

Risk factors and prevention of cardiovascular disease: a review

Guy G. De Backer, MD, PhD

Department of Public Health - Ghent University and Department of Cardiology - University Hospital - Ghent - BELGIUM

In light of the recently issued guidelines of the Fourth Joint Task Force of the European Society of Cardiology and Other Societies on CVD Prevention in Clinical Practice and of the Systematic COronary Risk Evaluation (SCORE) cardiovascular disease risk estimation charts, this review discusses the risk factor concept in relation to the prevention of cardiovascular disease in clinical practice, in particular in relation to atherosclerosis and its clinical manifestations such as angina pectoris, myocardial infarction, transient ischemic attacks, and ischemic stroke. Special attention is given to modifiable risk factors such as smoking, sedentariness, nutritional imbalance, impaired glucose tolerance and diabetes, blood pressure elevation, dyslipidemia, overweight and abdominal adiposity, and markers of chronic inflammation. Other emerging risk factors are gaining increasing importance in contributing to the estimation of total cardiovascular (CV) risk. These include heart rate, socioeconomic status, and gender. The latter are of great importance in helping the clinician tailor preventive strategies to individual patients. The estimated total CV risk should be handled as a continuum and not in a dichotomous way. The higher a patient's total CV risk, the more aggressively should CVD prevention be implemented.

Keywords: risk factor; prevention; epidemiology; atherosclerosis; blood pressure; blood lipid; smoking; total cardiovascular risk

Address for correspondence: Prof Dr Guy G. De Backer, Department of Public Health, Ghent University, University Hospital, De Pintelaan 185, B-9000 Ghent, Belgium
(e-mail: guy.debacker@ugent.be)

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This review is devoted to risk factors for cardiovascular disease (CVD), in particular in relation to atherosclerosis, which culminates in thrombus formation and gives rise to clinical manifestations such as angina pectoris, myocardial infarction, transient ischemic attacks, ischemic stroke, and intermittent claudication. Throughout the world, CVD is a leading cause of premature mortality and chronic illness—in other words, burden of disease, quantified in terms of disability-adjusted life years (DALYs)—and increasing health care costs.¹ Results from global burden of disease studies indicate that CVD will become even more frequent especially in developing countries.² The potential benefits of risk factor management with regard to prevention of CVD are solidly established by observational and experimental studies.

These issues have been addressed by the successive editions of the guidelines of the Joint European Task Force on CVD Prevention in Clinical Practice, the latest update of which has been published in 2007.^{3,4}

THE RISK FACTOR CONCEPT

Definition and uses

In the context of CVD, a risk factor can be defined as a characteristic that is associated with increased or decreased likelihood of subsequent development of CVD. This concept can be used for different purposes, each of which has its own strengths and limitations: to study the cause or pathophysiology of CVD; to estimate total cardiovascular (CV) risk; to understand the dynamics of the CVD epidemic within and between populations. It is important to point out the differences and complementarities between the public health and clinical practice approaches. Indeed, one should differentiate between risk factors concerning a given person and entire populations, as did the late G. Rose who made a clear distinction between sick individuals and sick populations.⁵

This is well illustrated by the case of arterial hypertension. There is a demonstrated relationship between blood pressure (BP) and CVD: the higher the BP the higher the risk for developing CVD. *Figure 1* shows simulated distributions of systolic BP (SBP) in two elderly populations; one could be from a Western European population group, the other from a primitive population group. This graph raises two questions, for which different approaches are needed:

- Why do some individuals develop hypertension and others not?
- Why is hypertension more common in one group compared to the other?

In terms of individual subjects, the answer to the first question is similar in both of the above population groups and involves genetics: some subjects are genetically more prone to hypertension than others. The obvious course of action here is to try to identify genetic determinants of arterial hypertension in both population groups.

However, genetics does not explain the marked difference in prevalence of BP elevation between these populations. This suggests that the determinants of mean elevated systolic blood pressure (SBP) in an entire group may be different from those in a given individual. Again, why is the entire distribution curve of SBP displaced in the Western European population group, with a mean SBP around 160 mm Hg versus 135 mm Hg in the other population group? In order to answer this, the groups should be studied as a whole, not the individuals. At the community level, environmental factors are more important than genetic factors, while the latter play a greater role at the individual level; nevertheless, in both cases, the outcome is determined by the interaction between environment and genetic makeup.

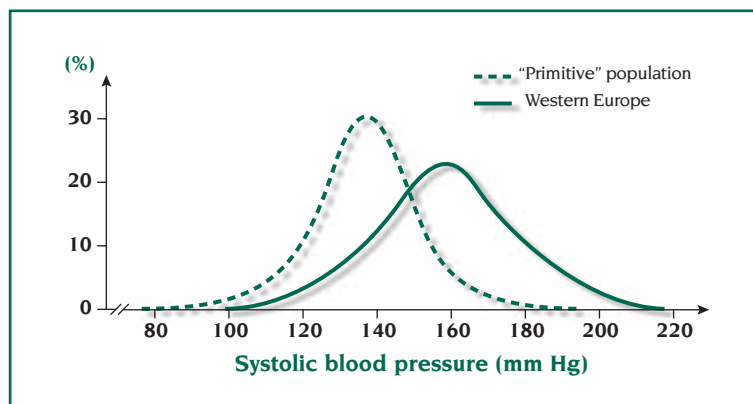


Figure 1. Simulated distribution of systolic blood pressures in two typical population groups.

The risk concept can also be used in clinical practice to determine the possible causes of CVD. In the search for the mechanisms of onset or progression of a disease, observational epidemiology will help identify associations (risk factors) explaining the pathophysiology. In this context, it is important to distinguish between nonmodifiable and modifiable risk factors. Thus, male sex is a nonmodifiable risk factor for CVD, which reflects the susceptibility conferred by the male sex and/or the protection conferred by the female sex; the same is true of a personal history of CVD or a family history of premature CVD. These indicators are important in estimating total CV risk in an individual, however, because they are not modifiable, they are less determining in terms of risk factor management. In contrast, risk factors such as smoking or dietary pattern can be considered as exposure, and are amenable to modification. When the aim is primarily to identify causal risk factors, it is recommended to study particular characteristics of the association between a risk factor and the disease; this has been clearly shown by Sir A. Bradford Hill.⁶ The nature of the relationship should be analyzed; in particular its strength, the consistency of findings, the specificity of the association, the relationship in time, the biological gradient, its biological plausibility, the coherence with other research findings, and, if applicable, how it changes in experimental settings.

Finally, some risk factors can be used independently of causality. One example is social class: in the most disadvantaged segments of the population, CVD occurs 2 to 3 times more frequently than in the highest social classes. Although social class is not a causal risk factor for CVD, it can be readily used to identify groups at higher need for prevention within a community. It is important to take such factors into account, firstly because resources for prevention are

SELECTED ABBREVIATIONS AND ACRONYMS

BMI	body mass index
CHD	coronary heart disease
CRP	C-reactive protein
CVD	cardiovascular disease
DBP	diastolic blood pressure
SBP	systolic blood pressure
SCORE	Systematic COronary Risk Evaluation
WC	waist circumference
WHR	waist-hip ratio



limited, and have to be used as efficiently as possible to identify subjects at high risk in whom intervention will yield the best absolute return, and secondly because classic risk scoring methods tend to underestimate risk in socioeconomically deprived people, further increasing disparities in CVD incidence between social classes.⁷

Thus, the risk factor concept can be used for different purposes, each of which requires a specific approach. This review focuses on the use of the risk factor concept in clinical practice, particularly on the importance of total CV risk estimation and on interactions between risk factors.

ABSOLUTE VERSUS RELATIVE RISK

Absolute cardiovascular (CV) risk is the probability that a person or a group of persons will develop CVD over a fixed period of time. For instance, results from the Systematic COronary Risk Evaluation (SCORE) project indicate that the risk of dying from CVD within the next 10 years for a man from northern or eastern Europe, aged 60 years, with an SBP of 160 mm Hg and a total cholesterol value of 7 mmol/L is 20% if he smokes and 10% if he does not smoke.⁸

Relative risk is generally expressed as a ratio comparing a person or a group of persons with another person or another group of persons that differ in terms of exposure. For instance, the example given above comparing men according to their smoking status yields a relative risk of 20/10, or 2: the man who smokes has twice the risk of dying in the coming 10 years from CVD compared with the nonsmoker.

Relative risk is of great scientific interest; it says something about the strength of the association. However, in terms of public health, absolute risk is also very important; a given relative risk reduction will end up in many more end points avoided if applied to a group of subjects at high absolute risk than one at low absolute risk.

IDENTIFICATION OF RISK FACTORS

Risk factors can be identified by means of cross-sectional or case-control studies. However, such study designs are more prone to various kinds of biases than prospective cohort studies. They are nevertheless of interest to answer specific questions, as shown recently in the INTERHEART study⁹ where it was reported that a limited set of risk factors (abnormal lipids, smok-

ing, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruits, vegetables and alcohol, and regular physical activity) account for most of the risk of myocardial infarction worldwide in both sexes and at all ages in all regions.

NONMODIFIABLE RISK FACTORS

Age is among the strongest CV risk factors; its relationship with CV mortality is exponential. It is an important factor to consider in total CV risk estimation, but its nonmodifiable nature limits its use in the management of CV risk. Given the nature of its association with CVD, it explains the paradox that if prevention of CVD is successful in a given generation, total CV mortality will increase: by preventing premature deaths, a larger proportion of the population will grow old and enter the age group (>85 years) where death is attributed to CVD in a majority of cases.

Other nonmodifiable risk factors are gender and a family history of premature CVD. Total CV risk levels in women tend to resemble those of men 10 years younger. Thus, risk is merely deferred by 10 years and ultimately more women than men die from CVD. Whether the modifiable risk factors are associated with different relative risks in men compared with women or whether there are gender-specific risk factors is discussed by Karin Schenck-Gustafsson in this issue of *Dialogues in Cardiovascular Medicine*.

The magnitude of the risk associated with a family history of premature CVD (usually defined as CVD in a first-degree male relative <55 years and female relative <65 years) is in the range of 1.5-1.7 and is independent of classic CV risk factors.

Genotypes are a class apart; several variants are associated with a significant although rather modest effect on CV risk; understanding genetic determinants may be useful in identifying high-risk subjects in the near future. See issue of *Dialogues in Cardiovascular Medicine* (2004;9:1-68) devoted to "Genetic Risk Factors and CVD."¹⁰

A special group of nonmodifiable risk indicators relate to existing CVD in a given person. Patients with established CVD are at high risk for recurrent events, but indicators of existing vascular damage in asymptomatic subjects can also help in the identification of high-risk subgroups in the community. Different techniques have been recommended such as the ankle-brachial index; the intima-media thickness of the carotid

artery; calcium deposits in the coronary arteries identified by CT scan; and left ventricular wall motion abnormalities identified by echocardiography. These factors should be considered as indicators of existing disease in asymptomatic subjects; they can be of help in developing prevention strategies, but are not further discussed here.

MODIFIABLE RISK FACTORS

Risk factors that can in principle be prevented, changed, or controlled are modifiable; but a modifiable risk factor per se does not equate with reversibility of CVD. Whenever possible, results from intervention trials should be used to prove that management of modifiable risk factors also results in a reduction of CVD.

Major modifiable risk factors include: sedentariness, smoking, dietary imbalance, impaired glucose tolerance and diabetes mellitus, elevated blood pressure, abnormal blood lipids, and obesity. Other factors are also of importance: psychosocial, such as perceived stress at work, symptoms of depression, low socioeconomic status, as well as indicators of chronic inflammation and hemostatic factors.

Sedentariness

We refer the reader to a previous issue of *Dialogues in Cardiovascular Medicine* on "Sport, Exercise, and the Heart" (2002;7:141-208).¹¹ There are no randomized controlled trials directly testing the hypothesis that physical activity prevents CVD or that inactivity induces clinical events. Problems related to study design and methodology prohibit direct testing of the exercise hypothesis. However, systematic reviews and meta-analyses of observational studies have evidenced reduced CV risk in physically active subjects.^{12,13} The protective value of physical activity is independent of measures of total CV risk, eg, the score estimated using the Framingham risk equation.¹⁴ All available evidence indicates that the association between physical activity pattern and CVD is causal. Physical activity has both a direct protective effect on the development of CV events and an indirect effect through its influence on risk factors.

Nutrition and CVD

"Lifestyle, Diet, and the Heart" has been the subject of yet another issue of *Dialogues in Cardiovascular Medicine* (2005;10:69-136).¹⁵ Worldwide there is strong and consistent evidence of graded relationships between saturated fat intake and the occurrence of CVD

at the community level. However, there is more to it than this: the development of CVD is also associated with other aspects of dietary imbalances related to the intake of hydrogenated fats, *trans* fatty acids, fiber, refined and processed sugars, salt, whole-grain products, or fruits and vegetables. Recently it was shown that a high dietary glycemic load and glycemic index increase the risk of CVD, particularly in overweight women.¹⁶

Dietary factors play a crucial role in population CVD prevention strategies. On an individual basis as well, dietary factors are essential in any preventive program. Translated into recommendations that have to be adapted into practical advices considering local cultural habits, this can be summarized as follows:

- Foods should be varied and energy intake must be adjusted to maintain ideal weight.
- The consumption of certain nutrients should be encouraged in almost all societies: fruits and vegetables, whole-grain cereals, low-fat dairy products, fish.
- In most societies, total fat intake is excessive and the intake of saturated fats should be reduced. Dietary cholesterol should be restricted to <200 to 300 mg/day.
- Salt intake should be restricted to <6 g/day.

These general recommendations should be adapted to the needs of a given individual depending on total CV risk and on particular risk factors such as body mass index (BMI), waist circumference, blood pressure, lipid profile, fasting and postprandial blood glucose, etc.

Tobacco smoking

There is overwhelming evidence for an adverse effect of smoking on health. In long-term smokers, smoking is responsible for 50% of all avoidable deaths and one half of these are due to CVD.¹⁷ This adverse effect of smoking is related to the amount of tobacco smoked daily and to the duration of smoking. Originally a male preserve, male and female smoking patterns in recent decades have become increasingly similar. In prospective studies, the relative mortality from vascular disease has been found higher in female smokers than in male smokers; this difference remains significant after adjustment for major CV risk factors.¹⁸

The impact of smoking on atherosclerosis progression is greater in subjects with diabetes and hypertension. The risk of future cardiovascular disease is particularly high if smoking starts before the age of 15 years. Passive smoking has now been shown to increase the risk of coronary heart disease and other smoking-re-



lated diseases¹⁹; the effects of passive smoke on the cardiovascular system may even be greater than expected; some of these effects appear rapidly and can precipitate acute manifestations of CVD.

Although the exact mechanisms by which tobacco smoking increases the risk of atherosclerotic disease are not yet fully understood, smoking enhances both the development of atherosclerosis and the occurrence of superimposed thrombotic phenomena. The latter effect may be even more important, because stopping smoking leads to a quicker reduction in the risk of subsequent coronary heart disease events in patients with established coronary heart disease than in asymptomatic individuals; in patients with established coronary heart disease, the risk falls within 2 to 3 years to the level of those coronary heart disease patients who never smoked, whereas in asymptomatic individuals up to 10 years are needed to reach the risk level of those who never smoked.

In a meta-analysis of cohort studies on the effect of smoking cessation on mortality after a myocardial infarction, all studies showed a mortality benefit with a combined odds ratio in those who quit of 0.54 (95% confidence interval [CI], 0.46-0.62). The mortality benefit was consistent regardless of sex, duration of follow-up, study site, and time period.²⁰ Therefore, stopping smoking after a myocardial infarction is potentially the most effective of all preventive measures. Appropriate effort should be devoted to this end.

Impaired glucose tolerance and diabetes

Epidemiological studies have consistently shown a linear relationship between nonfasting glucose values and risk of developing CVD. This is confirmed by 2-hour oral glucose tolerance test (OGTT) values²¹ and assay of glycated hemoglobin HbA_{1c}.²² The relationship between hyperglycemia and CVD should be considered as a continuum.

Impaired glucose tolerance is associated with an increased risk of developing coronary heart disease as well as other atherosclerotic diseases.²³ In diabetes, the relative risk of CVD is of the order of 2 to 3 in men and of 3 to 5 in women, while in people with impaired glucose tolerance the relative risk is 1.5 compared with people with normal glucose tolerance. Subjects with type 1 diabetes have a 2- to 3-fold increase in the risk of developing CVD. This increased risk is almost entirely confined to patients developing diabetic renal disease.

All type 2 diabetes patients are at increased risk of CVD, even in the absence of diabetic nephropathy. Finnish data published in 1998 suggested that the risk of developing a myocardial infarction in patients with type 2 diabetes was of the same order as for patients without diabetes who had already suffered a first myocardial infarction.²⁴ This finding had a decisive influence on the drafting of treatment guidelines, in which diabetes was labeled as a "CVD equivalent" in terms of risk assessment. Since then, however, many studies based on other study cohorts have addressed this issue and it has become clear that the concept of diabetes as a CVD equivalent was an oversimplification. Indeed, and the impact of type 2 diabetes on CVD risk is influenced by a number of factors, including duration of diabetes, age, and sex.²⁵⁻²⁸ Thus, the relative impact of type 2 diabetes on CVD risk is stronger in women than in men, suggesting that type 2 diabetes can be more convincingly considered as a CVD equivalent in women than in men.²⁹⁻³³ A substantial proportion of the excess risk of atherosclerotic disease in both type 1 and type 2 diabetes is caused by the diabetic state itself. However, conventional modifiable major cardiovascular risk factors (elevated blood pressure, elevated total (and low-density lipoprotein [LDL]) cholesterol and smoking) exhibit a similar relationship to risk of CVD in subjects with type 1 or 2 diabetes as in nondiabetic subjects. Because diabetes per se increases the absolute risk of CVD, the additional impact of conventional risk factors leads to a more dramatic increase in absolute risk than in nondiabetic subjects, and thus management of these risk factors offers a great potential for prevention. Diabetes also remains an important risk factor for mortality in patients with established CVD.³⁴

Blood pressure elevation

Elevated blood pressure has been identified as a risk factor for coronary heart disease (CHD), heart failure, cerebrovascular disease, and renal failure in both men and women in a number of epidemiological studies.²⁹ Compilation of observational data confirms that both SBP and diastolic BP (DBP) show a continuous and graded independent relationship with the risk of stroke and coronary events. Data involving more than one million individuals indicate that death from both CHD and stroke increases progressively and linearly from BP levels as low as 115 mm Hg systolic and 75 mm Hg diastolic upward.³⁵ Increased risks are present in all age groups ranging from 40 to 89 years old. For every 20-mm Hg systolic or 10-mm Hg diastolic increase in BP, there is a doubling of mortality from both CHD

and stroke.³⁵ The apparently simple direct relationship between increasing SBP and DBP and CV risk is confounded by the fact that SBP rises throughout adult age in the vast majority of populations, whereas DBP peaks at about age 60 in men and 70 in women, and falls gradually thereafter.

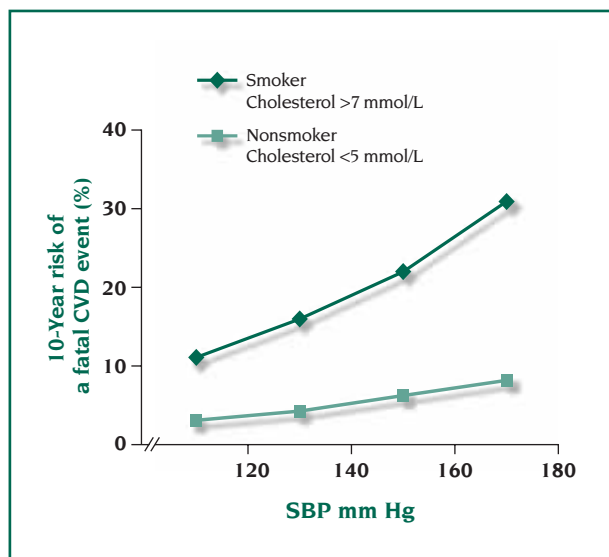


Figure 2. Systolic blood pressure (SBP) and 10-year risk of a fatal cardiovascular disease (CVD) event in men aged 60 years according to smoking and cholesterol status. (Based on data from reference 8.)

This observation helps to explain why a wide pulse pressure (SBP-DBP) has been shown in some observational studies to be a better predictor of adverse CV outcomes than either SBP or DBP individually and to identify patients with systolic hypertension who are at particularly high risk. However, in the largest meta-analysis of observational data in almost one million patients in 61 studies (70% of which have been conducted in Europe),³⁵ both systolic and diastolic BP were independently predictive of stroke and CHD mortality and to a greater extent than pulse pressure. This meta-analysis also confirmed the increasing contribution of pulse pressure after age 55. It has also been shown that, compared with normotensive individuals, those with an elevated blood pressure are more likely to have other risk factors for CVD such as diabetes, insulin resistance, and dyslipidemia and various types and degrees of target-organ damage. Because risk factors may interact positively with each other, the overall cardiovascular risk of hypertensive patients may be high even if blood pressure is only moderately raised.

This is illustrated in *Figure 2* with results from the SCORE project⁸; CVD mortality is shown as a function of SBP for a male of 60 years of age as a function of

his cholesterol level and smoking status. A high SBP may be associated with a lower risk for developing CVD than a low SBP, depending on the cholesterol level and smoking status: mortality is <10% with a SBP of 180 mm Hg, but in a nonsmoker with a total cholesterol <5 mmol/L while mortality is >10% despite a lower SBP of only 120 mm Hg in the presence of smoking and cholesterol elevation.

Long-term observational data provide evidence that, in hypertensive patients in whom treatment effectively controls BP, coronary, cerebrovascular, and overall CV morbidity remains higher than that of normotensive controls. This may be accounted for by factors such as irreversible organ damage at the time treatment is started, indicating the need for early identification and management of blood pressure elevation.

Dyslipidemia

Most of the blood cholesterol is normally carried on LDL particles. Over the entire range of total and LDL cholesterol concentrations there is a strong, continuous, graded, and independent positive association with risk of CVD. This association applies to women as well as men, and to old as well as younger people. The relationship is exponential, indicating that a given absolute difference in total or LDL cholesterol from any point in the distribution is associated with a constant percentage difference in CHD risk. This association is considerably modified by other risk factors such as age, sex, smoking, blood pressure, diabetes, and low high-density lipoprotein (HDL) cholesterol.

This is illustrated in *Table I* with results from the SCORE project⁸ showing that a person with a cholesterol of 8 mmol/L can be at 10 times LOWER risk than someone with a cholesterol of 5 mmol/L if the former is a

Sex	Age (years)	Chol (mmol/L)	SBP (mm Hg)	Smoking	Risk* (%)
F	60	8	120	No	2
F	60	7	140	Yes	5
M	60	6	160	No	8
M	60	5	180	Yes	21

Table I. Impact of combinations of risk factors on total cardiovascular risk. Results based on data from reference 8 (SCORE [Systematic COronary Risk Evaluation] project).

Abbreviations: Chol, cholesterol; F, female; M, male; *risk, risk of dying from cardiovascular disease within the coming 10 years; SBP, systolic blood pressure.



normotensive nonsmoking woman and the latter is a male hypertensive smoker. Therefore, decisions on drug treatment for hypercholesterolemia should not only be based on total or LDL cholesterol levels per se, but also on total CV risk. While audits such as EUROASPIRE (EUROpean Action on Secondary Prevention by Intervention to Reduce Events)³⁰ suggest inadequate risk factor management in very-high-risk subjects, it is also likely that, in the context of low-risk subjects who have not had a vascular event, there is the potential for substantial overuse of drugs by inappropriate extrapolation of the results of trials conducted mostly on men at high-risk to individuals at low risk. In general, women and old and young subjects have been underrepresented in the classic drug trials that have informed guidelines to date.

Coronary artery disease is rare in populations with total cholesterol less than 3 to 4 mmol/L (115-155 mg/dL), even in the presence of other risk factors. Conversely, coronary artery disease is inevitable in untreated patients with the severest forms of familial hypercholesterolemia, even in the absence of other risk factors.

The results of epidemiological studies, as well as trials with angiographic or clinical end points, confirm that the reduction of LDL cholesterol must be of prime concern in both primary and secondary prevention of CVD.

Triglycerides

Hypertriglyceridemia is also associated with the risk of developing CVD, but the association is not as strong as it is for hypercholesterolemia. Although the risk of cardiovascular disease does increase with hypertriglyceridemia, the risk is associated more strongly with moderate than with very severe hypertriglyceridemia, probably because the former is often due to accumulation in plasma of triglyceride-rich atherogenic intermediate-density lipoprotein (IDL) and small very-low-density lipoprotein (VLDL), whereas the latter can be due to nonatherogenic large VLDL and chylomicrons. A triglyceride value >1.7 mmol/L (≈150 mg/dL) is considered a marker of increased risk, but concentrations <1.7 mmol/L are not considered a goal of therapy.

High-density lipoproteins

Low concentrations of HDL, measured as HDL cholesterol, are clearly associated, not only with early development of atherosclerosis, but also with poor outcome in those who already have cardiovascular disease. The association is not invariable, since it is not apparent in societies in which the risk of atherosclerotic cardiovascular disease is low. Therefore, it has to be stressed

that smoking, sedentary lifestyle, obesity, and type 2 diabetes cause lower HDL cholesterol. The combination of moderately elevated triglycerides and low concentrations of HDL cholesterol is very common in patients with type 2 diabetes, abdominal obesity, insulin resistance, and physical inactivity at high risk for early-onset atherosclerotic disease. It is part of a pattern of deranged plasma lipoproteins characterized by a triad of increased concentrations of IDL and VLDL, the presence of small dense LDL, and low concentrations of HDL.

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

Other lipoproteins and lipoprotein components

- **Lipoprotein A, or Lp(a)** is a low-density lipoprotein to which an additional protein called apolipoprotein(a) is attached. It has no known physiological role, and high concentrations of Lp(a) (arbitrarily >30 mg/dL) are largely resistant to modification. They identify persons at increased risk of atherosclerotic disease.³¹
- **Apolipoprotein B (apoB)** is the major protein component of LDL, IDL, VLDL, and, in truncated form, chylomicrons. Since chylomicrons are not normally present in plasma in the fasting state, almost all apolipoprotein B is in atherogenic lipoproteins. Concentrations of apolipoprotein B are therefore a direct measure of the concentration of atherogenic lipoproteins in plasma. The measurement is a useful indicator of risk of atherosclerosis, particularly in patients with hypertriglyceridemia and in people with normal concentrations of LDL cholesterol.⁹ Values >150 mg/dL are clearly associated with increased risk.
- **Apolipoprotein A1** is the major apoprotein of HDL. Low concentrations of apolipoprotein A1 are, like low HDL cholesterol, associated with higher risk of cardiovascular disease. As for apolipoprotein B, since measurements of apolipoprotein A1 are not generally available to all physicians, it is not included in the guidelines for assessing cardiovascular risk.
- **The apolipoprotein B/A1 ratio** is beyond doubt one of the strongest risk markers. This is emphasized in the INTERHEART study.⁹ On the other hand, it has been shown that the prognostic power does not change when total cholesterol/HDL ratio is replaced by the apoB/apo A1 ratio.³²

Total cholesterol/HDL cholesterol

A total cholesterol/HDL cholesterol ratio >5 indicates increased risk and is particularly useful in the middle range of the cholesterol distribution (5-6.5 mmol/L, or 190-250 mg/dL). However, this ratio does not predict cardiovascular events better than simple total cholesterol measurement.⁸

Heart rate

There is robust evidence of a relationship between resting heart rate and life expectancy. Elevated resting heart rate has been found to be associated with an increased risk of total and CV mortality in numerous cohort studies in the general population, and in hypertensives, diabetics, and subjects with preexisting coronary artery disease.^{36,37} Most epidemiological studies have shown this relationship to be strong, incremental, and independent of other risk factors including BP and physical activity. The mechanism of the deleterious effect of elevated resting heart rate could be associated with arrhythmic or ischemic effects. Other possible mechanisms could be a direct effect of elevated heart rate on hemostasis, favoring the progression of atherosclerosis. Conversely, there is strong evidence that reducing the heart rate is beneficial, as shown by meta-analyses of trials of β -blocker and calcium-channel blocker therapy in post-myocardial infarction or congestive heart failure patients, and that the benefit achieved is a function of the reduction in heart rate.^{38,39} This topic is addressed more thoroughly by François Paillard and Jean-Claude Tardif in this issue of *Dialogues*.

Overweight, obesity, abdominal adiposity, and the metabolic syndrome

BMI ($\text{kg}/\text{height}^2 [\text{m}^2]$) has been extensively used to define overweight or obesity. In adults, overweight is defined by an increased BMI ranging from 25 to 29.9 and obesity by $\text{BMI} \geq 30$. Increasing BMI is highly associated with CVD. This association is, however, attenuated or disappears after adjustment for metabolic factors, indicating the important indirect role of overweight and obesity.

Other indicators apart from BMI have been proposed to assess body fat distribution. The waist-hip ratio (WHR) and waist circumference (WC) are now frequently used. Both the World Health Organization (WHO) report on obesity³³ and the American National Heart, Lung, and Blood Institute (NHLBI) expert panel on obesity⁴⁰ recommend the use of WC as an additional

indicator of CV risk. In European populations, two action levels are recommended. Action level 1 (WC ≥ 94 cm in men and ≥ 80 cm in women) represents the threshold at which no further weight should be gained. Action level 2 (WC ≥ 102 cm in men and ≥ 88 cm in women) represents the threshold at which weight reduction should be advised.

In longitudinal studies in men and women, increased WHR or WC was associated with increased risk of ischemic heart disease mortality. The INTERHEART case-control study compared 12 461 subjects with myocardial infarction and 14 637 controls and showed that both increased WC and WHR differentiate between myocardial infarction patients and controls even after adjustment for other cardiovascular risk factors and BMI. This suggests that abdominal obesity is an independent contributor to cardiovascular risk.⁹ In a recent metaregression analysis of prospective studies involving more than 250 000 participants, WHR and WC were found to be significantly associated with the risk of incident CVD events. A 1-cm increase in WC was associated with a 2% increase in risk of future CVD and a 0.01 increase in WHR was associated with a 5% increase in risk.⁴¹

The term "metabolic syndrome" refers to the fact that different risk factors tend to cluster in a given individual. Different definitions have been proposed, all centered around abdominal obesity, insulin resistance, elevated blood pressure, and dyslipidemia. In a meta-analysis of prospective studies in populations, the relative risks of all-cause mortality, CVD, and diabetes were estimated for the metabolic syndrome using the definitions developed by the National Cholesterol Education Program (NCEP) and the WHO, and yielded a relative risk of 1.27 for all-cause mortality, 1.65 for CVD, and 2.99 for diabetes.⁴² However, it remains uncertain whether the identification of subjects with the metabolic syndrome will bring additional information about CVD risk over and above that obtained from multifactorial CVD assessment tools such as the SCORE risk equation. Results from the Diabetes Epidemiology, Collaborative analysis of Diagnostic criteria in Europe (DECODE) study⁴³ indicate that the diagnosis of the metabolic syndrome may identify subjects with increased risk of CVD among those who would become classified as low-risk individuals using conventional tools for CVD risk assessment. In a recent 13-year follow-up study in elderly nondiabetic Finns, the results suggest that the metabolic syndrome is a marker of CV risk, but not above and beyond the risk associated with its individual components.⁴⁴ In contrast, from a



recent meta-analysis of the metabolic syndrome, it was concluded that the metabolic syndrome confers CV risk beyond that which is associated with its component risk factors.⁴⁵

An increased WC appears to be a useful warning sign and should stimulate a systematic search for other risk factors together with an active approach to controlling all components of total CV risk.

Psychosocial factors

There is increasing scientific evidence that psychosocial factors contribute independently to the risk of CHD, even after statistical control for the effects of standard risk factors. In addition to increasing the risk of a first event and worsening the prognosis in CHD, these factors may act as barriers to treatment adherence and efforts to improve lifestyle, as well as promoting health and well-being in patients and populations.

Low socioeconomic status, lack of social support and social isolation, stress at work and in family life, and negative emotions including depression and hostility, have been shown to influence both the risk of contracting CHD and the worsening of clinical course and prognosis in patients with CHD. Several behavioral and psychophysiological mediators and moderators of these effects have been identified. Whether psychosocial factors should be considered as traditional risk factors for CVD, as confounders, or as risk modifiers is the subject of a special article in this issue by Roberto De Vogli and Michael Marmot.

Inflammation markers, hemostatic factors, and other “emerging” risk factors

For many years, factors associated with many different biological systems such as those regulating platelets, coagulation, fibrinolysis, endothelial function, and the inflammatory response have been studied as potential risk factors for CVD. In addition to their potential utility in long-term risk prediction of CVD, close associations between inflammatory markers and obesity and diabetes have been demonstrated, which strengthens the case for their scientific investigation.

There is strong evidence from pathological and epidemiological studies that the circulating markers of activated inflammation and hemostasis are closely associated with the development of fatal and nonfatal myocardial infarction. A recent report from Europe, as part of the WHO's MONICA study (MONItoring trends

and determinants in Cardiovascular diseases), showed that population levels of certain hemostatic factors differed between participating centers and countries, and showed significant associations with the incidence of coronary heart disease in the centers.⁴⁶

Some studies have demonstrated that risk prediction for coronary heart disease⁴⁷ and CVD⁴⁸ can be improved by the addition of these newer risk factors to risk models that include all established risk factors. A report from the United States proposed that C-reactive protein (CRP) should be as an “option” in current guidelines,⁴⁹ but this proposal has been questioned both in the United States⁵⁰ and in Europe.⁵¹

Incorporation of CRP and other emerging risk factors into daily clinical practice for prediction of cardiovascular risk may be premature. Criteria for a rigorous evaluation of such factors have been proposed.⁵² These criteria include: applicability to all relevant clinical cardiovascular events; ability to predict in short, intermediate, and long-term follow-up; standardized measurements; examination of variability; the degree of correlation with established risk factors; and improvement in overall prediction, among other criteria. A number of meta-analyses of observational epidemiological studies have been conducted, eg, for CRP⁵³ and for fibrinogen.⁵⁴ Such meta-analyses provide evidence of possible utility of emerging risk factors in future clinical practice, but current investigation of determinants of inflammatory markers—which include physical activity, dietary factors, alcohol, and weight loss as protective factors, and infections such as periodontitis as a potentially treatable risk factor—encourage the detailed examination of this group of markers in future research.

Another important point regarding these meta-analyses is that CRP, fibrinogen, and possibly other biomarkers are often seriously confounded by other unmeasured variables and subject to reverse causality (ie, preclinical disease causes rises in CRP). Consequently, despite large-scale meta-analyses, like those cited above, there is a risk of falling into the trap of promoting the idea that the evidence of a causal link is strong. An alternative approach using Mendelian randomization has been carried out by several groups, demonstrating that predicted associations between CRP genotypes that code for higher levels of circulating CRP are not associated with CVD or CVD risk factors. An alternative that could be suggested given the actual state of knowledge is to use (high-sensitivity) hsCRP determination selectively in the intermediate-risk group.⁵⁵

There have been several other interesting suggestions as to “emerging” risk factors that could be added to the list; among them are homocysteine levels,⁵⁶ markers of renal function,⁵⁷ and N-terminal pro-brain natriuretic peptide.⁵⁸

All these interesting suggestions on adding new risk factors need to be validated, and this requires large population studies with integrated collection of biochemical and bioclinical factors and long-term follow up for hard key end points. Specific techniques should be used to evaluate the incremental value of the new risk markers in the prediction models. In the meantime, the potential for prevention using the guidelines that have been provided is enormous and there is no reason to wait for preventive actions until better models become available. We should never lose sight of the purpose of total risk estimation: to adapt the intensity of preventive action in accordance with the patient’s total CV risk. This by itself is to encourage greater equity in the delivery of effective therapies; at that level of prevention the problem is not the need of personalized treatment, but the failure to act in those who have the potential to benefit.

TOTAL CARDIOVASCULAR RISK

For more than a decade, guidelines on CVD prevention have been recommending the targeting of total CV risk rather than single risk factors, based on the knowledge that CVD is multifactorial in origin and that major risk factors interact with each other in a complex way to build up total CV risk, which is the probability of an individual developing CVD during a defined period of time.

THE PREVENTION PARADOX

In most societies, health care systems are “care driven” and limited resources are available for prevention; therefore efficient use of resources is even more crucial in preventive medicine.

Any preventive action that achieves a certain relative risk reduction will result in prevention of more events when applied to a high-risk group than a low-risk group. But this statement should be qualified. Let us suppose that statin therapy is applied in a low-risk population of 10 000 subjects with an estimated total CV risk of 5% over the next 10 years. As statin therapy is associated with a relative risk reduction of approximately 25%, this will result in 125 events prevented over 10 years. If the same action is applied in a high-risk population of 10 000 subjects with an estimated

total CV risk of 30 % over the next 10 years, the same relative risk reduction of 25% will result in 750 events prevented over 10 years. Contrasting with the above figures, it may seem paradoxical that, in real life, the majority of new events in a community occur in the large population at moderate risk and not in the smaller subfraction at highest risk. This is due to the fact that those at moderate risk outnumber those at highest risk to the extent that their moderate risk elevation results in a larger absolute number of new events than what is observed in the highest-risk group. This is why a comprehensive approach is needed.

Such a comprehensive strategy requires the following:

- A population strategy to alter lifestyle characteristics that underlie the mass occurrence of CVD. This should target the social and economic determinants of disease through political actions. This strategy should lead to changes in lifestyle such as less smoking, more people eating a healthy diet; and an increased number of physically active people. These goals can be reached in many different ways. Population strategies should therefore be adapted to national, regional, and even local conditions. In addition, the population strategy has to ensure equal access of all to preventive action in order to reduce the social differences in health.
- An aggressive strategy to reduce risk in those apparently healthy people identified as being at high risk.
- Secondary prevention to prevent recurrence of CVD in those who have already had a CVD event.

AGGRESSIVE STRATEGY FOR PRIMARY PREVENTION OF CVD IN CLINICAL PRACTICE

Defining high risk

There are numerous reports from expert committees on this subject. In this article, reference is given in particular to the guidelines issued in 2007 by the Fourth Joint European Task Force.^{3,4}

The first step is to identify those in the apparently healthy population who are at high risk for developing CVD in the coming years, so as to match the intensity of the preventive action to the observed total CV risk.

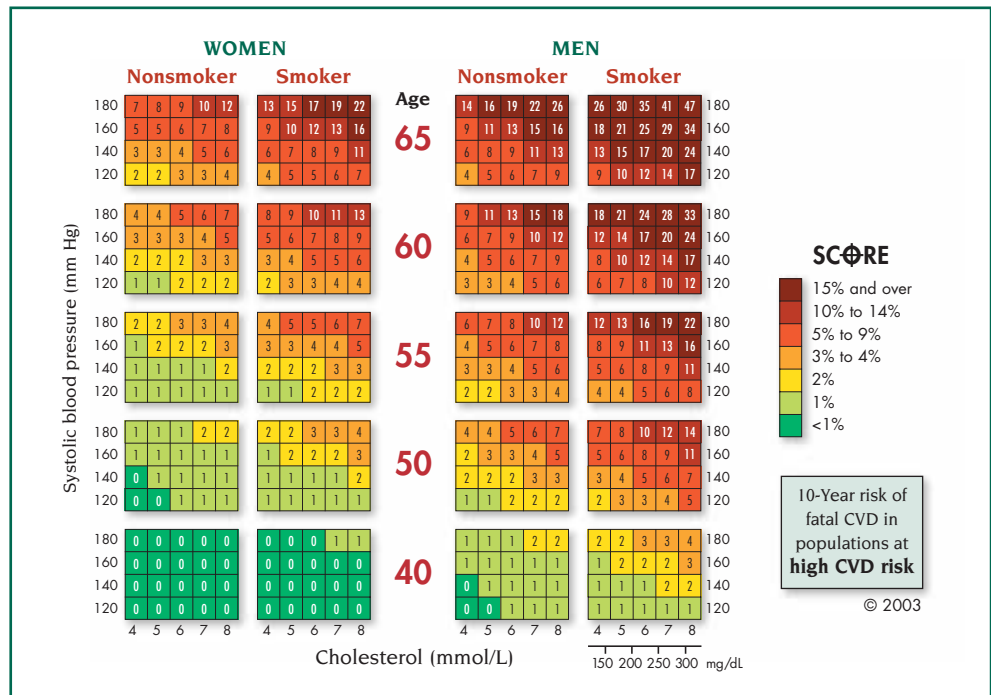
The guidelines of the Joint European Societies’ Task Force define high risk as patients with established CVD; this is covered by secondary prevention.

Within the population free of history of CV, high risk is further classified into three categories:



Figure 3. 10-year risk of fatal CVD in high-risk regions of Europe.

Reproduced from reference 4: Graham I, Atar D, Borch-Johnsen K, et al; Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts). European guidelines on cardiovascular disease prevention in clinical practice: executive summary. Eur Heart J. 2007;28:2375-2414. Copyright © 2007, Oxford University Press.



- Subjects with markedly raised levels of single risk factors, especially if associated with end-organ damage.
- Subjects with type 2 diabetes, or with type 1 diabetes and microalbuminuria.
- Subjects with multiple risk factors, resulting in an elevated total CV risk. Identification of these subjects requires the use of total risk estimation models.

Estimation of total cardiovascular risk

European guidelines recommend the use of a model for total risk estimation based on the SCORE project.⁸ In Figures 3 and 4 the risk charts for high- and low-risk countries, respectively, are given, based on observations in 12 European cohorts in the SCORE project.⁴

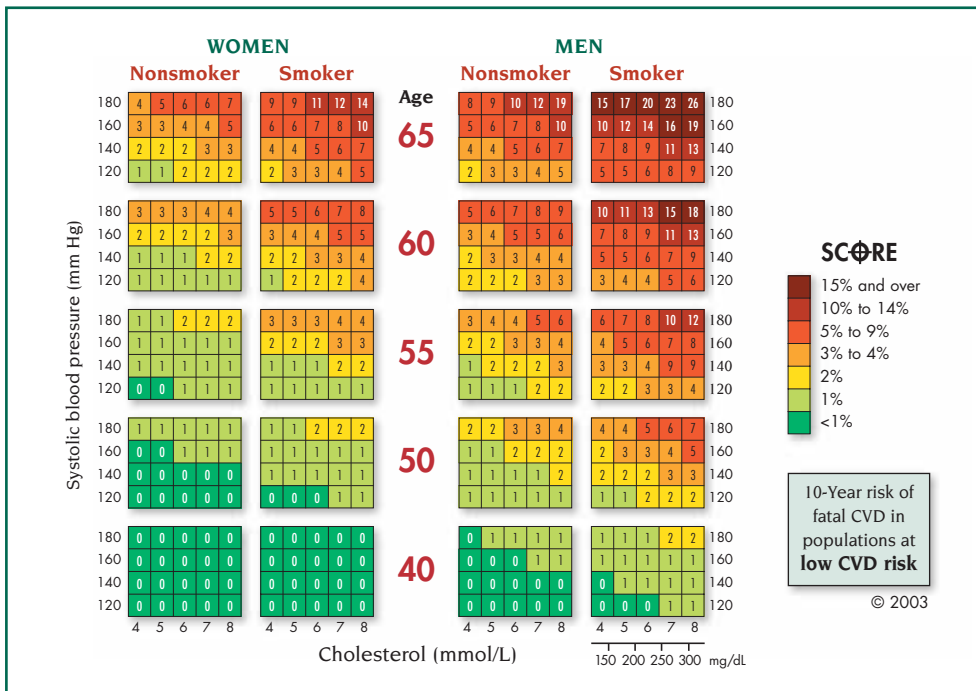


Figure 4. 10-year risk of fatal CVD in low-risk regions of Europe.

Reproduced from reference 4: Graham I, Atar D, Borch-Johnsen K, et al; Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts). European guidelines on cardiovascular disease prevention in clinical practice: executive summary. Eur Heart J. 2007;28:2375-2414. Copyright © 2007, Oxford University Press.

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

- In asymptomatic subjects with evidence of preclinical atherosclerosis
- In subjects with a strong family history of premature CVD
- In subjects with low HDL cholesterol levels, with raised triglyceride levels, with impaired glucose tolerance, with raised levels of C-reactive protein, fibrinogen, homocysteine, apolipoprotein B, or Lp(a)
- In obese and sedentary subjects, especially in the presence of central obesity
- In the socially deprived

Table II. Qualifiers to be used with the SCORE (Systematic COronary Risk Evaluation) risk charts.

One of the great advantages of the SCORE project is that the charts can be calibrated on the basis of national cause-specific mortality statistics and prevalence rates of established risk factors. Calibrated charts are already available for several European countries. These charts guide the practitioner on how aggressively lifestyle changes should be pursued and whether drugs should be used to manage risk factors. The chart allows easy estimation of the risk of dying from CVD in the coming 10 years as a function of age, gender, smoking, SBP, and total cholesterol. Total CV risk is given in absolute numbers, with a color-coded gradient from dark green to dark red corresponding to 7 categories from <1% to >15%. With the chart comes a table with qualifiers that should be taken into account to estimate total CVD risk (*Table II*).

Other risk estimation models are available. The most frequently used ones are based on results from the US Framingham study.⁵⁹ The principle is the same and the choice of the model by the practitioner depends on how closely the model reflects the population he/she is working with. However, the most important thing is that the concept of total CV risk is used to guide the intensity of the preventive approach in a given subject. It is a tool to help clinicians in deciding how aggressive their action should be, from simple reinforcement of a health education message to various combinations of intensive professional lifestyle change programs, in addition to drug therapies for elevated blood pressure, lipids, or abnormal blood glucose values.

In daily practice, clinicians often ask for thresholds to initiate intervention. This is problematic since total CV risk is a continuous variable. Thus, there is no pre-

cise cutoff point to automatically indicate when a drug treatment should be started. Cutoff points have nevertheless been introduced to define "high risk." In the Framingham model, a level of >20% risk for developing any coronary event in the next 10 years has been labeled as high risk; in the SCORE charts, a total risk of dying from CVD in the next 10 years of >5% has been described as "high risk." As this implies a 95% chance of not dying from CVD within 10 years, it is less than impressive when counseling patients. The new nomenclature in the 2007 guideline is that everyone with a 10-year risk of CV death of 5% or more is at increased risk. The risk of occurrence of any CVD event (fatal or nonfatal) is of course higher. Calculating total event rates from FINRISK suggests that, at the level (5%) at which risk management advice is likely to be intensified, total event risk is about 15% in younger men and somewhat less in women. The "multiplier" to convert CVD mortality to total events is smaller in older people, presumably because a first event is more likely to be fatal. It should be realized that the choice of cutoff points to define high risk is arbitrary and based on practical considerations stemming from the economic constraints of health care systems, health insurance plans, and health policy makers, but not on a strong scientific basis. This has had the detrimental effect of leading clinicians to divide the asymptomatic population into two groups: high-risk and all others. This is a mistake: in effect, the old dichotomy for single risk factors—hypertension vs normotension, hypercholesterolemia vs normal cholesterol—has simply been replaced by another dichotomy relating to total CV risk: high risk vs low risk.

The limitations of such an approach are strongly confirmed by recent observations from the Framingham study⁶⁰: long-term follow-up of the cohorts showed that the absence of established risk factors at the age of 50 years was associated with a very low lifetime risk, but that as soon as one risk factor was present, risk increased substantially in both men and women. Participants with an optimal risk factor profile (total cholesterol <4.65 mmol/L [180 mg/dL], blood pressure <120/80 mm Hg, nonsmoking, and nondiabetic) had a substantially lower lifetime risk of CVD compared with those with >2 major risk factors: 5.2% vs 68.9% in men; 8.2 vs 50.2% in women. Survival was also very different: >11 years in men, >8 years in women with an optimal risk factor profile. But it should be pointed out that only 3.2% of all men and 4.5% of all women in that cohort had an optimal risk factor profile. From the above, it can be concluded that prevention should begin at a young age, as the presence of

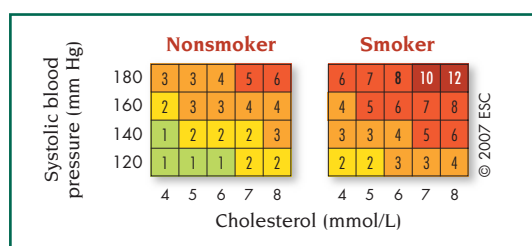


Figure 5. Relative risk chart: relative risk for CVD mortality/10 years as a function of smoking habits, systolic blood pressure level and cholesterol concentration, based on the SCORE (Systematic COronary Risk Evaluation) project.

Reproduced from reference 4: Graham I, Atar D, Borch-Johnsen K, et al; Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts). *European guidelines on cardiovascular disease prevention in clinical practice: executive summary.* Eur Heart J. 2007;28:2375-2414. Copyright © 2007, Oxford University Press.

even a single major risk factor is associated with substantially increased lifetime risk for CVD and markedly shorter survival. Lifestyle measures relative to diet and exercise in young adulthood and middle age could prevent the development of obesity, diabetes, hypertension, and dyslipidemia in large numbers of older individuals.

For instance, the SCORE low-risk chart (*Figure 4*) indicates that a 50-year-old nonsmoking man with a total cholesterol value of 7 mmol/L and an untreated BP of 160 mm Hg has an estimated 10-year risk of dying from CVD of 2%, which is considered as low risk in the guidelines.⁴ This means that many clinicians who are using total CV risk “dichotomously” will defer preventive action for another 10 years, by which time the same man will be 60, and his total CV risk will be above 5%, reaching the magic cutoff point enabling him to be labeled as “high risk.” However waiting until a person is old enough to reach that arbitrary threshold for active intervention means that a large proportion of potentially preventable events may have occurred.

The average lifetime risk for CVD at the age of 50 years in the situation described above is nearly 70% according to the Framingham Heart Study results⁶⁰ and the median survival is >11 years shorter than for a man of the same age with an optimal risk factor profile. These data placed in the clinical context may be more useful in motivating lifestyle changes and promoting adherence to therapy.

However, too much emphasis has been given to arbitrary high-risk cutoff points defined as a total risk of dying from CVD of 5% or more within the coming 10 years by the SCORE model or a total risk of developing CHD of 20% or more by the Framingham model. Some clinicians have reduced recommendations to only prescribing drug therapy for elevated BP and cholesterol if total CV risk exceeds that arbitrary cutoff point. This may have the disadvantage that in old subjects, especially men, the estimated total CV risk will exceed the 5% or 10% threshold based on age only even when other risk factor levels are relatively low; this could lead

to excessive usage of drugs in the elderly. Conversely, this may lead to the situation that very little is done in that large proportion of the asymptomatic population who are at lower risk, but certainly not at optimal levels. This is of particular importance in the young with high levels of risk factors, but a low absolute risk because of their age. The guidelines of the Third Joint Task Force suggested extrapolating risk to the age 60 to stress that a high absolute risk would occur if preventive actions were not taken. It was not intended that young persons should necessarily be treated as if they were 60, and a literal interpretation of this suggestion could lead to excessive drug treatment in young persons. In the recent guidelines, a relative risk chart has been added to illustrate that, particularly in young people, lifestyle changes can reduce risk substantially as well as reducing the increase in risk that will occur with aging. This is presented in *Figure 5*.⁴ The figure can be applied to both sexes and at all ages and is of particular value to indicate to young people who still are at a low absolute risk because of their age, that based on their smoking status, cholesterol level, and blood pressure, their relative risk for developing CVD can be as high as 12 times the most optimal situation.

CONCLUSION

Further considerations are provided by the other articles in this issue of *Dialogues*.

Elevated heart rate has been associated with an increased risk of total and CV mortality in numerous cohort studies in the general population. At present it is not included as a variable in risk estimation systems. (See article by François Paillard and Jean-Claude Tardif.)

Roberto De Vogli and Michael Marmot point out that indicators of socioeconomic class are important risk factors at the population level. Differences in CVD according to social class are well documented and only partially explained by the traditional risk factors. The socially deprived were added to the list of qualifiers for total CV risk estimation in the latest update of the guidelines. Indeed, while risk scores are superior to

clinical assessments alone, they can be misleading when used to guide the intensity of preventive actions among people at different levels of social class. By not considering the large gradient in CVD risk between socioeconomic classes, the Framingham and SCORE models may lead to an underestimation of total CV risk in the most socially deprived, thereby leading to undertreatment and exacerbating social disparities in CVD rates. We must strike a good balance between the failure to act in those who have the most to gain versus overmedicalization of those who have little to gain. Results from studies in the UK⁷ clearly demonstrate that in a socially mixed population, the most deprived people warrant preventive treatments at lower levels of total CV risk than others, in order to counterbalance their disadvantage health status.

Karin Schenck-Gustafsson stresses that all total CV risk estimation models are gender-specific. The prevalence of risk factors may be different between sexes, the relative risk related to risk factors may be worse in women, but the absolute risk at a given age is clearly lower in women. Can we identify more specifically what this gender-related risk protection in women is based on, and can we learn from that in terms of prevention?

Thus, total CV risk should definitely be used as a guide for implementing preventive strategies. However, the difficulty in imposing arbitrary thresholds or targets upon a continuous variable such as risk should be acknowledged. Risk charts such as those that have just been described in this article need to be adapted to take into account national specificities. In addition, risk prediction at the level of the individual stands to be improved by taking into consideration other factors such as heart rate, socioeconomic indicators, and gender.

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