-based interactive CVD risk assessment tool, HeartScore, by facilitating the translation, adaptation, and implementation of the European guidelines on CVD prevention. The adaptation/translation of the guidelines to the national situations will allow networking and development of national alliances among sister organizations (e.g., equivalent to the Joint Prevention Committee at European level).
- Local language versions of HeartScore.
- Capacity-building among health professionals through the implementation and adaptation to national situations of the European guidelines on CVD prevention.

Nowadays, it is very clear that such an extensive project as EuroHeart, to be successful, has to be led not only by experts in the field, but also by experts from recognized authorities as the NCS surely represents in most European countries. As shown in Table I, eleven NSCs are involved in the EuroHeart Project and many other societies are participating through their foundations (Table II, page 108).

### Table I. Overview of National Cardiac Societies’ participation in the EuroHeart project.

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<tr>
<th>Country</th>
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THE EUROPEAN HEART HEALTH CHARTER AT EUROPEAN AND NATIONAL LEVELS

The European Heart Health Charter was officially launched on 12 June 2007 in Brussels among European officials and many representatives of the NCS and Heart Foundations (Figure 1). Four months later, the ESC reported on how it felt about witnessing an unprecedented support from its member societies. In the final count, 24 countries have launched their own national version of the Heart Health Charter, with the involvement and commitment of national officials and partner organizations, hence promoting alliances and creating a favorable environment for heart health promotion. The Charter was translated by NCS or Heart Foundations into 24 European languages, all available on the Web site dedicated to the Charter (http://www.heartcharter.eu/read-charter/default.aspx).

A common feeling shared by all was the enthusiasm generated by the Charter and its launch at national level. Most launches were blessed with the presence of at least the Health Minister, which shows that exchange and communication is possible with the highest health authorities.

Cyprus was luckier, with the additional presence of fellow citizen Markos Kyprianou, European Commissioner for Health at that time, who, by his attendance, reiterated his interest in heart health promotion across Europe. Pambis Nicolaides, President of the Cyprus Cardiac Society, noted that,

The presence of politicians was important, because they realized that health campaigns organized by doctors and the Foundation were not enough, and that effective policies measures and intervention changes in the legislation, educational programs, and agriculture policies were needed in order to promote a healthier environment and a healthier Europe.

Although most launches across Europe borrowed some elements of the European launch in Brussels, each country adapted it to the local context.

For instance, the launch of the Charter in Austria received a particular European focus as it took place at the opening of the ESC Congress 2007 in Vienna and involved the Health Minister Klodsky.

Iceland in particular aimed at a very definite target. In mid-August, the Icelandic Cardiac Society and its president Karl Andersen, along with the Health Minister and the Icelandic Heart Association, were determined to “eradicate preventable...
heart disease in this country, and
(…) are dead serious about it!"
For Karl Andersen,
the launch of the European Heart
Health Charter in Brussels managed
to reach the ears of governments and
health policy makers all over Europe.
In Iceland, the health authorities lis-
tened.
In Romania, the alliance created
around the Romanian Cardiac So-
ciety, the College of Physicians, and
the Romanian Societies of Diabetes,
Nephrology and Obesity, along with
the Health Minister and the State
Secretary of the Ministry of Educa-
tion, Research and Youth, are de-
termined
for the first time in the long history
of Romanian medical specialties, (…) to reduce the cardiovascular burden
in Romanian population using Pre-
vention strategies,
says Dan Gaita. In Cyprus, the
launch also took place in the
House of Parliament.

Other countries rightly took the
opportunity of World Heart Day on
30 September 2007 to organize
events. This was the case in partic-
lar for Slovenia, Slovakia, and
Estonia. In Slovakia the alliance
was created around the Slovak So-
ciety of Cardiology, the Slovak Heart
Foundation, the Slovak Heart to
Heart League, the WHO office in
Slovakia, the Office for public health
along with the Health Minister
(Figure 2). The European Heart
Health Charter official signing was
the beginning of the nationwide
educational campaign on the topic
of cardiovascular prevention called
MOST (mesiac o srdcových témach =
Month Of Heart Topics) and simul-
taneously a part of the final prepara-
tion of the National Cardiovascular
Program.1 In Bosnia and Herzeg-
govina, an event similar to that in
Brussels was arranged, when the
Foundation of Health of Bosnia and
Herzegovina and Heart of the Re-
public of Srpska, invited local chil-
dren to participate in a balloon re-
lease. Some countries, like Belgium,
Greece, or Poland have had diffi-
culty in fixing a convenient date, due
to the relatively unstable political
situation or general elections, but
the commitment and conviction of
local stakeholders is still very strong.
The launch in Belgium finally took
place on 23 October in Brussels, in
the presence of the Belgian Commu-
nity Health Ministers. In Lithua-
nia, where the Health Program has set
the target to reduce mortality rates
from both coronary heart disease
(CHD) and strokes for the popula-
tion under 65 years of age by 15%
through the limitation of major risk
factors for CHD in the whole popu-
lation, the launch, attended by the
President of the Lithuanian Society
of Cardiology, the Health Minister,
and the Director of Kaunas Univer-
sity Hospital, is
expected to address the inadequate
control of risk factors of community
and health care authorities. It was
also the occasion to plant an oak tree
beside the Library of Kaunas Univer-
sity of Medicine.
Press and media are constant factors in and partners of all national launches, with good coverage desirable in local newspapers and on television. Indeed, the word “historic” comes back on many occasions at the launches’ events. As Nick Boon, president of the British Cardiovascular Society puts it:

This is truly an historic moment in the battle against CVD. For the first time all EU Governments will work together to implement a range of uniform measures, including tobacco control and marketing campaigns to improve unhealthy diets and help people to do more exercise.

According to Lars Rydén (Co-Chair of the European Heart Health Charter Steering Committee, Co-Chair of the ESC Committee for European Union Relations) the wide acceptance of the European Heart Health Charter in Europe represents a great step forward. The ESC together with its NCS have been able to work together very successfully with the European heart Network, WHO, and the European Commission. The necessary support from Member States to adopt Council Recommendations has been built and the Committee can be even more demanding and ambitious in its relationship with European Institutions.

The ESC has been able to create platforms where organizations from various groups can keep their individual identities while at the same time working toward an exactly shared goal. The fact that the joint European prevention guidelines have been signed by all these different professional organizations has certainly helped establish legitimacy in maintaining alliances and promoting good clinical practice.

**SHOULD CVD PREVENTION BE UNDERTAKEN BY NATIONAL CARDIAC SOCIETIES?**

Coming back to the main issue raised by this article “whether CVD prevention should be undertaken by national cardiac societies,” the answer is quite obvious.

NCSs represent an extraordinarily huge potential of experts and specialists in cardiovascular medicine nowadays. Their role can be perceived in the following areas:

• An NCS usually represents the highest national level of authority in the field of CVD prevention.
• Most of them have in their structure a Working Group on CVD Prevention, which is particularly focused on the topic of CVD prevention.
• As the relevant scientific authorities, NCSs continuously elaborate or translate the latest Prevention ESC Guidelines, which are ultimately published not only in each NCS’s official journal, but also on its Web site, which has a link to the ESC Web site.
• NCSs prepare all the latest relevant scientific statements, which are to be implemented to the National Heart Health Plans or to national legislation, with a view to reaching the highest possible nationwide implementation in real life.
• NCSs actively organize scientific meetings with the aim of improving education and implementation of the latest Guidelines using HeartScore, not only by specialists, but mainly by general practitioners.
• Some NCSs founded their own Heart Foundations which, in contrast to an NCS as a professional organization for cardiologists, can act more actively toward patients’ education, media cooperation, etc.
• NCSs, in cooperation with their foundations, should produce educational materials on healthy lifestyle, in their native languages. Educational materials are in print and/or on a Web site.
• Nationwide projects (shorter or longer duration) oriented to population education including risk factor measurements, should be continuously introduced and implemented by NCSs and their Heart Foundations in cooperation with other professional organizations.
• NCSs and their Heart Foundations should prepare and implement nationwide registers of high-risk patients with the aim of obtaining reasonable information on the level of risk factor control, so as to eliminate the usually great regional socioeconomic differences in cardiovascular mortality and morbidity.

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Should cardiovascular disease prevention be undertaken by politicians?

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The incidence of cardiovascular disease (CVD) has been increasing steadily over the past several years and is currently one of the biggest public health concerns in Italy. One of the chief objectives in CVD prevention is primary prevention of coronary artery disease (CAD). Longitudinal epidemiological studies have confirmed the benefit of lifetime maintenance of the population at low levels of risks. CVD prevention cannot and should not be the responsibility of doctors alone, but should involve politicians/policymakers, as well as the media, local institutions, schools, food producers, etc. These players should avoid futile prohibitions, and work together to “make health choices easy.” Primary prevention is an investment for the future. The Italian operational model is based on a three-pronged policy including individual prevention, community prevention, and surveillance.

THE BURDEN OF CARDIOVASCULAR DISEASE

Cardiovascular disease (CVD) is without doubt the most severe and frequent health disorder in industrialized countries. In the Western world, as well as in developing countries, the burden of CVD has been rising dramatically, year after year. In Italy, 1 out of 2 deaths is due to CVD, and out of a total population of 57 million, at least 1.5 million suffer from a serious form of coronary artery disease (CAD) at any time. The situation is similar in the rest of Europe. While mortality rates in Italy are gradually falling thanks to earlier diagnosis and treatment, the incidence of coronary events is increasing due to the rapidly aging population. Figure 1 shows the incidence and 28-day mortality of myocardial infarction and stroke in Italy, in the 35-to-74-year age-range.1,2

The remarkable success achieved by early diagnosis and treatment has considerably reduced mortality. But although CAD no longer represents an immediate threat to life, a majority of CAD survivors continue to suffer from chronic disease. This has a considerable negative impact on their quality of life and imposes a heavy burden in terms of health care–related costs and loss of productivity on society. In other words, the huge gains achieved in reduction of mortality and morbidity come at the expense of a steady rise in the demand for health care and social resources by CAD sufferers. All prospective disease prevention public health models concur in their predictions that in the near future the weight of chronic diseases will consume the greatest part of available health resources, thus deeply undermining the present universal health care system that provides free care for all in Italy.

Since the 1970s, there have been repeated calls in Italy to address the CAD epidemic by implementing recommendations to improve the population's lifestyle by increasing the awareness of the risks caused by deleterious behaviors and by encouraging initiatives by physicians for the evaluation and intensive care of patients at high risk.3 Nevertheless, over the last 30 years, in spite of the steadily increasing incidence of CAD, the overall record of public health authorities in terms of prevention has been poor.4

CAD PREVENTION

The main determinants of CAD are well known: smoking, alcohol, unhealthy diet, sedentariness, hypertension, and high levels of cholesterol, together make up more than 80% of the factors incriminated. Over the last 30 years, countless studies have confirmed the strength of this evidence. In parallel, intervention

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studies have overwhelming demonstrated how modifying these risk factors significantly reduces the incidence of CAD, with greater effectiveness than pharmacological and surgical treatments. This is exemplified by the effect of the recent ban on smoking in public places to eliminate passive smoking in Italy, the outcome of which was to reduce hospital admissions for myocardial infarction by 10% by the first year of implementation.

**PRIMARY PREVENTION FOR CAD IS POSSIBLE, EFFECTIVE, AND VITAL**

Longitudinal epidemiological studies have shown the benefit of lifetime maintenance of the population at low levels of risks (ie, blood pressure lower than 120/80 mm Hg, cholesterol <200 mg/dL, body mass index (BMI) <25, no smoking, absence of diabetes). Such a benefit is difficult to prove, as the population’s prevalence of CAD at low risk is low (4% in Italy) and observational epidemiological studies of many years’ duration are required to show a benefit, such as ARIC (the Atherosclerosis Risk In Communities trial), MRFIT (the Multiple Risk Factor Intervention Trial), the Chicago Gas Company Study, or the Italian Cuore Project.

The Chicago Gas Company Study in particular showed that people at low risk survive longer, with better quality of life, and lower health care costs in their latter years of life than people at high risk.

Effective prevention implies setting up a health policy with the support of health care professionals and citizen associations, at national, regional, and district levels. Although we need to know more about the contribution of other risk factors such as genetics, environmental pollution, etc, what we already know is sufficient to achieve significant success in prevention.

**SOCIAL INEQUALITY**

An important aspect to take into account is the consequences of social inequality: the incidence of risk factors (smoking, alcohol, unhealthy diet, and physical inactivity) differs according to social status. There is extensive evidence that lower social levels (in terms of education, income, geographic localization) experience a higher prevalence of smoking, alcoholism, physical inactivity, and poor dietary habits. The prevalence is even greater in the more vulnerable segments of the population such as children, women, and the elderly.
CAD prevention therefore has a role of primary social and political importance. Equal rights to health or to a universal health care system are illusory, as long as this problem of severe social inequality with regard to the prevalence of major risk factors of CAD is not adequately addressed.

**WHO SHOULD BE IN CHARGE?**

While it is the purview of the health care system to address the aforementioned CVD and CAD risk factors and their consequences, other instances should be involved with respect to defining policies in terms of the tobacco, alcohol, and food industry, and promoting regular physical activity. The medical profession has a role in advocacy, in counseling, in encouragement. But regulating the aforementioned huge tobacco, alcohol, and food markets is not in their hands. The main role of health professionals is to restore damage to health caused by others, and even the best efforts by doctors in support of risk prevention policies often has no demonstrable impact on the incidence of diseases determined by those factors.

Thus, successful prevention of CVD and CAD cannot and must not be merely the prerogative of physicians, and it is an illusion to believe that the medical profession alone can effectively combat the ill effects of the tobacco, alcohol, and food industry. Politicians are needed to set standards in terms of economy, education, advertising, agricultural production, etc. What is required is a true inter-institutional synergy: health is no longer the exclusive concern of health professionals, but a shared and collective responsibility encompassing the major players of society. Therefore it is crucial that the awareness of their important role in preserving public health is adequately shared by all sectors involved.

The above considerations are consistent with the “Health in all policies” framework as formulated by the World Health Organization (WHO) and the European Union (EU). Each social sector has to take responsibility for its role in health and adhere to the “inter-institutional pact” proposed by the public health authorities so as to implement improvements in education, the economy, in working conditions, etc. Alliances should be established with schools, food producers, trade interests, local institutions, the media, the industry, in order to carry out concrete actions. In doing this, one should avoid illusory prohibitions and seek to find common grounds among all stakeholders so as to “make health choices easy.”

Only through mobilization of all of these players can CVD and CAD prevention aim to achieve success.

**AN ECONOMIC CONCEPT**

The slogan “prevention is economically advantageous” still reigns supreme in the medical world. Although this concept may be appealing at first glance with respect to prevention models, which argue that today’s disease prevention–related costs will translate into savings associated with each illness prevented, its actual economic outcome often remains doubtful. Physicians today in Italy solicit funds from the Director General of the Health Administration for prevention measures such as information campaigns, screenings, laboratory tests. These demands are based on old established methods involving the NNT (number needed to treat), cost-benefit ratios, etc. Thus, to give an example, it is claimed that it is worthwhile to measure the blood pressure of a thousand individuals because by doing so, it is possible to detect 20 people with permanent hypertension, even though they are unaware of this. So we treat 20 people suffering from permanent hypertension for the rest of their lives, hoping that in following years, the incidence of CAD will drop from 10 to 5.

Even in this oversimplified example, the model remains logical, because we reduce expenses, allow people to live their last years of life in a better way, and reduce the incidence of stroke, which is a burden for the patients and their families.

But what is the point of view of those who must make the necessary decisions and allocate funds? The sad truth is that the Director General of the Health Administration is acutely aware of the cost of prevention, but, during his/her usually short term in office, will not see any economically convincing returns on this investment.

The paradox about primary prevention is that doctors ask persons not to smoke, not to drink alcohol, to exercise more, etc, while at the same time up to 75% of the cost of cigarettes goes to taxes for the State. Alcoholic beverages are also a valuable source of taxes for the State. The Italian automobile industry, a pillar of our economy, is strongly supported by the State, at the expense of alternatives that would result in less sedentariness. And so we arrive at the absurdity that the doctors dealing with prevention are actually paid on public funds stemming from taxes paid by those very industries that promote unhealthy behaviors.

Primary prevention results in a net loss in economic terms, as it involves extensive spending for public aware-
ness campaigns and generates no money-bringing activities. In contrast, secondary prevention involves a wide range of periodic tests and long-term prophylactic treatments, in other words, it generates a market that feeds a specific economy with many beneficiaries.

Within the 10 coming years there will certainly be fewer cases of CAD. This will lead to an increase in working productivity and a reduction in health care expenditure. Whether this will balance out the increase in preventive costs and the costs for regular periodic health controls remains unclear.

We are beginning to realize that it is not periodical checks that lower cholesterol: cholesterol is reduced by physical activity and a healthy diet. Thus we can encourage people to reduce their salt intake, improve their diet, and walk more, in order to keep their blood pressure down and their cholesterol under control.

The implication is that primary prevention requires a lot of time and professional skill. The current financial context, which is decidedly gloomy, explains the reluctance of society for funding primary prevention. Politicians, like the Director General of the Health Administration, only see the costs, not the benefits. Can we expect that a Health Councillor, and the Director General, who, in Italy, is in office for only a short period of 2 years, will put up with a budget in the red, all in the name of a future benefit which is not even clearly definable?

**WHAT IS THE ROLE OF POLITICIANS?**

It is easy to object that politicians should not only take into consideration short-term objectives or be only concerned with addressing a nation’s most immediate needs, but that they should also plan for a better tomorrow.

Public schools in Italy result in a net financial loss for the State. But since when is investment in education supposed to provide economic returns? And yet, schools and universities also represent a huge market that provides work for millions of employees, as well as being the key to prevention. Again, what about research? Only a small sector of research is economically beneficial over the short term. For the most part it provides no immediate benefits at all, but only over long periods of time.

As far as the health sector is concerned, the greater part of public investment is used to sustain the universal health care system: more than three quarters of this investment is spent on personnel salaries and costs of hospitalization for 10 million Italians each year. Each year, surgery is carried out on 4 million patients, medical examinations are performed on tens of millions of people. The entire health system is geared toward responding to the health demands of sick people, which represent the “principal market” of health care efforts.

Even though the Italian population today is beginning to perceive the need for prevention and demand that it be implemented, usually this is limited to secondary prevention.

What they are saying is, in essence “I want medical examinations and tests to see if I am well or have a disease, or whether I am at risk of any disease.” In contrast, there is only a token demand for primary prevention. This begs the question, should there be a substantial offer for primary prevention if consumer themselves do not ask for it?

In other words, notwithstanding the sound economics that must be applied to the health care system, we cannot restrict ourselves to the mere goal of balancing the economic budget. We must also take into account the fact that a significant share of public health investment should be considered as insurance for the future, such as supporting prevention, and be prepared to acknowledge that public health budgeting should aim beyond potential short-term economic returns.

Two approaches to prevention exist: (i) helping subjects at high risk to avoid complications, or (ii) identifying people at high risk in order to help them achieve low-risk status by implementing a healthy lifestyle. Each of these approaches is efficacious, provided there is synergy between action at the individual level and at the community level.

**EVIDENCE-BASED PREVENTION**

With each passing day, evidence of the effectiveness of prevention accumulates. Even though there are instances of intervention trials that were launched with great hopes, but failed to live up to expectations, many more confirmed how relatively simple measures could have great preventive efficacy, both with regard to the behavior of the individual as well as to social policies.

In assessing the value of primary prevention measures versus secondary prevention measures, the scales unquestionably tip in favor of the first, as primary prevention ensures added years of good quality of life, while secondary prevention (screening, chemotherapy) adds to therapeutic efficacy (thereby creating very important markets for diagnostics and pharmaceuticals: with regard to CVD prevention, statins, for exam-
people, are the one most important item of cost in public health spending in Italy. The change needed in attitudes toward prevention is simple: these should evolve from considering health as a cost to considering it as investment and insurance for the future. Furthermore, we believe that CVD prevention should not concern the medical profession alone, but above all should be undertaken by the community, in view of the common good.

**IS PREVENTION ONLY AN INDIVIDUAL RESPONSIBILITY?**

It is both useless and counterproductive to envisage prevention as placing blame on individuals or institutions for lifestyles and behaviors that put health at risk. Prohibitions and punitive policies with regard to individual behaviors, even though motivations may be laudable, fail to achieve any long-lastingly significant results. The only workable alternative is to reach a consensus on policies aiming to achieve a progressive awareness of the need for implementation of healthy behaviors by the population.

Thus, although it is impossible to simply outlaw smoking, it is possible to increase cigarette prices. Although we cannot eliminate alcohol, retail sales can be restricted by imposing strict age limitations. We do not seek to establish a vegetarian world, but we do want fruit and vegetables to be easily available. We do not want to give up our cars, but we would like to be able to enjoy more pedestrian zones in our cities, and walk without risking being driven over.

Paramount is the education of the individual, which also entails education at institutional level. Campaigns aimed at individuals only are doomed to fail, they should be directed at institutions, the industry, and all stakeholders as well, and always seek to establish a consensus by generating freely agreed upon commitments by all.

**WHO SHOULD BE RESPONSIBLE: THE DOCTOR OR THE POLITICIAN?**

Is all this the responsibility of the medical profession? Is it the doctor who has to create pacts and alliances with schools, with industry, with agriculture, etc? Are doctors the most appropriate players to plan and carry out these tasks?

The GP, and above all the cardiologist, naturally have far deeper knowledge about CVD prevention issues that any politician, whose knowledge of health issues will extend only as long as his/her mandate. Thus politicians must rely on health professionals as technical consultants, who will deliver their expertise on the why and wherefore, though it is the politician who allots the resources to be used for prevention who will have to make decisions on the how, where, and when.

However, individuals and communities, by following the advice of health professionals, may also exert a significant influence by adopting healthier lifestyles and asking politicians to provide for prevention measures to be set up, in particular primary prevention. Politicians will eventually have to listen to their constituents’ demands if they want to keep their votes. Thus, even though health professionals have a vital role with regard to primary prevention (take, for example, anti-smoking counseling), politicians are responsible for making strategic choices based on realistic goals and able to achieve realistic results.

**WHAT IS BEING DONE IN ITALY?**

CVD in Italy is one of the biggest public health concerns and one of the main causes of morbidity and mortality in our country. All health and social indicators (mortality, hospital discharges, invalidity pensions, pharmaceutical costs) concur to reflect the huge human, social, and economic burden associated with CVD.

In addition, CVD is compounded by the fact that it constitutes one of the most important risk factors for diseases linked to aging, cognitive capacity, and disability. In a country such as Italy where life expectancy is continuously rising, it is therefore of utmost importance to set up CVD preventive measures, in order to achieve better health conditions and preserve the population’s quality of life.

In view of the overwhelmingly conclusive evidence that correcting cardiovascular risk factors markedly reduces the risk of CVD, the Italian Ministry of Health has made CVD prevention a top priority and has been gradually putting in place a comprehensive strategy, with the following landmarks:

- In 2003-2005, the National Health Plan promoted action aimed at reducing CVD and cerebrovascular disease mortality and implementing an integrated system of care and assistance to patients suffering from these diseases.
- In 2004, Law No. 138 implemented “urgent procedures to confront situations dangerous to public health” under the purview of the Ministry of Health’s National Center for the Prevention and Control of Diseases (CCM, Centro nazionale per la prevenzione e il controllo delle malattie), which drew inspiration from the experience of the interna-
tional community in dealing with chronic diseases. To address cardiovascular risk, the CCM created the CUORE (Heart) project, which aims at better prevention through a Cardiovascular Risk Charter to encourage community physicians to act to reduce risk factors and reinforce epidemiological surveillance.

On 23 March 2005, a Memorandum laid out an agreement between State, Regions, and Autonomous Provinces to include CVD prevention in the 2005-2007 National Prevention Plan, and earmarked financial resources for its implementation. Each region has already made prevention plans for the reduction of cardiovascular risk, while operations for secondary prevention are in the planning stages. The National Center for the Prevention and Control of Diseases (CCM) has set down guidelines relating to the “spreading of the Cardiovascular Risk Charter” and how to avoid relapses in subjects having already suffered cardiovascular disorders.

The operational model provides for the development of three planning areas: individual prevention, community prevention, and surveillance (Figure 2).

Individual prevention predominantly involves the sphere of primary care. In compliance with the terms of the Cardiovascular Risk Charter, primary care physicians and allied professionals evaluate their patients’ cardiovascular risk and suggest changes in lifestyle to reduce this risk and, where necessary, prescribe drugs to control blood pressure, and blood glucose and lipid levels.

At the population (community) level, effective public health initiatives have been implemented to reduce cardiovascular risk. These include societal measures such as the recent law protecting nonsmokers by banning cigarette smoking in public places, increasing the price of cigarettes, and banning cigarette advertising, and other measures to encourage physical activity, such as banning automobile traffic in historic centers of cities, building bicycle lanes and creating pedestrian zones. Educational programs are aimed at the public in the form of campaigns and groups, such as those found in schools.

Preventive operations involve the entire Italian health care system (SSN, Servizio sanitario nazionale), beginning with the Department for Prevention, hospitals and hospital specialists, and health care centers, all the way to primary care physicians, health workers, and social health services.

The road ahead is still a long and difficult one, but Italy is making steady headway in bringing about momentous changes in cultural attitudes and medical practice, and showing encouraging progress in achieving ambitious national health objectives in the field of CVD prevention.
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The theme common to the previous Trails of Discovery essays1,2 has been to identify specific scientists whose research was fundamental to the introduction of novel cardiovascular drugs into clinical practice. A subsidiary theme has been to examine the contribution of academic and industrial research collaboration to such advances, suggesting perhaps that the current vogue of “translational medicine” has a longer history than is currently recognized. This essay summarizes the events leading to the discovery and development of aldosterone antagonists and their evolution over the subsequent 50 years of research.

DISCOVERY AND SYNTHESIS OF ALDOSTERONE

The existence of aldosterone, previously termed electrocortin, had been debated since the mid-1930s following the identification of cortisol, corticosterone, and desoxycorticosterone (DOCA). After extraction of these steroids from adrenal glands there was a residual amorphous material that had some biological activity, first identified by Kuizinga and Cartland in the late 1930s.3 Over the next 15 years there was intense both basic and applied research on a range of anti-inflammatory steroids and sex hormones. A potentially confounding issue was the fact that cortisol possessed effects both on carbohydrate metabolism and electrolyte secretion, leading to a widely held opinion that cortisol was the physiologically important mineralocorticoid hormone.4 The first isolation of electrocortin (subsequently termed aldosterone) relied on two important technical developments: (i) the use of partition chromatography pioneered by Martin and Synge, and (ii) the development of a specific radiolabeled bioassay (Na24/K42).5

The imaginative application of these new techniques by the Taits (Figures 1 & 2), working at the Central Middlesex Hospital in London, led to the purification of a very small quantity of aldosterone.6,7 They carried out pilot studies and identified some chemical groupings. In 1952, they began a collaboration with Professor Tadeus Reichstein in the Department of Chemistry, Basel. Reichstein had been awarded the Nobel Prize in Physiology or Medicine in 1950 for his previous work on adrenal corticosteroids (Figure 3, page 120). He had identified the glucocorticoids cortisol and cortisone, as well as the min-
eralocorticoid activity of deoxycorticosterone. Furthermore, he identified compounds with dual activities, ie, corticosterone and 17-hydroxydeoxycorticosterone. The Taits collaborated with Reichstein from 1952 to 1958. There is a fascinating account in great detail of the correspondence between the British and Swiss collaborators during this period, which describes many of the ups and downs encountered before finally identifying the structure of aldosterone.

The first crystallization of aldosterone was achieved on July 11th, 1953, in collaboration with the medicinal chemists of Ciba AG, Basel, ie, Wettstein, Neher, and von Euw. At that time there was a large medicinal chemistry steroid group led by Wettstein. Ciba had been working on steroid research since the mid-1930s and an excellent account of their studies over the next 30 years has been published.

In the early 1950s, Green, the Director of the Biology Division at Searle, initiated a research program seeking novel antihypertensive agents. The hypertension model used was the DOCA salt rat in which a 20-mg pellet of DOCA induced an early DOCA-dependent rise in blood pressure and a later (21 days onwards) phase independent of the presence of DOCA. This secondary phase was referred to as the metacorticoid hypertension.

Green left Searle in the mid-50s to take up an academic post and the antihypertensive program was taken over by Frank Sturtevant, who has described briefly how the first aldosterone antagonists were found. He writes:

...in the 1950s, biologists at Searle were allowed to devote 50% of their time to research of their own choosing. Thus when top management decided that there was no more interest in the pharmacologic screening of the spironolactone series synthesized by Jack A. Cella and Bob C. Tweit, for reasons of their own, we independently chose to transfer our activities from this interesting series of compounds to our respective basic research programs.

Sturtevant was working on experimental mineralocorticoid and renal hypertension while in the nearby labs Charlie Kagawa was examining the effects of the suspended spironolactone series in blocking the activities of the sodium-retaining actions of DOCA and aldosterone. Over a chance meeting at lunchtime, Kagawa, Sturtevant, and van Arman discussed their exploratory findings with the spironolactones and suggested that the compound (SC-5233) be taken into clinical trials.

Table I. Cyclopentanophenantrene patent claims (Searle 1956-61).

<table>
<thead>
<tr>
<th>Year/patent No.</th>
<th>Claim</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. April 1955 2 705712</td>
<td>Cardioregulatory agents specifically for treating cardiac arrhythmias or hypotension</td>
</tr>
<tr>
<td>2. April 1958 2 875 195</td>
<td>The capacity to decrease serum concentration of cholesterol without estrogenic side effects</td>
</tr>
<tr>
<td>3. December 1959</td>
<td>Unique capacity to block (DOCA) actions on urinary sodium and potassium</td>
</tr>
<tr>
<td>Subsequently abandoned</td>
<td>The compounds are antihypertensive agents</td>
</tr>
<tr>
<td>4. December 1961 3 013 012</td>
<td>Example CPD7 is spironolactone They are diuretic agents To block the effects of DOCA</td>
</tr>
</tbody>
</table>
Thus the first aldosterone antagonist (SC-5233) was discovered serendipitously using compounds synthesized for very different reasons (Table I).

The first aldosterone antagonist to be studied clinically was the spironolactone SC-5233, the pharmacology, specificity, and preclinical toxicology of which are described by Kagawa et al in their 1959 paper.16 It would seem that the senior management in Searle accepted the proposal to take the first antagonist, SC-5233, into clinical trials. The serendipitous nature of this decision is emphasized if one reviews the history of the series of spironolactone patents that were published between 1953 and 1963 by the Head of Chemistry, Cella. A range of biological properties were listed in different patents (Table I). The claim for clinical utility in these differing patents suggests that the original chemistry program was one in search of a disease target, which presumably led research management to abandon the chemistry synthetic program in 1957, but reconsidered this decision some years later. Notably, the first patent to describe the antialdosterone actions of spironolactone as a novel diuretic was published in 1963, several years after Liddle published the clinical effects of five spironolactone analogs in trials between 1957 and 1960.

The initial clinical studies were performed by Liddle’s group at Vanderbilt University, Nashville (Figure 4). In a seminal paper, published in Science in 1957,17 Liddle showed that SC-5233 (which he somewhat confusingly termed spirolactone) increased the urinary excretion of sodium in a patient with congestive heart failure, as well as the sodium-retaining actions of DOCA in patients with Addison’s disease. Liddle had been studying the pathogenesis of edematous states with Bartter’s group at the National Institutes of Health (NIH) and had published a bioassay in the dog to measure the content of aldosterone in the urine of patients with congestive heart failure and ascites secondary to hepatic cirrhosis.18

In the same volume of Science, the Searle researchers showed that both SC-5233 and a more potent analog (SC-8109: the 19-NOR analog) reversed the sodium-retaining actions of DOCA and aldosterone in adrenalectomized rats. It was this model devised by Kagawa that enabled the screening of compounds for aldosterone antagonist properties. In the paper, Kagawa et al showed that the two compounds caused a dose-dependent inhibition that was reversible.16

Three years later, Liddle’s group published the clinical effects of five analogs of SC-5233 in edematous patients.19 They concluded that:

...a number of steroid 17-spirolactones have proved to be effective diuretic agents in man...by antagonizing the renal tubular actions of aldosterone.

Kagawa et al showed that the two compounds caused a dose-dependent inhibition that was reversible.16

One of the four spirolactone analogs marketed as spironolactone. While Liddle viewed spironolactone as a novel diuretic to be used as supplementary therapy with diuretics working by a different mode of action,19 Sturtevant showed that the spironolactone SC-5233 and SC-8109 reduced metacorticoid-induced hypertension in rats. He concluded that:

...the mineralocorticoid and antihypertensive properties of SC-5233 are not directly related.20

**SPIRONOLACTONE: CLINICAL ASPECTS**

It would seem that the introduction of SC-9420 (spironolactone) was based on a series of comparative trials with other analogs from the same chemical series (Figure 5, page 122). Thus, investigators in Canada21 and the UK22 both worked with SC-8109, while another UK group23 worked with the earlier compound SC-5233. Presumably it was the combination of potency and oral activity that led to the final selection of spironolactone, whose oral activity was 46 times more potent than SC-5233 and 5 times more potent than SC-8109.

The objective in developing spironolactone (aldactone) for clinical use was as a novel diuretic agent that had a complementary mode of action to that of the well-established popular thiazide diuretics. The advantage was that when coadministered with a thiazide, it caused an additional Na/water loss, but also reversed the hypokalemia ef-
effects of chronic thiazide therapy. The first published symposium on the clinical use of aldosterone antagonists, in 1960, which was sponsored by Searle, comprises 17 papers presented by leading American clinical scientists in the field of cardiorenal research. Presentations were made on the effects of spironolactones on: primary aldosteronism, congestive heart failure, nephrosis, hepatic failure, and hypertension. The eminent editor, Professor Bartter, described the purpose of the meeting as “pooling of clinical results” because of limitations both of drug supply and patient material.24 By 1960, it became clear that spironolactone was a novel diuretic with additional antihypertensive effects.25

While Searle was pursuing the exploitation of the spironolactones, the Ciba scientists were also synthesizing many analogs of aldosterone, but for use as an agonist with potential utility in Addison’s disease and postoperative shock. In 1958, Desaulles, working at the Ciba Laboratories, provisionally identified an endogenously produced antagonist of aldosterone, which he termed sodium excretion factor.26 Unfortunately, other investigators could not confirm these findings. It is noteworthy that no attempt was made by the aldosterone research group to identify aldosterone antagonists. This is somewhat surprising in that Franz Gross was carrying out experimental canine studies to examine the action of electrocortin in adrenalectomized dogs, a preparation his group had been using for the previous 10 years. It is perhaps ironical that Professor Liddle, who had been so deeply involved in aldosterone research, published an appreciation of Gross’s work in 1978,27 in which he recollected that in a paper in 1958 entitled “Renin und Hypertensin, physiologische und pathologische Wirkstoffe?” he proposed the hypothesis that the renin-angiotensin system stimulated aldosterone secretion, and was in turn suppressed by

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**Figure 5. The relative potencies of three spironolactones in a single system (reversal of urinary Na/K ratio in adrenalectomized rats receiving desoxycorticosterone acetate) are as follows:**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Subcutaneous</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC-5233</td>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td>SC-8109</td>
<td>250</td>
<td>9</td>
</tr>
<tr>
<td>SC-9420</td>
<td>70</td>
<td>46</td>
</tr>
</tbody>
</table>

---

**Figure 6. The Gross hypothesis for the mechanism through which renin and aldosterone secretion are controlled (translated from the German). F. Gross, Senior Cardiovascular Pharmacologist, Ciba AG. After reference 28: Gross F. Klin Wochenschr. 1958;36:693-706. © 1958, Springer Verlag.**
the sodium-retaining action of aldosterone (Figure 6). Thus, given the considerable biological expertise present at Ciba, it remains a mystery as to why no attempt was made to find an aldosterone antagonist.

Spironolactone was marketed in the early 1960s for the indications listed in Table II. Initially, the therapeutic emphasis was on its diuretic activity, and, subsequently, as second-line therapy in essential hypertension. The recommended daily dose for treating hypertension was 100 to 300 mg daily. The optimal hypotensive effect is observed after about 2 weeks' dosing. In the context of serendipity, pharmacokinetic studies subsequently found that spironolactone is metabolized in the liver to three metabolites, two of which have equal antialdosterone activity to the parent compound, each having a terminal plasma half-life of 13 to 15 hours compared with the parent compound, which has a half-life of 2 hours. Thus, spironolactone is basically a prodrug.

While spironolactone has useful clinical effects, it has significant tolerability problems due to painful gynecomastia and menstrual disturbances in premenopausal women. These side effects are attributed to its androgenic and progesteronergic properties. For these reasons, spironolactone was not used in trials of the effects of antihypertensive therapy on morbidity and mortality in the 1980s.

Given the affinity of spironolactone and its metabolites, not only for the mineralocorticoid receptor, but also for the reproductive hormonal receptors, there was clearly a need to identify a compound with significantly greater receptor selectivity and consequently improved patient tolerability. Thus, new chemical analogs were identified in a revived program at Ciba Geigy in the late 1970s, stimulated by the then Research Director Dr. Heini Keberle and led by Dr. Kalvoda, who applied novel molecular modeling techniques to the problem (personal communication). Advances in the molecular biology of steroid receptors permitted chemical analogs to be tested for selective receptor binding properties. Several hundred steroid analogs were tested for their competitive affinities for mineralocorticoid, androgen, and progesterone receptors. The introduction of 9α, 11α epoxy groups into the spironolactone molecule resulted in the discovery of more potent and highly selective aldosterone antagonists, of which epoxymerenone (CGP-30083) proved to be the optimal compound. This compound, now called eplerenone, was patented between 1983/84 (US patent number 4559332) and subsequently taken into clinical trials.

Due to an assessment of the costs of preclinical and clinical development in relation to the probable financial return, the compound was not developed by Ciba Geigy but licensed to, ironically, the Searle company. As a result of these delays the compound, which was shown to be effective for the treatment of hypertension and congestive heart failure (1994-2002), was finally registered in the United States approximately 18 years after its chemical synthesis. Extensive clinical trials have confirmed that the improved specificity of eplerenone is reflected in the absence of gynecomastia and menstrual disturbances.

**DISCUSSION**

The evolution of our understanding of the role of aldosterone in the pathophysiology of cardiovascular disease over the past 50 years is an excellent example of the pivotal role of translational medicine in finding improved medicines. The academic/industrial collaboration between the Taits, Reichstein, and the Ciba steroid chemists made aldosterone available for physiological studies. No doubt other groups would eventually have characterized and synthesized aldosterone. It was the Searle biologists Sturtevant and Kagawa who had the imaginative interest to examine the abandoned spironolactone compounds in their novel adrenalectomized and DOCA rat models. The simultaneous collaboration with the clinical scientist Liddle in Nashville must have been a decisive factor in finally identifying spironolactone (aldactone) as the preferred compound among five analogs by studying them in human subjects. Presumably, the eminent Research Director in Searle, Professor Victor Drill, had a major influence in the decision to pursue these compounds. This is something that would be impossible in today's strict ethical and regulatory environment, although the Food and Drug Administration (FDA) is now trying to encourage companies to carry out early proof-of-concept clinical trials.

For the next 30 years, spironolactone was regarded as a moderately useful agent among the enlarging pool of other cardiovascular agents such as diuretics, angiotensin-converting enzyme inhibitors, and β-blockers for treating both hypertension and congestive heart failure. It was the realization in the 1980s that aldosterone had a range of extrarenal receptors and ac-
This new paradigm concerning the systemic pathophysiological role of aldosterone led to the evaluation of aldosterone antagonists for their therapeutic effects on morbidity and mortality in patients with congestive heart failure. Pitt et al.\(^3\) in a groundbreaking trial, showed that adding spironolactone (25 mg daily) to standard therapy for congestive heart failure reduced morbidity and mortality by 30% in patients with New York Heart Association (NYHA) class III/IV. An analogous study with eplerenone (25 mg daily) to standard therapy for congestive heart failure, showed that adding spironolactone or eplerenone administration. Clinical studies reveal that elevated plasma aldosterone levels increase both vasculopathy and cardiac dysfunction.\(^34\)

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Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. 
Cardiovascular Disease Prevention

Summaries of Ten Seminal Papers

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Dialogues Cardiovasc Med. 2009;14:127-137

1. The strategy of prevention: lessons from cardiovascular disease

2. Sick individuals and sick populations
   G. Rose. Int J Epidemiol. 1985

3. An updated coronary risk profile. A statement for health professionals
   K. Anderson and others. Circulation. 1991

4. Management of raised blood pressure in New Zealand: a discussion document
   R. Jackson and others. BMJ. 1993

   K. Pyörälä and others. Eur Heart J. 1994

6. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project
   R. M. Conroy and others. Eur Heart J. 2003

7. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials

8. Meta-analysis: secondary prevention programs for patients with coronary artery disease
   A. M. Clark and others. Ann Intern Med. 2005

9. Multiple risk factor interventions for primary prevention of coronary heart disease
   S. Ebrahim and others. Cochrane Database of Systematic Reviews. 2006

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Selection of seminal papers by David A. Wood, MSc, FRCPE, FFPHM, FESC; Kornelia Kotseva, MD, PhD, FESC, Cardiovascular Medicine National Heart and Lung Institute (NHLI) - Imperial College London Charing Cross Campus - Fulham Palace Road, London W6 8RF - UK

Highlights of the years by Ian Mudway, MD
Lung Biology - Division of Life Sciences
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The strategy of prevention: lessons from cardiovascular disease

G. Rose


Rose coins the term “the prevention paradox” in this paper based on his Adolf Streicher memorial lecture in 1980; defined as “a measure that brings large benefits to the community offers little to each participating individual.” He juxtaposes the “mass” and “high-risk” strategies for cardiovascular prevention. The mass approach is based on the principle of shifting the whole distribution of a risk factor in the population, e.g., reducing blood pressure by reducing population salt consumption, as compared with a “high-risk” strategy that identifies those individuals with very high blood pressure and advises them individually to reduce their salt intake and take drug therapies. Although these individuals are at very high risk of cardiovascular disease (CVD), there are relatively few of them at the top end of the distribution of blood pressure. So however successful this individualized strategy may be for those being targeted, it cannot impact on the larger proportion of deaths occurring among the many people with slightly raised blood pressure. Although their CVD risk is only modestly increased, there are many more of them and so their relative contribution to the total burden of CVD is much greater. So hypertension clinics only offer a limited answer to the wider population who will develop CVD. Therefore, Rose argues that a mass strategy is inherently the only answer to the problem of a mass disease. In this case: reduce the exposure of the whole population to the determinants of raised blood pressure rather than targeting only those individuals who have very high blood pressure. However, from the individual’s perspective the mass strategy offers little: some more than others and some not at all, whereas the high-risk strategy will definitely benefit those specific individuals to the extent that they comply with the advice and treatment. This is the medical approach—doctors identifying individuals at high risk and managing them accordingly. The mass approach is political.

The Centers for Disease Control and Prevention report that 5 homosexual men from Los Angeles have a rare form of pneumonia associated with a weakened immune system: the first recognized cases of AIDS; the Israeli Air Force destroys Iraq’s Osirak nuclear reactor; and 800 passengers are killed when seven coaches of an overcrowded train fall off the tracks into the River Kosi in Bihar, India.
Sick individuals and sick populations

G. Rose

Int J Epidemiol. 1985;14:32-38

In this classic paper, Rose reflects on the etiology and prevention of disease as a clinician concerned with sick individuals, and as an epidemiologist concerned with sick populations. He was throughout his professional life both a physician and an epidemiologist. Here Rose compares two approaches to prevention of cardiovascular disease: the “high-risk” strategy, which seeks to identify high-risk individuals and offer them individual protection; and the “population strategy,” which seeks to control the determinants of disease incidence in the whole population.

The high-risk strategy is the traditional medical approach to prevention and has several advantages. The intervention is appropriate to the individual. Individuals will be motivated to do something about their increased risk and so will physicians. It is a cost-effective use of resources, and the benefit-to-risk ratio is favorable. However, this approach has a number of disadvantages. It involves screening to identify those at high risk. It does not address the underlying causes of the disease in the population, but only identifies those individuals who are susceptible to such causes, and, however effective our individual care is, they will always be replaced by more and more of the same. The potential for this approach is limited because predicting those individuals who are going to develop the disease is very uncertain, at least in the short term. It is also limited because a large number of people at a small risk may give rise to more cases of disease than the small number who are at high risk. Finally, it requires an individual to change their behavior (eg, to give up smoking), which may run counter to the behavioral norms for that population, and thus more difficult for the individual to achieve.

The population strategy, in attempting to control the determinants of disease incidence, has several powerful advantages. First, it is radical because it aims to remove the underlying causes that make the disease common. It also has a much larger potential, compared with the high-risk strategy, to prevent disease in the population as a whole. Finally, it shapes the norms of behavior for the population (eg, a smoking ban in all public places) and so it is much easier for the smoking individual to quit. However, this approach also has its disadvantages of which the most important is that a preventive measure that brings much benefit to the population offers little to each participating individual—which Rose termed the “prevention paradox.”

Although these two approaches are complementary, the population strategy is paramount. Managing high-risk individuals is a temporary expedient.

British telecom announces it is phasing out its emblematic red telephone booths; Coca-Cola releases “New Coke”: the new drink is a failure and the original formula is back on the market after only 3 months; and US Route 66, established on November 11, 1926, dubbed “Main Street of America,” is decommissioned.
An updated coronary risk profile. A statement for health professionals

K. Anderson, P. W. Wilson, P. M. Odell, W. B. Kannel

_Circulation_. 1991;83:356-362

The Framingham epidemiological study, which started in 1948, followed up a cohort of healthy white Americans who were free of cardiovascular disease (CVD), and related their lifestyles, physiology, and biochemistry to subsequent development of CVD. These pioneering investigators coined the term “risk factor” to describe those personal characteristics—smoking habits, blood pressure, cholesterol, diabetes—that were shown in this prospective cohort study to be independently related to the risk of developing CVD.

Twenty-nine years later, Truett published a coronary heart disease (CHD) risk equation for use by clinicians based on a multivariate analysis of CHD. In addition to age and sex, risk factors included systolic blood pressure, serum cholesterol, cigarette smoking, glucose intolerance, and left ventricular hypertrophy on the electrocardiogram. CHD risk tables in the form of a handbook, based on Framingham equations, were published in 1973, and this was followed by an even simpler version of the equations on a pocket-sized card. Yet, although the Framingham study became famous for being the first to define the causes of CVD, which led to risk factor intervention trials to reduce risk, the CHD risk tables did not engage the interest of physicians. Blood pressure was assessed and treated by physicians in isolation as a disease called “hypertension” rather than seen as one component of the total CVD risk of an individual.

This seminal paper by Anderson provided an update on the equations, which informed the development of the CHD risk chart in the Joint European Societies recommendations on prevention of CHD published in 1994, as well as many other versions of risk estimation around the world. What distinguished Anderson’s updated coronary risk profile from previous versions? First, the baseline examination was a larger and more recent examination from this study (1968-75) and included members of the original Framingham cohort who were free of CVD and the second-generation study population, the Framingham Offspring Cohort. Second, the contribution of high-density lipoprotein (HDL) cholesterol, which was measured for the first time in the Framingham study in 1968, was included. The new equations were used to derive a worksheet for clinicians to estimate CHD risk of patients by assigning a point score to each risk factor, e.g., cigarette smoking scored 4 points, diabetes in women 6 points, and left ventricular hypertrophy on the ECG 9 points. By adding up these points you could relate this score to the probability (%) of developing CHD over 5 or 10 years. The authors also provided a table to compare the estimated risk for a given patient’s age and sex to the average 10-year risk for the Framingham population. Anderson et al suggested that estimating CHD risk could be useful in projecting patient progress in clinic at which preventive cardiology is the goal, such as managing blood pressure and lipids.

Risk scores can provide a framework for intervention. They did so for the first time in an official guideline in 1993 when Jackson recommended managing blood pressure in the context of absolute CVD risk.

1991

Edith Cresson is appointed France’s first female prime minister by President François Mitterrand, but her unpopularity compels her to leave office after less than one year; Queen Elizabeth II addresses the US Congress, the first British monarch to do so; and Prince Norodom Sihanouk returns to Phnom Penh, Cambodia, after 13 years of exile, becoming king two years later. The _Guinness Book of World Records_ identifies him as the politician having served the world’s greatest variety of political offices since 1941.
Management of raised blood pressure in New Zealand: a discussion document

R. Jackson, P. Barham, J. Bills, T. Birch, L. McLennan, S. MacMahon, T. Maling

BMJ. 1993;307:107-111

Jackson and colleagues’ seminal paper on the management of raised blood pressure represented a paradigm shift in thinking about the concept of “hypertension” and its treatment. In the 1950s, the first drugs for lowering blood pressure were used to treat malignant hypertension, often symptomatic, with very high blood pressure levels, and usually fatal if left untreated. Subsequently, randomized controlled trials showed that treating less extreme cases of raised blood pressure reduced the risk of cardiovascular disease (CVD)—initially stroke and then coronary disease and renal disease. As a consequence, the level for initiating antihypertensive drug treatment was progressively lowered. However, blood pressure is a risk factor for CVD, not a disease in itself. As the blood pressure rises, so does risk of CVD, and so the definition of high blood pressure is arbitrary. Yet, in the early 1990s, guidelines for the management of blood pressure based all decisions to treat on the blood pressure level alone.

Jackson et al asked the question, when is the risk of CVD sufficiently high, in someone with raised blood pressure, to justify drug treatment? In other words, they put the management of blood pressure in the context of total CVD risk. He illustrated this principal with a simple clinical example. A 60-year-old woman with a diastolic pressure of 100 mm Hg, but no other risk factors, has an absolute risk of developing CVD of about 10% over 10 years, but would be eligible for antihypertensive drug therapy. In contrast, a man of 70 years with multiple risk factors for CVD, but a diastolic blood pressure of 95 mm Hg, which would give him an absolute risk of developing CVD of about 20% over 10 years, may not receive drug therapy. So he proposed that estimation of absolute risk of developing CVD, based on an assessment of all risk factors, is a prerequisite to a decision about treating blood pressure with drugs.

Jackson et al recommended that people with an absolute risk of 20% or more in 10 years, and a sustained blood pressure of greater than 150 mm Hg systolic or 90 mm Hg diastolic (phase 5), should be considered for treatment to lower blood pressure. To calculate absolute CVD risk, they used data from the Framingham epidemiological study and expressed this as a figure relating different levels of blood pressure to numbers of risk factors (one, two, three, or major) for men and women at different ages from 40 to 70 years. He defined risk factors as cigarette smoking, diabetes, a ratio of cholesterol to high-density lipoprotein of >6.1, a body mass index of >30 kg/m2, and a family history of premature CVD (in a parent or sibling before the age of 55 years). A major risk factor was principally defined as the diagnosis of symptomatic CVD. The authors qualified this recommendation on absolute risk by acknowledging that younger people in their 20s or 30s with blood pressures greater than 150 mm Hg systolic or 90 mm Hg diastolic may require blood pressure treatment even though they are at low absolute risk. Similarly, people between the ages of 40 and 60 years with blood pressure levels above 170 mm Hg systolic or 100 mm Hg diastolic may also benefit from blood pressure-lowering even when their absolute risk of CVD is less than 20%.

This recommendation to view blood pressure management in the context of absolute CVD risk challenged the traditional view of “hypertension” and its management and was followed by a succession of risk charts starting with the Joint European Societies’ CHD Risk Chart in 1994 and then the New Zealand Cardiovascular Risk Chart the following year. The principle of total CVD risk being the overriding determinant of whether or not to treat blood pressure in the context of primary prevention is now universally accepted by all international guidelines on CVD prevention.
Prevention of coronary heart disease in clinical practice. Recommendations of the Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension

K. Pyörälä, G. De Backer, I. Graham, P. A. Poole-Wilson, D. Wood

Eur Heart J. 1994;15:1300-1331

In 1992, Kalevi Pyörälä, Professor of Medicine at the University of Kuopio, brought together the European Society of Cardiology, European Atherosclerosis Society, and European Society of Hypertension in a unique partnership to create a common European agenda for prevention of coronary heart disease (CHD). The recommendations of these three Societies for clinical practice were announced at the World Congress of Cardiology in Berlin in 1994. Central to this guidance was the concept of risk: “For a proper assessment of CHD risk in an individual, the presence or absence and the degree of severity of each individual risk factor has to be considered.”

Up to this point, risk factor guidelines addressed single risk factors, e.g., management of “hypertension” or “hyperlipidemia,” resulting in undue emphasis being placed on individual risk factors rather than total CHD risk. A new Coronary Risk Chart was the centerpiece of these recommendations, based on a risk function derived from Framingham. Using this chart, clinicians could estimate the probability of their patients developing CHD over 10 years, based on age, sex, smoking habit, systolic blood pressure, and total cholesterol. A CHD risk of 20% or higher was a signal for intensive risk factor modification, including the use of drugs, if appropriate. The chart was published in black and white to facilitate dissemination throughout Europe, and a full color version was distributed at the World Congress. This European risk chart was the first of its kind and was followed by the New Zealand Cardiovascular Risk Chart, and other variations on the central theme of targeting those patients at highest multifactorial risk; the higher the total risk the more intensive the intervention. This unique European partnership between these three major Societies broke the silo mentality of treating single risk factors in isolation. This first Task Force laid the foundations on which three subsequent Task Forces on cardiovascular disease prevention in 1998, 2003, and 2007 were able to enlarge this European collaboration of professional Societies and produce updated guidelines for evidence-based preventive cardiology practice founded on the central principal of total risk assessment and management.

1994

The Zapatista Army of National Liberation begins its war in Chiapas, Mexico; the Church of England ordains its first female priests; and Nature reports the finding of the first complete Australopithecus afarensis skull in Ethiopia.
The Joint European Societies’ recommendations on coronary heart disease (CHD) prevention in 1994 broke the mould of single risk factor management by advocating total CHD risk estimation as the prerequisite to deciding to treat blood pressure or lipids. The CHD risk charts were based on the Anderson Framingham equation, with the caveat that this epidemiological study may underestimate CHD risk in very-high-risk European populations, such as countries in Eastern Europe, and underestimate risk in low-risk populations of southern Europe.

A European epidemiological database was needed and this was the birth of the SCORE (Systematic COronary Risk Evaluation) project. Graham and colleagues pooled datasets from 12 European prospective cohort studies—205 178 persons (117 098 men and 88 080 women) with 2.7 million years of follow-up and 7934 cardiovascular deaths, of which 5652 were deaths due to coronary heart disease—compared with just […] individuals in the Framingham study. Ten-year risk of fatal cardiovascular disease was calculated using a Weibull model in which age was used as a measure of exposure to risk (time) rather than as a risk factor. Equations were calculated for high-risk and low-risk regions of Europe, and for each of these regions you can either calculate cardiovascular disease (CVD) risk using total cholesterol or the ratio of total cholesterol/high-density lipoprotein (HDL) cholesterol. The risk threshold for intervention was defined as a total CVD risk of 5% or higher for fatal cardiovascular disease over 10 years.

The final signal is received from NASA’s Pioneer 10 space probe 7.5 billion miles from Earth; an American businessman is admitted to the Vietnam France Hospital in Hanoi with the first diagnosed case of SARS; and the Human Genome Project is completed, with 99% of the genome sequenced.
Evidence for cardiac rehabilitation was first summarized by Oldridge who reported in 1988 that patients receiving exercise therapy had fewer cardiac deaths and longer survival compared with those with usual medical care. Subsequent updates of this original meta-analysis, three in total, and further trials, found the same result: reductions in total and coronary mortality ranging from 20% to 32%, but no reduction in the risk of recurrent myocardial infarction or revascularization.

Taylor and colleagues’ paper updated the systematic review of exercise-based cardiac rehabilitation and meta-analysis and addressed previous concerns regarding applicability of this evidence to routine clinical practice. Previous meta-analyses had not reported outcomes of secondary prevention through risk factor modification and the impact of modern cardioprotective drug therapies on the magnitude of benefit of exercise-based cardiac rehabilitation. A total of 48 randomized controlled trials were included with a total of 8940 patients with coronary artery disease. Of these, 19 trials were exercise only, 30 were comprehensive cardiac rehabilitation (in combination with psychosocial or educational interventions), and 1 trial directly compared exercise with a comprehensive approach. Overall cardiac rehabilitation was associated with a significant reduction in all-cause mortality (odds ratio [OR], 0.80; 95% confidence interval [CI], 0.68 to 0.93), and total cardiac mortality (OR, 0.74; 95% CI, 0.61 to 0.96), and trials conducted in the last decade (with increasing use of revascularization and cardioprotective drug therapies) continued to show benefits of cardiac rehabilitation. However, there were no differences in rates of nonfatal myocardial infarction, coronary artery bypass grafting (CABG), or percutaneous coronary intervention (PCI) with cardiac rehabilitation.

For risk factor management, the proportion of patients who were smoking was reduced significantly with cardiac rehabilitation (OR, 0.64; 95% CI, 0.50 to 0.83). However, other risk factor changes were more modest. Systolic blood pressure was significantly reduced, but only by 3.2 mm Hg (95% CI, −5.4 to −0.9 mm Hg), and there was no reduction in diastolic pressure. Total cholesterol was only reduced by −0.37 mmol/L (95% CI, −0.63 to −0.11 mmol/L) with no significant difference in low-density lipoprotein (LDL) levels. These modest reductions suggest that drug treatments were not being effectively used in these programs. So, apart from smoking, these cardiac rehabilitation programs did not impact on risk factor management to the extent now possible with a combination of a lifestyle intervention, focusing on both diet and physical activity, and using modern drug therapies to lower blood pressure and modify blood lipids. Diabetes, which is an important risk factor for coronary artery disease, was not addressed in this meta-analysis.

Interestingly, Taylor et al tested several a priori hypotheses on the effect of cardiac rehabilitation on total mortality across particular subgroups: type of cardiac rehabilitation (exercise only versus comprehensive cardiac rehabilitation); dose of exercise intervention (based on a composite measure of duration of exercise, plus intensity, frequency, and length of exercise sessions), and program duration. There was no difference in outcome, expressed as total mortality, between exercise-only versus comprehensive cardiac rehabilitation. Nor was there any difference by exercise dose (which is surprising) or duration of the programs. The latter finding is in contrast to the first review by Oldridge who reported a greater reduction in all-cause death, with rehabilitation trials with follow-up lasting more than 36 months.

So, do we only need to offer our coronary patients an exercise program of light intensity and short duration? The answer is unequivocally no. These results are hypothesis-generating and need to be rigorously evaluated in randomized controlled trials assessing clinical and cost-effectiveness.

Arsenal FC remains undefeated for a whole season to win the Premiership title; the last Oldsmobile rolls off the assembly line; and Canada wins the World Ice Hockey Championship in Prague.
Clark et al. in this meta-analysis, aimed to determine the effectiveness of secondary prevention programs, with and without exercise, in patients with coronary artery disease. Sixty-three randomized controlled trials were identified, including 26 trials that were not included in a systematic review of cardiac rehabilitation (see Taylor RS et al., *Ann J Med.* 2004;116:682-692), and this meta-analysis is based on 21,295 patients. The risk ratio for all 40 trials reporting all-cause mortality was 0.85 (95% confidence interval [CI], 0.77 to 0.94), and this result differed over time: 0.97 (95% CI, 0.82 to 1.14) at 12 months and 0.53 (95% CI, 0.35 to 0.81) at 24 months. In those trials reporting follow-up at least 5 years after initiation of the program the benefit was clearly sustained with a risk ratio of 0.77 (95% CI 0.63 to 0.93). There was no heterogeneity in treatment effect between the three types of secondary prevention programs included, namely, programs without exercise, programs with exercise, and exercise-only programs. The risk ratio for all-cause mortality in all exercise-based programs (27 trials and 6,940 patients) was 0.83 (95% CI, 0.72 to 0.96) compared with a risk ratio of 0.87 (95% CI, 0.76 to 0.99) for the nonexercise-based programs (14 trials and 9,202 patients). The risk ratio for recurrent myocardial infarction was 0.83 (95% CI, 0.74 to 0.94) over a median follow-up of 12 months, and this outcome did not differ between the three types of programs. These beneficial results should not be viewed as “best case scenario,” as trial participants assigned to control groups also received better than usual care, and therefore the impact on all-cause mortality and recurrent myocardial infarction is likely to be even greater in everyday clinical practice.

Despite these impressive benefits, other studies consistently demonstrate that fewer than 50% of patients with coronary artery disease access prevention and rehabilitation programs. In addition, those groups less likely to be referred, to attend, and to complete such programs are often those in greatest need, such as women, the elderly, low-income groups, and ethnic minorities. The clinical challenge is to increase access to, and participation in, comprehensive prevention and rehabilitation programs for all patients with atherosclerotic disease.

In Bucharest, Romania, Adriana Iliescu gives birth at 66, becoming the oldest woman in the world to do so; Prince Charles weds Camilla Parker Bowles, who assumes the titles of Her Royal Highness and Duchess of Cornwall; and on December 31st, another second is added, 23:59:60, called a leap second, to end the year 2005: the last time this occurred was on June 30, 1998.
Evidence from single risk factor interventions such as lowering blood pressure, or lowering cholesterol, is impressive. So when you intervene on all cardiovascular risk factors at the same time—stopping smoking and reducing blood pressure and cholesterol—you would expect the combined effect to be impressive. In this systematic review from the Cochrane Collaboration the evidence from randomized controlled trials of multiple risk factor interventions in primary prevention of cardiovascular disease (CVD) is summarized with surprising results.

Interventions used counseling and/or educational approaches with or without pharmacological interventions in relation to smoking cessation, reducing blood pressure, and cholesterol. Thirty-nine trials meeting the selection criteria were analyzed and 10 of these reported clinical events. The pooled odds ratios for total and coronary heart disease (CHD) mortality were 0.96 (95% confidence interval [CI], 0.89 to 1.04) and 0.96 (95% CI, 0.92 to 1.01), respectively. So multiple risk factor interventions have very limited, if any, impact on mortality. However, the authors qualify this statement by pointing out that a small (about a 10% reduction in coronary mortality), but potentially important benefit of treatment may have been missed. Importantly, in the 38 trials reporting risk factor changes, the odds of a reduction in risk factor prevalence were 20% (95% CI, 8% to 31%), which is an important health benefit. In contrast, the mean difference in systolic blood pressure between intervention and control was only −3.6 mm Hg, and the reduction in cholesterol only −0.07 mmol/L, which, although statistically significant, is very modest. Indeed these differences may be overestimates of the treatment effect, because they are based on those who stayed in the trials. More intensive lifestyle intervention, and the appropriate use of drug therapies, would produce larger differences in risk factor control, which would be expected to further reduce CVD.

What this review highlights is the apparent discrepancy between the unequivocal benefit of single risk factor trials, eg, to lower blood pressure, and those observed in multiple risk factor trials.

World Health Organization

WHO Library: Geneva, Switzerland, 2007

Noncommunicable diseases, of which half are due to cardiovascular disease (CVD), are predicted to increase substantially over the coming years, and much of this disease burden will fall on low- and middle-income countries. This World Health Organization (WHO) report departed from the traditional view of CVD prevention by this organization in moving the focus from single risk factors to total risk assessment and management. In contrast to the 2003 WHO/International Society of Hypertension (ISH) statement on management of “hypertension” (the single risk factor approach), this document provides guidance to policymakers and health care workers on how to target individuals at high risk of developing CVD, at all levels of the health system and in different resource settings, using evidence-based and cost-effective preventive approaches. This guide to CVD prevention was based on the total risk approach to prevention of CVD elaborated in the World Health Report of 2002. The centerpiece is the new WHO/ISH cardiovascular risk prediction charts that were developed for each of the 14 WHO subregions.

The charts only provide approximate estimates of CVD risk in people who have not already developed cardiovascular disease. These risk estimates represent the average for the subregion and do not capture the variation in CVD risk within subregions or countries. They are a useful tool for health care workers to identify those at high CVD risk, and to motivate patients, particularly to change behavior and, when appropriate, to take antihypertensive and lipid-lowering drugs and aspirin. The charts are available for people with and without diabetes. In settings where facilities for measuring cholesterol are not available, versions of the prediction charts that do not use cholesterol are available. The risk factors included in the charts—age, sex, smoking habit, systolic blood pressure, cholesterol, and diabetes—do not encompass all factors that contribute to the development of CVD. Health care worker must therefore take into account obesity (and especially central obesity), family history of CVD, a sedentary lifestyle, low high-density lipoprotein (HDL) cholesterol, raised triglycerides, dysglycemia (impaired fasting glucose and glucose intolerance), and other factors such as ethnicity and socioeconomic status. The CVD risk thresholds for intervention are stratified according to resource setting: high-resource, 20%; medium-resource, 30%; and low-resource, 40% risk of developing CVD over 10 years. There are huge differences in the prevalence of high-risk individuals between WHO regions. For example, in European region C, about 40% of men have a CVD risk of 30% or higher, compared with only 4% in African region E.

The objective of this report is to reduce the incidence of heart attacks, strokes, renal failure associated with hypertension and diabetes, as well as the need for amputation of limbs because of ischemia, by reducing total CVD risk. It is an evidence-based framework for CVD prevention that can be adapted to suit different political, social, cultural and medial circumstances.

Ban Ki-moon becomes the new United Nations Secretary-General; former chess world champion Garry Kasparov is arrested in Moscow for participating in a banned march; and Gordon Brown is elected Leader of the UK Labour Party and Prime Minister of the United Kingdom.
Cardiovascular Disease Prevention

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