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Invited Editorial

Ian M. Graham, FRCPI, FCCP

CARDIOVASCULAR RISK ESTIMATION AND MANAGEMENT: CAN WE GLIMPSE THE FUTURE?

"risk factor" is generally defined as a characteristic of an individual that is associated with the subsequent development of a disease. Establishing a causal link between a putative risk factor and a disease is easy if a single factor is associated with the disease and if its removal is curative; myxedema is caused by deficiency of thyroxine, and its supplementation is curative. Sometimes a causal agent, for example, the tubercle bacillus, needs the appropriate circumstances to become clinically manifest. But the atherosclerosis underlying heart attack and stroke is associated with multitudinous factors. Many of these are markers of a developed or “Western” lifestyle, but only some are “causal” in the sense that the likelihood of causality is sufficient to justify a clinical or public health intervention. Defining the criteria for causality and judging when the benefits of intervention outweigh adverse effects has challenged basic science, epidemiology, and clinical and public health medicine for the past century.

In his lead article in this issue of Dialogues, Guy De Backer casts a dispassionate eye on risk. He notes that the concept can be extended beyond prevention in the individual to public health strategy and to gaining insight into possible pathophysiological mechanisms. The primacy of the “big five”—age, gender, blood cholesterol, blood pressure, and smoking—remains intact. Of these, age is not a risk factor as such, but merely a measure of exposure time—the older one is, the longer one may have been exposed to a raised blood cholesterol or smoking. But raised blood pressure and cholesterol and smoking are clearly causal and their removal or reduction unequivocally reduces risk. Female gender, as we shall see, implies a deferral, but not a reduction in risk.

The benefits of exercise, avoidance of overweight, and healthy nutrition are based on observational epidemiology, clinical trials, meta-analyses, and systematic reviews. While none of these factors is as amenable to randomized control trials like blood pressure or hyperlipidemia, there is little doubt that attention to these aspects can reduce the

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risk of the “metabolic syndrome,” diabetes, hypertension, hyperlipidemia, consequent cardiovascular disease (CVD), and many comorbidities. The role of psychosocial factors is also considered in this issue, and De Backer looks also at possible new risk factors.

The balance between total and absolute risk is dealt with carefully. While absolute risk guides management decisions in the individual, a high relative risk in a young person may flag the need for lifestyle measures to prevent a high absolute risk in later life. The assessment of both requires the ability to assess the impact of multiple risk factors using a assessment tool such as the Systematic COronary Risk Evaluation (SCORE) risk charts.1

Most deaths in a community come from those at only modestly increased risk simply because they are so numerous, yet high-risk individuals gain most from preventive measures2; so community and high-risk detection strategies should be regarded as complementary rather than competitive.

Karin Schenck-Gustaffson establishes clearly that the apparent protection of women from CVD is a myth—40% of women die from CVD, compared with 3% of deaths from breast cancer. They merely die later than men, and more frequently from stroke. Current risk estimation systems underestimate the problem, especially by not accommodating older women. There is a dilemma in that younger women may be undermanaged (too little risk assessment and advice), but potentially overtreated with drugs such as statins (low absolute risk and inadequate trial evidence of benefit). Above all, there is a need for increased awareness of the problem of CVD as the major cause of death in women, the recruitment of more women into trials of risk factor management, and research into strategies of risk assessment and management that are focused on women.

“The poor die young.” A cliché, perhaps, but nonetheless true. Roberto De Vogli and Michael Marmot find that the usual considerations as to whether socioeconomic conditions may be risk factors, confounders, or modifiers of risk insufficient. Rather, they argue that socioeconomic factors are the “cause of the causes” of heart disease. Risk factor management at the individual level may not reduce the inequalities in risk that are socially determined. A broader approach would seem to be needed to address poverty, inequality, urban planning, social participation, transportation, and the work environment. The potential role of multinational corporations for good or bad is enormous: do they merely transfer the sale of tobacco and foods high in saturated fats to developing countries? Can business interests be harmonized with social responsibility?

The idea that all animals, including man, enjoy a finite number of heartbeats before they die is fascinating. François Paillard and Jean-Claude Tardif note that an increased heart rate seems to promote atherogenesis, ischemia, dysrhythmias, and death. β-Blockade
reduces heart rate. It reduces mortality in subjects after myocardial infarction and in heart failure. It is tempting, maybe logical, to conclude that β-blocker–independent heart rate reduction will improve life expectancy. We may hope so, but we do not yet know so.

Anthony Wierzbicki does a noble job in summarizing 10 seminal papers concerned with risk factors. He defines the characteristics of healthy populations, especially with regard to blood pressure, cholesterol, vegetable consumption, and exercise. One might take issue with the admonition “no sex”—“no unsafe sex” might be preferable. Your editorialist knows of no evidence that sex as such is other than healthy. Also, for “no alcohol” the evidence might perhaps permit modest—but not excessive—alcohol.

So, what are the challenges for the prevention of CVD? Perhaps to:
• Understand the social determinants of health and how to change them.
• Understand how to promote exercise, healthy nutrition, avoidance of overweight and tobacco, and do not ban the moderate use of alcohol.
• Listen and learn with regard to gender inequalities.
• Use drug treatments effectively and in accordance with the evidence base.
• Understand the power of health professionals as political advocates for health.
• Engage with multinational companies to encourage them to adopt socially responsible policies that conform to public health requirements.

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Risk factors and prevention of cardiovascular disease: a review

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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.

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. Results from global burden of disease studies indicate that CVD will become even more frequent especially in developing countries. 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.

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.
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.

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. 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

![Figure 1. Simulated distribution of systolic blood pressures in two typical population groups.](image_url)
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 be-
cause classic risk scoring methods tend to underesti-
mate risk in socioeconomically deprived people, fur-
ther increasing disparities in CVD incidence between
social classes.  

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 con-
cept 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.  

**Relative risk** is generally expressed as a ratio compar-
ing a person or a group of persons with another per-
son 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 some-
thing 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 ab-
solute risk.

**IDENTIFICATION OF RISK FACTORS**

Risk factors can be identified by means of cross-sec-
tional 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 recent-
ly in the INTERHEART study\(^9\) where it was reported
that a limited set of risk factors (abnormal lipids, smok-
ing, hypertension, diabetes, abdominal obesity, psy-
chosocial 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 relation-
ship with CV mortality is exponential. It is an impor-
tant factor to consider in total CV risk estimation, but
its nonmodifiable nature limits its use in the manage-
ment 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 mor-
tality 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 attrib-
uted 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 dis-
cussed 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 rela-
tive <65 years) is in the range of 1.5-1.7 and is inde-
pendent of classic CV risk factors.

Genotypes are a class apart; several variants are asso-
ciated 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.”  

A special group of nonmodifiable risk indicators re-
late 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 asymp-
tomatic subjects can also help in the identification of
high-risk subgroups in the community. Different tech-
niques 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). 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. The protective value of physical activity is independent of measures of total CV risk, eg, the score estimated using the Framingham risk equation. 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). 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.

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. 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.

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 diseases<sup>19</sup>, 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 even be 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.<sup>20</sup> 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) values<sup>21</sup> and assay of glycated hemoglobin HbA<sub>1c</sub>.<sup>22</sup> 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.<sup>23</sup> 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.<sup>24</sup> 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.<sup>25-28</sup> 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.<sup>29-33</sup> 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.<sup>34</sup>

**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.<sup>29</sup> 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.<sup>35</sup> 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. 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.

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), 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 project 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

![Figure 2](image)

**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.)

**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).

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (years)</th>
<th>Chol (mmol/L)</th>
<th>SBP (mm Hg)</th>
<th>Smoking</th>
<th>Risk* (%)</th>
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<td>M</td>
<td>60</td>
<td>5</td>
<td>180</td>
<td>Yes</td>
<td>21</td>
</tr>
</tbody>
</table>

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

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 project 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
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) 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.

- **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 apo-lipoprotein 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. 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. 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.
**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.  

**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.  

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. 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 (kg/height² [m²]) 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 BMI ≥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 obesity and the American National Heart, Lung, and Blood Institute (NHLBI) expert panel on obesity 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. 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. 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. 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) study 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 non-diabetic 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. 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 disease\(^{47}\) and CVD\(^{48}\) 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 States\(^ {50}\) 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 CRP\(^ {53}\) 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, markers of renal function, and N-terminal pro– brain natriuretic peptide.

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 approach 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.

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:
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. 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.


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. 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 precise 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 study. 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
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. 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 results 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. 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 UK 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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Risk Factors & Cardiovascular Disease

Expert Answers to Three Key Questions

1

Should socioeconomic factors be considered as traditional risk factors for cardiovascular disease, as confounders, or as risk modifiers?

R. De Vogli, M. Marmot

2

Heart rate: is it joining the ranks of key risk factors?

F. Paillard, J. C. Tardif

3

How do gender differences affect cardiovascular risk factors?

K. Schenck-Gustafsson
blanche pour voir
Should socioeconomic factors be considered as traditional risk factors for cardiovascular disease, as confounders, or as risk modifiers?

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There is strong evidence that cardiovascular disease (CVD) and its traditional risk factors are associated with socioeconomic conditions. However, the latter’s etiological role in the development of cardiovascular outcomes is not always well understood, and it is unclear whether they should be considered as traditional risk factors for CVD, as confounders, or as risk modifiers. After examining whether socioeconomic conditions meet the criteria for the three definitions, we argue that none of them fully captures the complexity of their contribution in shaping the epidemic of CVD across and within societies. We argue instead that socioeconomic factors are the “causes of the causes” of CVD. Implications for research and interventions to reduce CVD are discussed.

A considerable body of evidence indicates that cardiovascular disease (CVD), a leading cause of morbidity and mortality worldwide, is associated with socioeconomic factors. Research consistently shows that people in lower socioeconomic positions are more likely to be affected by CVD and its related risk factors. Although these associations are well established, the contribution of socioeconomic factors to the etiology of cardiovascular outcomes is not always well clarified. In order to fully capture the complexity of their role in influencing cardiovascular outcomes and risk factors, coherent theoretical conceptualizations and methodologies are needed.

In this article, we have been asked to address the following question: should socioeconomic factors be considered as traditional risk factors for CVD, as confounders, or as risk modifiers? In the attempt to provide the readers with an answer, we will first examine whether socioeconomic conditions meet the criteria for the three definitions. Then, we will argue that none of these definitions fully captures the complexity of their etiological role in influencing heart disease and its related risk factors. Finally, we argue that socioeconomic factors should be considered as the “causes of the causes” of heart disease. A substantial body of evidence on the relationship between changes of socioeconomic conditions and changes of the heart disease epidemic across and within societies supports such a definition. Implications for research and interventions on the reduction of cardiovascular disease are discussed.

SHOULD SOCIOECONOMIC FACTORS BE CONSIDERED AS TRADITIONAL RISK FACTORS FOR CVD?

Smoking, hypertension, diabetes, unfavorable lipid profile, and physical inactivity have traditionally been considered as the primary risk factors for CVD.4-5 However, the extent to which these risk factors account for the entire variation of CVD remains controversial.6-8 Of the factors that are believed to improve the explanatory power of models estimating CVD, socioeconomic factors are the most important. Numerous studies have shown that socioeconomic conditions are independent predictors of cardiovascular outcomes.1-9 Their effects remain significant even after adjustment for traditional risk factors for CVD and only a small proportion of the socioeconomic gradient in heart disease is explained by these factors.10 Figure 1 (page 104) shows mortality from coronary heart disease over 25 years in the first Whitehall study.
showing the contribution of risk factors to the social gradient. Results indicate that adjusting for traditional risk factors such as smoking, blood pressure, plasma cholesterol, short height, and blood sugar accounted for less than one third of the socioeconomic gradient in mortality.

Kaplan and Keil, in a review of the literature, showed that socioeconomic factors met most of the nine criteria set forth by Kuller as rules to be adopted in the search for new risk factors for cardiovascular disease. In light of such evidence, should socioeconomic factors be added to the list of primary or traditional risk factors for CVD?

Although socioeconomic factors satisfy most of these criteria for being included in the list of risk factors for CVD, their etiological role is very different from that of traditional risk factors. Unlike the latter group of factors, socioeconomic conditions exert their health effects through large-scale social and societal processes that, in turn, are translated into the body through multiple emotional, behavioral, and biological mechanisms. When compared with the traditional risk factors for CVD, socioeconomic factors have a more pervasive and complex role in influencing heart disease. While smoking, hypertension, diabetes, unfavorable cholesterol profile, and physical inactivity are “proximal” determinants of cardiovascular outcomes, socioeconomic conditions such as education (a proxy measure of early life circumstances and parental social class) can be considered as “distal” causes influencing both CVD and the traditional risk factors through multiple pathways. Because of such etiological differences, we believe it is inappropriate to consider socioeconomic factors as another group of traditional risk factors for CVD.

SHOULD SOCIOECONOMIC FACTORS BE CONSIDERED AS CONFOUNDERS?

If socioeconomic factors cannot be considered as traditional risk factors for CVD, should we consider them as confounders? Epidemiological confounding refers to the failure of a crude (or partially adjusted) association to properly reflect the magnitude of an exposure effect, due to differences in the distribution of extraneous risk factors among exposed and unexposed individuals. Confounding can occur when it is assumed that the relationship between a given exposure and an outcome is not “real,” but attributable to a third variable, or confounder. In order to be treated as a confounder, a third factor needs to be “extraneous” to the causal model or involving a mechanism other than the one under investigation. Socioeconomic conditions have sometimes been modeled as confounders to adjust the relationships between traditional risk factors for CVD (eg, hypertension) and health outcomes. However, such analyses have been based on an inadequate understanding of the “antecedent role” played by socioeconomic conditions in the causal model connecting CVD with its risk factors. As socioeconomic conditions affect individuals earlier in time than traditional risk factors for CVD, they are causally antecedent to both CVD and these risk factors. Traditional risk factors for CVD should therefore be considered as mediators of the relationship between socioeconomic conditions and CVD. Treating socioeconomic factors as confounders may result in biased estimates of the relationship between traditional risk factors and CVD and theoretical misinterpretations of research findings. Rather than being considered “extraneous” to the mechanism under investigation, socioeconomic factors should be treated as key determinants of the causal model estimating CVD.
**SHOULD SOCIOECONOMIC FACTORS BE CONSIDERED AS RISK MODIFIERS?**

In the previous paragraphs, we have claimed that socioeconomic factors should not be considered as traditional risk factors or confounders. Should they be considered as risk modifiers? Risk modification refers to a variation in the magnitude of an effect measure across levels of a third variable or risk modifier. When an association between a given exposure (e.g., hypertension) and an outcome (CVD) is modified by a third variable (e.g., socioeconomic factors), the strength of the association varies across levels of the third variable. In the literature, socioeconomic status has been shown to modify the relationship between risk factors and CVD, thus meeting the criteria of risk modifier. Vitaliano et al found that emotion-related support was associated with a composite measure of cardiovascular risk for low-income patients, but not for patients with higher incomes. These results indicate that socioeconomic factors should be sometimes considered as risk modifiers. However, such a definition is not entirely adequate to explain their complex role in the development of heart disease and risk factors. Socioeconomic factors do not merely modify the effect of certain risk factors on CVD. They actually causally influence both CVD and risk factors and their effects are usually consistent across different levels of socioeconomic status. This is in line with research showing that the association between socioeconomic conditions and health at the individual level is not characterized by thresholds effects. Research shows that every step down the socioeconomic ladder is generally associated with a decrement in health status. Although socioeconomic factors can sometimes play the role of risk modifiers, they are more than that.

**Socioeconomic factors, the “causes of the causes” of heart disease**

Although socioeconomic factors are sometimes considered as traditional risk factors for CVD, confounders, or risk modifiers, in this article we argue that they should be treated as “the causes of the causes” of heart disease. An appropriate theoretical conceptualization of the role of socioeconomic factors in the etiology of heart disease is presented in Figure 2. In this conceptual framework, socioeconomic factors produce “direct” effects on heart disease (or through “direct” pathways such as chronic stress) as well as “indirect” effects mediated by traditional risk factors for CVD.

The definition of socioeconomic factors as the “causes of the causes” of heart disease is supported by scientific evidence across and within societies. Across societies, the epidemic of heart disease changes in response to changes in socioeconomic conditions that profoundly affect standards of living and habits. Within societies, there are consistent socioeconomic gradients of heart disease and traditional risk factors for CVD and these gradients vary according to the stage of socioeconomic development of a given country.

**Socioeconomic factors and cardiovascular disease across societies**

The emergence of CVD in different societies has been associated with the advent of industrialization and urbanization that improved socioeconomic conditions and changed the way of living. The diffusion and decline of this health condition changed according to the stage of socioeconomic development in the context of the epidemiological transition from infectious to chronic diseases. Although heart disease has often been regarded as a disease of affluent societies, the rapid socioeconomic changes that transformed patterns of consumption and lifestyle have rapidly affected developing countries as well. Rates of coronary heart disease are still low in the poorest regions of the world including sub-Saharan Africa, and the rural areas of South America and South Asia. They have become more common in regions characterized by increasing wealth, longevity and lifestyle changes in diet, exercise, and smoking such as India and Latin America. They are declining in Western Europe, North America (excluding some parts of Mexico), Australia, and New Zealand as changes in the way of living delay ischemic heart disease and stroke to more advanced ages.

Whereas the epidemic in affluent societies increased and declined over the course of a century, the
transition in the developing world has been compressed into a few decades. More recently, this process of rapid diffusion of heart disease has been exacerbated by the “westernization” of lifestyle and economic globalization that produced further changes in terms of urbanization, agricultural production, and food consumption. One of the effects of globalization is what has been called the “coca-colonization” of living habits including increased consumption of fats and sweeteners. As countries are more progressively integrated in the world economy they converge to more homogeneous patterns of lifestyle and consumption leading to similar chronic diseases. The globalization of lifestyle patterns has been particularly strong among younger generations with the United States leading the change, and exporting conditions such as obesity to less developed societies.

Although the progression from one stage of socioeconomic development to the next tends to proceed in a predictable manner, there are important differences between societies. Several hypotheses have been proposed to explain such variations including the income inequality and social cohesion hypotheses. Evidence shows that more egalitarian societies tend to have lower risks of coronary heart disease compared with highly unequal societies. Furthermore, low social cohesion or social capital have been found to be predictors of coronary heart disease. Japan, a country characterized by low inequality and high social cohesion, is unique among high-income countries, because the transition started later, but proceeded much more rapidly than in other affluent nations. It is often considered a puzzle in the epidemiological transition because, despite having one of the highest rates of smoking in the world, Japan experiences very low rates of heart attacks. On the opposite side, in the former Soviet Union and other socialist countries, drastic increases of income inequality and disruption of social organization were accompanied by unprecedented increases in coronary heart disease. The importance of social cohesion and its effect on CVD has also been shown by changes in myocardial infarction in Roseto, a small Italian-American community in Pennsylvania. Roseto, which in the 1960s was characterized by close-knit social relations and egalitarian values, experienced a rate of heart attacks about 40% lower than expected, a figure that could not be explained by the prevalence of traditional coronary heart disease risk factors including smoking, overweight, and diet. However, as community bonds weakened in the following years, Roseto caught up with the prevalence of adjacent towns and lost its protection from heart disease. The hypothesis that social cohesion provides benefit to heart health may also help to explain why in southern European countries (Spain, Portugal, Italy, France, and Greece) characterized not only by the Mediterranean diet, but also by extended systems of social relations, heart diseases remained low, despite rapid socioeconomic and lifestyle changes.

Socioeconomic factors and cardiovascular disease within societies

The effect of socioeconomic factors on CVD is also manifested as socioeconomic inequalities in the distribution of this health outcome and its related behavioral risk factors. Such patterns of inequalities change according to the stage of epidemiological transition. People in higher socioeconomic positions are the first to be affected by the disease and related behaviors, but then they are also the first to experience a decline of both the condition and risk factors. Later in the transition, such conditions become progressively more prevalent among lower socioeconomic groups with socioeconomic gradients of heart disease and risk factors that reverse over time.
ic position observed during the 20th century, with a widening mortality gap over time. The “switchover” has been documented in England and Wales where there has been a greater decline in coronary heart disease mortality among higher socioeconomic groups during the latter part of the century, which has increased inequalities over time.

As countries “develop” they converge to a more homogeneous social pattern with low socioeconomic position that progressively becomes a systematic risk factor for coronary heart disease both in affluent and less affluent societies.

**Socioeconomic factors and traditional risk factors for CVD**

The epidemiological transition of CVD across socioeconomic groups coincides with the transition of conventional CVD risk factors including health behaviors. The most affluent social groups are the first to change their lifestyle and consumption that lead to the development of risk factors such as obesity, physical inactivity, smoking, high blood pressure, and high cholesterol levels. However, as these changes influence society as a whole, behavioral risk factors for heart disease become more common among less privileged socioeconomic groups both in affluent and less affluent societies.


As countries reach the later stages of socioeconomic development, the relationships between low socioeconomic position and CVD behavioral risk factors become more homogeneous. In most developed societies the relationship between low socioeconomic status and behavioral risk factors is consolidated and consistent across individual-level and area-level indicators. The poorest sectors of society almost everywhere now use tobacco with greater frequency than their most privileged counterparts in terms of income, education, and occupation.

Although behavioral risk factors become more prevalent among the lower socioeconomic groups in almost any nation, there are some exceptions to the rule. Perhaps, the most notable ones are represented by the weaker, absent, or inverse social gradients of behavioral risk factors in southern European countries that are also characterized by lower rates of coronary heart disease compared to northern Europe, the US, and the UK. Such international differences in the transition of the social gradient of health behaviors remain largely unexplained, and further research is needed to analyze the interrelations and relative importance of social causes versus risk factors in determining heart disease and the social gradient of heart disease.

**IMPLICATIONS FOR RESEARCH AND THE PREVENTION OF CARDIOVASCULAR DISEASE**

The theoretical conceptualization of the associations between socioeconomic factors, traditional risk factors, and CVD, and the empirical evidence supporting them, have important implications for research and intervention. In terms of research, treating socioeconomic factors just as another group of traditional risk factors, confounders, or risk modifiers could result in biased associations between risk factors.
and CVD and potential misinterpretations of research findings. When developing research models estimating the risk of CVD, socioeconomic factors should be considered as distal determinants of CVD or “the causes of the causes” of heart disease. In terms of intervention, although CVD is mainly addressed through clinical and behavioral interventions, in order to reduce it effectively, prior concern should always be to address the ultimate causes of incidence of these outcomes at the population level. Changes in the distributions of CVD and traditional risk factors for CVD such as smoking, hypertension, diabetes, unfavorable cholesterol profile, and physical inactivity are intrinsically intertwined with socioeconomic conditions. Therefore, in order to address these risk factors effectively, it is necessary to tackle the socioeconomic factors that cause them in the first place. Also, as shown by previous research, traditional risk factors play only a minor role in explaining inequalities of heart disease. Therefore, even if we were able to reduce such risks, inequality in CVD would continue. Although measures promoting healthy lifestyles such as restrictions of smoking in public spaces, increased availability of healthful foods, and quality and safety of recreational areas may be important in reducing CVD, they also need to be complemented with broader socioeconomic measures affecting poverty and inequality, policies regarding the agriculture, food, and tobacco industries as well as changes in urban planning, social participation, the work environment, and transportation.

Although most health professionals may see CVD merely as a problem of the individual, socioeconomic factors are key determinants of CVD and its related risk factors. The rise of CVD in the developing world and the welcome decline in the developed world have often been attributed to changes in smoking, cholesterol level, high consumption diet, physical inactivity, and obesity. However, as shown by evidence reviewed in this chapter, all these factors are socially patterned or strongly influenced by socioeconomic changes across and within societies. While the control of traditional risk factors is not compatible with strategies at the societal level, in order to effectively reduce CVD and inequalities in CVD at the population level, in both developed and developing societies, a broader socioeconomic approach is needed.

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Heart rate: is it joining the ranks of key risk factors?

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Heart rate is a potent predictor of major cardiovascular events in the general population and in patients with cardiovascular disease. High heart rate facilitates atherogenesis and atherosclerosis progression. It is an important determinant of the occurrence of myocardial ischemia and malignant arrhythmias. Despite its associations with other risk factors, it remains an independent risk predictor in epidemiological studies. Heart rate reduction is associated with clinical benefits in the treatment of coronary artery disease and heart failure. Promoting heart rate from a risk predictor with important prognostic implications to a risk factor will require formal demonstration that pure heart rate reduction will decrease cardiovascular event rates in a prospectively conducted clinical trial. This hypothesis is currently being tested in the BEAUTIFUL and SHIFT trials.

Numerous epidemiological studies have consistently indicated that a higher resting heart rate (HR) is an independent predictor of cardiovascular (and all-cause) mortality.1-5 Heart rate is an important determinant of atherosclerosis,6-11 myocardial ischemia,12 and arrhythmias13,14 Heart rate reduction provides clinical benefits. Despite these concordant data, why has resting HR, a simple clinical tool, not yet joined the ranks of key risk factors?

EPIDEMIOLOGIC DATA
Results of many cohort studies accumulated over the last 30 years have consistently shown a gradual increase in cardiovascular mortality with increasing resting HR, both in the general population and in coronary heart disease (CHD) patients. With a follow-up of 30 years in 5070 subjects free of cardiovascular disease at entry, the Framingham study reported a progressive increase of all-cause, cardiovascular, and coronary mortality rates with increasing resting HR, in both sexes and at all ages.

SELECTED ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>ACRONYM</th>
<th>DEFINITION</th>
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<tr>
<td>AMI</td>
<td>acute myocardial infarction</td>
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<tr>
<td>BCAPS</td>
<td>Beta-blocker Cholesterol-lowering Asymptomatic Plaque Study</td>
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<tr>
<td>BEAUTIFUL</td>
<td>Morbidity-mortality EvAlUaTion of the I1 inhibitor ivabradine in patients with coronary artery disease and left ventricULar dysfunction</td>
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<tr>
<td>CAD</td>
<td>coronary artery disease</td>
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<tr>
<td>CIBIS</td>
<td>Cardiac Insufficiency Bisoprolol Study</td>
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<tr>
<td>COMET</td>
<td>Carvedilol Or Metoprolol Evaluation Trial</td>
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<tr>
<td>HR</td>
<td>heart rate</td>
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<tr>
<td>hr</td>
<td>hazard ratio</td>
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<tr>
<td>INITIATIVE</td>
<td>International Trial of the Antianginal effects of IvabradinE compared to atenolol</td>
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<tr>
<td>PPS</td>
<td>Paris Prospective study</td>
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<tr>
<td>AMI</td>
<td>acute myocardial infarction</td>
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<tr>
<td>MERIT-HF</td>
<td>MEtoprolol controlled release Randomized Intervention Trial in Heart Failure</td>
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<tr>
<td>SHIFT</td>
<td>Systolic Heart failure treatment with I1 inhibitor ivabradinE Trial</td>
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Keywords: heart rate; risk factor; cardiovascular event; atherosclerosis; arrhythmia; myocardial ischemia; epidemiology; coronary artery disease; heart failure; ivabradine

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All-cause and cardiac mortality increased steadily with resting and exercise HR in the Paris Prospective study (PPS) of 5713 healthy men, aged 42 to 53 years, and followed up for 23 years. In those two studies, the relationship was much steeper for sudden cardiac death. In the PPS, men with a resting HR >75 bpm had a relative risk of sudden cardiac death of 3.46 by comparison with men whose HR was <60 bpm, even after adjustment for age, use of tobacco, physical activity, diabetes, body-mass index, blood pressure, cholesterol, parental history of sudden death or myocardial infarction, and exercise duration (Figure 1). HR has also been shown to predict mortality in hypertensive populations and in elderly patients.

In CHD patients, HR was a significant predictor of mortality at 30 days and 10 months after an acute coronary syndrome. We have reported the results of a study that evaluated the relationship between resting HR and future cardiovascular events in 24,913 patients included in the Coronary Artery Surgery Study (CASS) registry undergoing coronary arteriography for the presence of suspected or proven coronary artery disease (CAD), with a median follow-up of 14.7 years. After adjusting the multivariable Cox proportional hazard model for age, sex, diabetes, hypertension, cigarette smoking, left ventricular ejection fraction, number of clinically significant diseased coronary vessels, type of recreational activity, and concomitant treatments (including β-blockers), total mortality was increased in patients with HR between 77 and 82 bpm (hazard ratio [hr], 1.16; (99% confidence interval [CI], 1.04-1.28) and those ≥83 bpm (hr, 1.32; CI, 1.19-1.47) when compared with the reference quintile (<60 bpm). Cardiovascular mortality was also increased in the 77 to 82 bpm (hr, 1.14; CI, 1.00-1.29) and in the > 83 bpm (hr, 1.31; CI, 1.15-1.48) groups. The association between heart rate and total mortality held true in all analyzed subgroups (Figure 2). The predictive value of HR for mortality remained true both in men and women in this large study, in contrast to some studies in the

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**Figure 1.** Relative risks of death from any cause and of nonsudden and sudden death from myocardial infarction, according to the quintile of resting heart rate.

**Figure 2.** Subgroup analyses on total mortality for a 1-SD increment in heart rate (12.4 bpm) in patients with suspected or proven CAD.

**Subgroups**

**Abbreviations:** BMI, body mass index; LVEF, left ventricular ejection fraction.

general population,1,3 in hypertensive subjects,3 or in patients with myocardial infarction.16 Data from our study in patients with stable CAD therefore indicate that a higher HR can also be deleterious in women. The clinical measurement of HR could be considered as a crude estimation. However, despite its better reproducibility,17 ambulatory HR assessment did not provide any additional prognostic information over and above the standard clinical measurement of HR in the Syst-Eur study.4 The variations in HR during and after exercise also carry additional information,2 but this issue is beyond the scope of this article. Beyond the human species, Levine has shown an inverse semilogarithmic relationship between HR and life expectancy among mammals (Figure 3).18 The only exception to this relationship is in fact humans, but the dramatic extension of life expectancy is relatively recent in human history. Our ancestors’ life expectancy would have seemed much less eccentric with respect to the general relationship. The total number of heartbeats in a lifetime seems to be remarkably constant among mammals, in the area of $7.3 \times 10^8$ beats (Figure 4) and could be linked to a constant energy consumption/heart beat.18

The contribution of genetic and environmental factors to resting HR has also been evaluated. The heritability of HR has been estimated to be 21% in the Framingham study.19

PATHOPHYSIOLOGICAL MECHANISMS RELATING HEART RATE AND CORONARY HEART DISEASE

The importance of HR in cardiovascular prognosis can probably be explained by its relationship with major pathophysiological determinants (Table I, page 114).

Atherosclerosis

Experimental and clinical evidence suggest that sustained elevations in HR may play a direct role in the pathogenesis of coronary atherosclerosis and its complications. Heart rate was significantly correlated with the severity and progression of atherosclerosis on coronary angiography among men who had developed myocardial infarction at a young age.6 Accelerated atherogenesis resulting from increased HR may be due to both mechanical and...
Table 1. Pathophysiological mechanisms relating an increased heart rate and cardiovascular disease.

- Increased severity and progression of coronary atherosclerosis
- Lesser development of collaterals
- Increased risk of coronary plaque disruption
- Increased arterial rigidity
- Greater myocardial oxygen consumption (MVO₂)
- Decreased myocardial perfusion (shortening in the duration of diastole)
- Increased susceptibility to arrhythmias
- Marker of sympathetic overactivity
- Increased risk of left ventricular dysfunction

metabolic factors. Increased vascular stresses associated with higher HR may contribute to endothelial injury, potentially promoting the complex cascade of events leading to increased atherosclerosis. Experimental data have also demonstrated that a lower heart rate can delay the progression of coronary atherosclerosis in monkeys. Male cynomolgus monkeys subjected to sinus node ablation or those with innately low heart rates had significantly less coronary atherosclerosis than animals with higher heart rates. These observations are supported by results from the Beta-blocker Cholesterol-lowering Asymptomatic Plaque Study (BCAPS), which have shown that a β-blocker reduced the rate of progression of carotid intima-media thickness in asymptomatic patients. A high HR has also been associated with an increased risk of coronary plaque disruption. In this retrospective angiographic study evaluating patients who underwent two coronary angiograms within 6 months, logistic regression analysis identified a positive and independent association between plaque disruption and a mean heart rate >80 bpm. This association again indicates that hemodynamic forces may play a critical role in the process of plaque disruption. A high HR is also strongly associated with increased arterial rigidity, reduced vascular distensibility, and elevated pulse-wave velocity, characteristics that are all associated with an increased risk of myocardial infarction and cardiac death. In a retrospective study, a larger number of patients with obstructive CAD whose HR were <50 bpm had developed collateral vessels (potentially decreasing the ischemic burden) compared with those with HR >60 bpm. The presence of collaterals was independent of the history of angina or the use of β-blockers.

Myocardial ischemia

A high heart rate is a major determinant of myocardial ischemia, because it leads to both greater myocardial oxygen consumption (MVO₂) and decreased myocardial perfusion, the latter because of the shortening in the duration of diastole. The likelihood of the occurrence of an ischemic episode increases at higher baseline heart rates. With a baseline HR less than 60 bpm, the likelihood of occurrence of ischemic episodes with heart rate acceleration was 8–7%, while at resting heart rates in excess of 90 bpm, the likelihood increased to 18.5%. Autonomic nervous system and susceptibility to arrhythmias

There is a closer relationship of HR with sudden cardiac death than with other causes of cardiac deaths. A high HR is a major determinant of the occurrence of ventricular tachycardia or fibrillation during experimentally induced acute ischemia in dogs. Decreased HR variability is also associated with an increased risk of malignant arrhythmias after an acute myocardial infarction (AMI). A high HR could also reflect an imbalance of the autonomic nervous system and may therefore be a marker of sympathetic overactivity; alternatively, a higher HR could also lead to greater activity of the adrenergic nervous system. Impaired nitric oxide (NO) synthesis may increase sympathetic activity and also facilitate arterial wall disease.

Heart failure

Heart failure is often associated with an elevated HR, secondary to an increased sympathetic tone, which may contribute to pathological ventricular remodeling. In a dog model of left ventricular dysfunction, the benefit of β-blocker treatment was abolished with pacing that prevented the pharmacologically induced bradycardia. In patients with left ventricular systolic dysfunction, reversal of β-blocker-induced bradycardia with pacing at 80 bpm as compared with 60 bpm had deleterious effects on left ventricular volumes and ejection fraction.

CLINICAL BENEFITS OF PHARMACOLOGICAL HEART RATE REDUCTION

Although heart rate reduction obtained with β-blockers has documented clinical benefits, these agents also have other pharmacological effects, which may reduce their usefulness. Recently, a new heart rate-reducing approach has shown promising results.

β-Blockers

Post-myocardial infarction

Kjaekhus has reported a strong association between the reduction in HR with β-blockers given within 6 h
of the onset of symptoms of myocardial infarction and the reduction in infarct size. In 10 long-term randomized controlled trials of \(\beta\)-blockers after AMI, a correlation was shown between resting HR and total mortality.\(^{23}\) Cucherat recently published a metaregression analysis of 17 randomized clinical trials and confirmed that resting heart rate reduction was correlated with reduction in all-cause, cardiac, and sudden deaths (\(\text{Figure 5}\)).\(^{24}\) Each 10-bpm reduction in HR is estimated to reduce these mortality rates by 22%, 33%, and 41%, respectively. It should be noted, however, that these results may be potentially affected by some known and unknown confounders. In particular, blood pressure reduction induced by these drugs is in part correlated with HR reduction.

**Stable angina**

Heart rate reduction is the cornerstone of the management of exercise-induced angina and ischemia and its benefits explain the wide use of \(\beta\)-blockers, verapamil, and diltiazem-type calcium channel antagonists in this setting. In a double-blind study of low and high doses of calcium channel blockers in stable angina patients, there was a close relationship between the improvement in time to ischemia during the bicycle exercise test and the reduction in exercise HR.\(^{26}\)

**Heart failure**

A higher heart rate is associated with adverse outcomes in heart failure. \(\beta\)-Blockers have become an integral part of the treatment of patients with heart failure. HR reduction is most likely an important mechanism of the benefits of this class of agents in this setting. In the Cardiac Insufficiency Bisoprolol Study (CIBIS), multivariate analysis showed that the reduction in HR with bisoprolol (~15 bpm) was the most powerful predictor of survival.\(^{27}\)

In the Carvedilol Or Metoprolol Evaluation Trial (COMET) trial, HR on treatment was a predictor of mortality, but did not explain the superiority of carvedilol as compared to metoprolol in multivariable analysis.\(^{28}\) In contrast, the risk-reducing effect of metoprolol in the Metoprolol controlled release Randomized Intervention Trial in Heart Failure (MERIT-HF) trial was not explained by its effect on HR.\(^{29}\) Nevertheless, there is a clear relationship between changes in HR with different therapies and mortality in heart failure.\(^{30}\)

**\(I_f\) current inhibition and cardiovascular disease**

Recent advances in the understanding of sinus node activity have led to the novel therapeutic concept of "pure HR reduction." \(I_f\), a \(\text{Na}^+\)-\(\text{K}^+\) inward current activated by hyperpolarization and modulated by the autonomic nervous system, is one of the most important ionic currents for regulating pacemaker activity in the sinoatrial node.\(^{31}\) Ibaradine is a novel, specific HR-lowering agent, which acts in sinoatrial node cells by selectively and specifically inhibiting the pacemaker \(I_f\) current in a dose-dependent manner.\(^{32,33}\) This agent slows the diastolic depolarization slope of the action potential of sinoatrial node cells, thereby resulting in pure HR reduction.
Antianginal efficacy in patients with stable angina pectoris

This initial randomized trial in 360 patients used exercise test parameters to compare ivabradine versus placebo at trough of plasma drug levels over a 14-day treatment period. Time to 1-mm ST-segment depression in the ivabradine 5-mg and 10-mg groups increased compared with placebo (P<0.005), as did time to limiting angina (10 mg: P<0.05). In the INternational Trial of the AnTianginal effects of IVabradinE compared to atenolol (INITIATIVE) trial, the noninferiority of ivabradine 7.5 and 10 mg twice daily compared with atenolol 100 mg once daily was demonstrated for all exercise parameters, both for their antianginal and anti-ischemic effects (Figure 6). The increase in time to 1-mm ST-segment depression indicates that the improvement in total exercise capacity with ivabradine is associated with its anti-ischemic effect. Interestingly, ivabradine induced a similar or greater improvement in exercise capacity than atenolol for comparatively smaller reductions in HR and rate-pressure product.

Possible long-term clinical benefits of If current inhibition in chronic heart failure.

The effect of long-term (90 days) HR reduction with ivabradine was investigated in a rat model of ischemic heart failure. Ivabradine decreased HR over the 90-day treatment period (by 18% vs controls), without modifying blood pressure. Ivabradine significantly reduced left ventricular end-systolic diameter, which resulted in preserved cardiac output via increased stroke volume. Ivabradine also decreased left ventricular collagen density and increased left ventricular capillary density without modifying left ventricular weight. Three days after interruption of treatment, the effects of ivabradine on left ventricular geometry, shortening, and stroke volume persisted despite HR normalization. Diastolic dysfunction is an increasingly frequent cause of HF, especially in older patients. A higher HR is deleterious for left ventricular diastolic function. The guidelines recommend to slow the HR and eliminate tachycardia in patients with diastolic heart failure. The negative lusitropic effect of β-blockers may represent a disadvantage in this setting. The properties of ivabradine may be of particular interest to control HR in this condition because of its absence of deleterious effect on systolic and diastolic function.

HEART RATE AND CARDIOVASCULAR RISK: CAUSAL RELATIONSHIP?

The issue of a causal relationship between HR and cardiovascular events can be addressed on the basis of the Bradford-Hill criteria. (i) The relationship between HR and cardiovascular event rates has been found to be consistent, strong, and preexisting cardiovascular disease, and the association is stronger in men than in women in some studies. (ii) It has been reported in populations both without and with progressive cardiovascular disease. Obviously HR increases with poor fitness and...
Heart rate: Is it joining the ranks of key risk factors? - Paillard and Tardif

...with cardiac dysfunction, two conditions associated with an altered prognosis. The predictive value of HR, however, persists even after adjustment for physical activity, exercise capacity,2 cardiac function,3 and the history of previous cardiac disease.1,4 A high HR is also associated with smoking,40 high blood pressure,1,40,41 and many metabolic risk factors (body weight, hyperinsulinemia, hyperglycemia).40-43 These associations can be linked to common pathophysiological disturbances, including sympathetic overactivity, which is associated with the metabolic syndrome and insulin resistance.42-44

Nevertheless, in most recent epidemiological studies, HR remains an independent risk predictor after adjustment for the other known risk factors. β-Blockers have improved cardiovascular outcomes after myocardial infarction and in patients with heart failure, but it is difficult to confirm that heart rate reduction is the sole reason for their beneficial effects in these settings. Raising HR from the level of a risk predictor after adjustment for physical activity, exercise capacity,2 cardiac function,3 and the history of previous cardiac disease.1,4 A high HR is also associated with smoking,40 high blood pressure,1,40,41 and many metabolic risk factors (body weight, hyperinsulinemia, hyperglycemia).40-43 These associations can be linked to common pathophysiological disturbances, including sympathetic overactivity, which is associated with the metabolic syndrome and insulin resistance.42-44

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How do gender differences affect cardiovascular risk factors?

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Cardiovascular disease (CVD) kills almost as many women as men. Of 17.5 million persons worldwide dying from CVD each year, over 8.6 million are women, more than from all cancers (including breast cancer), tuberculosis, HIV/AIDS (human immunodeficiency virus/acquired immune deficiency syndrome), and malaria combined. Most cardiovascular deaths could be prevented in both sexes. Risk factors may differ in impact according to gender. Ischemic heart disease presents later in women, who are therefore older and more likely to suffer from comorbidities such as diabetes and hypertension. Specific hormone-related risk factors include polycystic ovarian syndrome, premature menopause, and gestational diabetes or hypertension. Hormone replacement therapy has failed to show any benefit in terms of CVD in women, mainly because of associated adverse effects.

Keywords: cardiovascular disease; risk factor; gender; mortality; comorbidity; hormone-replacement therapy

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Cardiac valve disease (CVD) has traditionally been considered as a “man’s disease,” but this perception is changing as it being increasingly realized that CVD kills almost as many women as men. Of the 17.5 million persons who die of CVD each year throughout the world, over 8.6 million are women, ie, more than the total number of women who die of all forms of cancer (including breast cancer, with a mortality of 3%), tuberculosis, HIV/AIDS (human immunodeficiency virus/acquired immune deficiency syndrome), and malaria combined. In Europe, 23% of women die of ischemic heart disease (IHD) versus 21% of men, and 18% of women die of stroke versus 11% of men. For complete data, the reader is referred to www.who.int/whosis/en/index.html (Figure 1).

These figures of CVD mortality are all the more tragic as most CVD deaths could be prevented in both sexes.

CARDIOVASCULAR RISK FACTORS IN WOMEN: CURRENT ISSUES

Owing to higher female life expectancy, women who develop cardiovascular disease tend to be older or elderly, a fact that has specific management implications in itself. Despite the international focus on cardiovascular disease in women over recent years, there has been little change in mortality, especially as far as premenopausal women are concerned. According to the World Heart Federation, CVD is indisputably the most serious neglected health problem in women, both in developing and in developed countries. The lack of awareness among women is especially marked in countries of low to middle economic ranking where the majority of public health expenditure is almost exclusively devoted to maternal and child health.

According to the findings of the INTERHEART study published in 2004, nine factors are responsible for 90% of all IHD. These factors are dyslipidemia, hypertension, smoking, stress, diabetes, obesity (especially abdominal fat), physical inactivity, bad eating habits with too little fruit and vegetables, and

SELECTED ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
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<td>ARB</td>
<td>angiotensin receptor blocker</td>
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<td>CAD</td>
<td>coronary artery disease</td>
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<td>CHD</td>
<td>coronary heart disease</td>
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<td>CVD</td>
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<td>DM</td>
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<td>hormone replacement therapy</td>
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<td>IHD</td>
<td>ischemic heart disease</td>
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<td>SCORE</td>
<td>Systematic CORonary Risk Evaluation</td>
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alcohol consumption. Some risk factors for CVD are unique to women, such as older age at presentation, which is an important risk factor. Premature menopause, ie, before the age of 45 years, and pre-eclampsia during pregnancy, as well as gestational diabetes and hypertension, are other important risk factors in women. Polycystic ovarian syndrome, known as the “woman’s metabolic syndrome,” also increases the risk of CVD. The American Heart Association (AHA) issued separate guidelines in the prevention of CVD in women 2004,3 and the European Society of Cardiology (ESC) published a policy document in 2006, stressing the need for more knowledge about gender aspects in CVD.4 In addition to the aforementioned well-known and recognized risk factors, there are many other potential targets for treatment, which, although currently still hypothetical, may in future be included in risk modulation recommendations. These include, among many others, abnormal levels of circulating lipoprotein A, C-reactive protein, serum amyloid A, homocysteine, interleukin-6, and intercellular adhesion molecule–1, as well as low socioeconomic status.5

In Europe, the Systematic COronary Risk Evaluation (SCORE) system for the evaluation CVD risk is used (www.escardio.org) (see Lead article by Guy De Backer in this issue). One critical point is that this system only addresses subjects up to the age of 65 and therefore misses most women.

Although all current guidelines are based on traditional risk factors, some reports indicate that many cardiac events can occur in women independently of the presence of the traditional risks. In contrast, the opposite is also true, namely, the absence of cardiac events in spite of the presence of classic risk factors. It is paradoxical that the same risk factors have been used in risk calculations over the past 40 years in spite of increasing recognition of the influence of gender.

Paul Ridker et al6 suggested in JAMA in 2007 that a different score system should be used for women. These authors used the simplest version of the Reynolds score, based on age, systolic blood pressure, HbA1c in diabetics, smoking, total cholesterol, high-density lipoprotein (HDL) cholesterol, high-sensitivity CRP, and hereditary factors, eg, whether the mother had a history of myocardial infarction before the age of 60. They applied this score to CVD events that had occurred over a 10-year period in 25 558 women aged more than 45 years in the Women’s Health Study. Based on this new adjusted scoring system, the authors found that 40% to 50% of the women were reclassified from a middle-risk group to either a low-risk or a high-risk group. It was concluded that the new scoring system predicted CVD risk much more precisely than classic instruments.

**SPECIFICITIES OF CARDIOVASCULAR RISK FACTORS IN WOMEN**

**Lipids**

The association between elevated total cholesterol and low-density-lipoprotein (LDL) cholesterol and increased cardiac risk is beyond dispute, as are the benefits of lipid reduction in high-risk individuals. Interestingly, the Lipid Research Clinic’s follow-up study showed that low HDL cholesterol was the most significant predictor of death due to IHD in women after adjustment for age.7 Swedish National guidelines recommend a cholesterol
target of less than 5 mmol/L for primary prevention and less than 4.5 mmol/L for secondary prevention. In the UK, the National Service Framework for coronary heart disease (CHD) advocates a cholesterol target less than 5 mmol/L both for primary and secondary prevention. In our own Stockholm female Coronary Risk Study, we found that hyperlipidemia was the most significant risk factor for coronary stenosis in women, as compared with hypertension and diabetes (Figure 2).

More recent guidelines recommend targets of less than 4 mmol/L for total cholesterol. Low HDL levels have been found in epidemiologic studies to have a greater impact in women, but intervention studies independently focused on HDL are difficult to design. However, most recent guidelines recommend treatment for those with concentrations below 1 mmol/L. In women, hypertriglyceridemia is an independent risk factor for coronary artery disease (CAD), while this is still disputed as far as men are concerned. An increase in 1% in HDL is associated with 3% to 5% decrease in risk for women, but only a 2% decrease for men. In the two major trials that have enrolled a significant number of women, lipid-lowering therapy was found to benefit women to an equal if not greater extent than men. In the simvastatin arm of the Heart Protection Study (HPS), there was a significant reduction in all-cause mortality and a 24% reduction in vascular events, and women had the same benefit as men. HPS is one of few lipid studies to have been powered before the start of the study in order to determine the adequate numbers of men and women. All other lipid studies have calculated the risk for women as a subgroup defined subsequently.

The treatment of dyslipidemia combines better dietary habits, more exercise, and medication. 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are the mainstay of therapy. Early concerns about the safety of these agents, particularly with respect to carcinoma of the breast, have proven unfounded. Other agents include bile acid binders like ezetimibe and fibric acid derivatives (gemfibrozil and fenofibrate), no gender-specific outcomes with these agent have been reported.

Hypertension

Meta-analysis of prospective data on over 1 million adults (aged 40 to 69 years) has shown that a 20 mm Hg systolic or 10 mm Hg diastolic increase in average blood pressure doubles the death rate from CHD. One third of the British population is hypertensive, compared with one fourth of the population in Sweden (but over half of the above-60 population in Sweden). Van der Giezen et al found a 3-fold increase in IHD and stroke among women with systolic blood pressure (SBP) >185 mm Hg as compared with women with SBP <135 mm Hg.

The treatment of hypertension combines better dietary habits, more exercise, and medication. The Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommends BP values <140/90 mm Hg in all hypertensive patients and <130/80 mm Hg in diabetics—a target agreed by most national societies. The treatment of hypertension is so far the same in men and women, that is, in most cases medication together with lifestyle changes.
The first-line drugs are angiotensin-converting enzyme (ACE) inhibitors (or angiotensin receptor blockers [ARBs] if not tolerated), diuretics, calcium channel blockers, and β-blockers. If there is not enough of a response, α-blockers and others can be tried. Women report more adverse effects (like cough) with ACE inhibitors than men.

Diabetes
Cardiovascular events are the leading cause of death especially in type 2 diabetes mellitus (DM). Men with type 2 DM have a 2- to 4-fold greater annual risk of CVD, whereas women have a significantly higher proportional risk (up to 3- to 5-fold). The INTERHEART study estimated that 15% of heart attacks in Western Europe and 9% of heart attacks in Central and Eastern Europe were due to diagnosed diabetes.

Smoking
That smoking predisposes to IHD is not disputed. In the Nurses’ Health Study including over 120,000 healthy nurses, only 4 to 5 cigarettes daily almost doubled the risk and 1 pack daily increased the risk 6-fold. Achieving a reduction in the number of male smokers has been a public health victory; sadly the number of female smokers (initially lower than men) has not declined to the same extent, and this is particularly true of younger women, who thus are creating significant vascular problems for themselves in later life. In Sweden, more women than men smoke and lung cancer is more common in women. Regular exposure to secondhand smoke increases risk of CHD by 25%. The World Health Report 2002 estimates that in developed countries around 12% of the disease burden and over 20% of CVD are due to smoking.

The INTERHEART case-control study estimated that 29% of heart attack cases in Western Europe were due to smoking, and smokers and former smokers are at almost twice the risk of a heart attack compared with never smokers. Women are said to have more difficulties to stop smoking, one reason being the greater concern about weight gain. Cigarette smoking decreases endogenous levels of estrogens in women, advancing the onset of menopause, which in itself predisposes to future CVD.

Obesity
One of the findings of the Nurses’ Health Study was that there is a gradient of coronary risk, with the heaviest category of women having a 3-fold risk for IHD compared with lean women. Much evidence has focused on the distribution of fat, with an android (apple) shape representing a higher cardiac risk than the gynoid (pear) shape. In general, skin fold measurements only marginally improve risk prediction of IHD as measured by the body mass index (BMI), but central obesity, as measured by the subscapular skin fold, is predictive independently of BMI. Based on the Nurses’ Health Study, the recommended target BMI is 18.5-24.9 kg/m² with a waist circumference of <82 cm for women and <98 cm for men.

Sedentariness, physical activity, and exercise
Blair et al observed in their prospective observational study that a lower fitness level was associated with a 4-7-fold increased risk for CAD (0.44) and stroke (0.51), independent of other vascular risk factors.

The reported beneficial effect of exercise on the CAD risk profile is less marked in women compared with men, with a smaller increase in HDL and less weight loss resulting from similar exercise training. Nevertheless, in the Nurses’ Health Study, two aspects were particularly important: brisk walking conferred the same benefit as vigorous exercise, and sedentary women who became active late in life reaped similar benefits as those who remained active throughout.

Stress
In the general population, psychosocial stress has always been associated with myocardial infarction or stroke. The popular phrase about someone “dying of a broken heart” has recently gained scientific backing because of the increasing number of patients, usually female, referred to hospitals with sudden onset of severe congestive heart failure and chest pain associated with ECG changes suggestive of an anterior wall myocardial infarction, after having experienced a highly stressful event.
bulges out to take the shape of a balloon (resembling a traditional Japanese octopus trap, or “takotsubo”) (Figure 3). Interestingly, if patients with broken heart syndrome (= takotsubo syndrome) survive the initial presentation, they will recover normal left ventricular function after 1 to 2 weeks. Elevated stress hormones (catecholamines) is the only abnormality reported, in the absence of any significant coronary artery blockage evidenced by coronary angiography.27

Compared with other risk factors, psychosocial variables are more difficult to define and measure objectively. Nevertheless, several dimensions within the broader definition of psychosocial factors are now associated with the risk of myocardial infarction. Stress at work and in the family, negative life events, lack of control, badly functioning social networks, low socioeconomic status, and depression are some of the factors that have an impact both on the risk and prognosis of IHD.

Until now, most studies have looked at work-related stress, especially in men. The finding of a relationship between stress and myocardial infarction has been attributed to low socioeconomic status rather than stress, but there is no confirmation that stress is more prevalent among poor people than among affluent people. Several recent studies show a clear relationship between work-induced stress and both stroke and myocardial infarction.

In women, stress in the setting of the family, including marital stress, has been shown to increase the risk of IHD.28 In the INTERHEART study, stress at work or at home was more common among patients with myocardial infarction than their controls, and stress represented 30% of the total risk.29 Depression is one of the aspects of psychosocial stress, and more women than men fall prey to depression after myocardial infarction. Also, depression is a stronger risk factor for IHD in women than in men.

To conclude, stress can both induce IHD and make it worse, probably through its deleterious effect on atherosclerosis, endothelial function, fibrinolysis, coagulation, inflammation, and vascular function.

Alcohol intake

Moderate alcohol intake may have a protective effect against IHD in middle-aged and elderly people. In contrast, too much alcohol definitely has harmful effects on many organs, including the heart. However, the grade of evidence isn’t very high, mainly because of the difficulty of performing placebo-controlled studies. In addition, bias may be introduced because control groups are always teetotalers who very often are “sober alcoholics.”

The type of alcohol is not as important as the when and how. A low-to-moderate daily intake may be protective, while binge drinking is harmful for the heart and liver. It is therefore not easy to make evidence-based recommendations, but there is no reason to ask people to stop moderate drinking after a myocardial infarction. This however by no means implies that one should encourage people to start drinking in order to prevent the onset of IHD or a recurrence of myocardial infarction. Light-to-moderate alcohol intake is defined as 1 standard glass daily for women and 2 for men. Women metabolize alcohol much slower than men and therefore their intake should be only half that allowed for men. A standard glass is defined as 12 g of alcohol, which is equivalent to 15 cL of wine.

Food intake

The so-called “Mediterranean diet” (at least 500 g of vegetables and fruit daily) is well known to possess beneficial effects in terms of total cholesterol, LDL cholesterol, blood pressure, as well as morbidity and mortality associated with myocardial infarction. The mechanisms behind these beneficial effects are multiple. Diet should always be combined with other lifestyle changes like exercise. The effects are probably iden-
Male sex hormones are potent modulators of cardiac risk factors at virtually every level of the atherosclerotic process. CHD and stroke are rare before the menopause. It is difficult to dissociate the change in CAD prevalence at or around the time of menopause from the age-related increase in CAD incidence in both men and women. The exponential nature of the increase in cardiac incidence around the age of 55 to 60 in women falsely exaggerates the apparent effect of the menopause. Further doubt has been cast on the effect of sex hormones by the observation in a wide variety of randomized clinical trials that HRT does not reduce—and if anything slightly increases—the risk of cardiac events. These recent findings contradict previous observational data suggesting a cardio-protective effect of HRT. The explanation would appear to reside in differences in the HRT and the non-HRT-taking population, which tend to confer a lower risk on the former. There is little difference between opposed and unopposed estrogen in relation to cardiac end points. Nevertheless, HRT, in its proper indication, which is climacteric symptoms, remains a useful treatment and its risks should not be exaggerated.

CONCLUSION

IHD presents later in women, who are therefore older at onset and more likely to suffer from comorbidities such as diabetes and hypertension. Specific hormone-related risk factors include polycystic ovarian syndrome, premature menopause, gestational diabetes or hypertension, and birth complications. Women have generally been either excluded or underrepresented in cardiovascular trials, and as such the evidence base is rather unsatisfactorily drawn either from observational cohorts or from small numbers within larger randomized trials. There is therefore a pressing need to ensure that cardiovascular trials are specifically designed to incorporate sufficient numbers of women to allow gender-specific efficacy analyses to be undertaken. This being said, the absence of specific data should not be used as an excuse for undertreating women, who in general respond well to the aggressive therapies used in men. Raising the awareness of women about the symptoms and risks of CVD will facilitate earlier and more effective therapy.

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Tales from the past, when told to a new generation, create little interest, particularly when they recount personal events only. However, when they deal with flesh and blood men and women, and of the eddies in the stream of time, they hold our attention. A look in the past can reveal the origin of ideas and relate them to the men and women who created them. This tale is an attempt to recount developments in medical science as personally experienced during the last seventy years. I hope this will show that science is a child of its time bound to thoughts and technology of its time. Therefore, we should not apply today’s standards to the work that came before us.

In 1935, a year after I had obtained my MD degree, I was a research fellow at the Carlsberg Biological Institute in Copenhagen, Denmark, which was financed by the Carlsberg Brewery. The institute was built primarily for the study of cell cultures. The director of the Institute was Albert Fischer, a student of Alexis Carrel from the Rockefeller Institute, now the Rockefeller University in New York City. What was tissue culture like in the early part of the 20th century? I had been exposed to this technique in the early 1930s as a medical student in Berlin, volunteering for Rhoda Erdman, a pioneer in the field of tissue cultures. The director of the Institute was Albert Fischer, a student of Alexis Carrel from the Rockefeller Institute, now the Rockefeller University in New York City. What was tissue culture like in the early part of the 20th century? I had been exposed to this technique in the early 1930s as a medical student in Berlin, volunteering for Rhoda Erdman, a pioneer in the field of tissue cultures. In 1907, Ross Granville Harrison, when at Johns Hopkins Hospital, was the first to devise a method to grow tissue fragments outside the body. He not only initiated this technique, but also was able to show that nerve fibers develop from particular nerve cells in the brain and the spinal cord. Harrison placed the tissue derived from a frog on a cover slip, inverted it over a hollow ground microscope slide, and sealed it with paraffin. When Harrison was proposed for the Nobel Prize for a second time, the committee eliminated him because “of the rather limited value of the method and the age of the discovery.” In my early Hopkins days in 1943 my laboratory at Johns Hopkins Hospital was close to that of George Otto Gey, who, using his roller tube technique, propagated cells, viruses and malignant cells in vitro for long periods of time. Gey is remembered particularly for his growth of malignant He-La cells in cell cultures. The word He-La is an abbreviation of the name of a young woman with cervical cancer whose tissue was cultured. Gey was a tall outgoing man who always welcomed young investigators to his...
Harrison’s experiments attracted the attention of Alexis Carrel. In 1909, Carrel sent his assistant Montrose T. Burrows to Harrison to learn the method and adapt them to the tissues of warm-blooded animals. Carrel introduced sterile technique and the Carrel flask, which could accommodate more tissue and medium. This led to the development of synthetic and defined media. In 1913, Conti in France introduced the time-lapse camera, which showed migrating and dividing cells. Today’s tissue culture has become an essential tool in the growth of viruses, of cancer cells, and the study of biology of tissue.

In 1937, I received a Rockefeller fellowship to work at the Rockefeller Institute in New York with Alexis Carrel. Carrel was born in France and received the Nobel Prize for his work on organ transplantation; he also contributed to the development of cell culture. He was an unusual scientist who believed in parapsychology, but he was an inspired innovator, a scintillating personality whose interests in nonscientific matters did not endear him to the staff at the Rockefeller Institute. He made the vital mistake of returning to France when the Nazis occupied it, in the vain hope of helping his beleaguered country. To me, Carrel was a great teacher and a friend. Among the scientists at the Rockefeller Institute were Oswald Avery, Peyton Rous and Karl Landsteiner. I had the opportunity to talk to members of their department, the contact facilitated by a faculty dining room, presided over by a painting of Lavoisier and his young wife. Landsteiner had received the Nobel Prize for his discovery of blood groups. He was one of those scientists who liked to work at the bench, trusting only results which he himself had personally obtained. A simple experimental arrangement led to his discovery of blood groups. As he wrote in his Nobel lecture from 1930, “my experiments consisted of causing the blood serum and erythrocytes of different human subjects to react with one another.” He concluded that “it became clear that the reactions follow a pattern which is valid for the blood of all humans, and that the peculiarities discovered are just as characteristic of the individual as are the serological features peculiar to an animal species. Basically, in fact, there are four different types of human blood, the so-called blood groups. The number of the groups follows from the fact that the erythrocytes evidently contain substances with two different structures, of which both may be absent, or one or both present in the erythrocytes of a person.” His discovery made the use of blood transfusions possible.

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Another Nobel Prize winner at the Institute was Peyton Rous. I found him always willing to talk about his work. He had been for many years the editor of the *Journal of Experimental Medicine*, and was a strict judge. He even edited the famous paper by Avery on the transformation of pneumococci, but it is questionable whether this great contribution needed his editorial work. He received the Nobel Prize in 1966, when he was over 80, for the discovery of a virus which produces tumor in chickens. Rous in 1910 “described a malignant chicken sarcoma which could be propagated by transplanting its cells, these multiplying in their new hosts and forming new tumors of the same sort.” He mentioned that “its cells yielded a causative virus.” It is now recognized that cancer is the result of many genetic mutations and dysregulations of cellular pathways, which lead to the formation of new blood vessels through angiogenesis. In solid tumors, the cells form a wide variety of signaling systems, which include angiogenic factors. Viruses are just some of the myriad of factors which can lead to dysregulation. The search goes on!

The third in this constellation at the Rockefeller Institute was Oswald Avery. He never did receive the Nobel Prize, although he richly deserved it. A Canadian by birth, he received his MD from the College of Physicians and Surgeons of Columbia University. He became interested in the factor which transforms rough into smooth pneumococci; Avery demonstrated that DNA and not proteins is responsible for the transformation into the genetic machinery of the rough cells.

After a surgical internship at the College of Physicians and Surgeons of Columbia University under A. O. Whipple, the initiator of the Whipple procedure for carcinoma of the pancreas, I joined the department of physiology at New York University under Homer W. Smith whose scientific interest was renal physiology. Smith was also a great writer, a novelist who had the gift to express his ideas on evolution with originality and style. In renal physiology Smith used the concept of clearance introduced by Rehberg and van Slyke. Biochemistry had not made inroads into renal physiology. At Bellevue, Homer W. Smith was the center of the group working on the role of the kidney in hypertension and shock, and Dickinson Richards and André Courmand began their work on catheterization of the heart, primarily interested in pulmonary circulation. Courmand was a careful and systematic worker, while Richards was interested in the grand design. He was a humanitarian and a scholar, a highly cultured New Englander and an all-round scholar. Cardiology at that time was primarily concerned with flow and pressure, and right heart catheterization was an ideal tool to study these new parameters.

During World War II, I spent time in the medical corps and the chemical warfare division of the US Army. I later joined the department of Surgery at Johns Hopkins Hospital under Alfred Blalock, to work on congenital heart disease. It was an exciting time. Cardiac surgery was in its early stages and Blalock had just published his early results on the surgery of congenital heart disease. This gave us the opportunity to define, by means of right heart catheterization and other physiological tests, the circulatory changes in these disorders. Open-heart surgery was still in the future; therefore Blalock’s technique was limited to conditions that could be treated by methods that
avoided direct surgery on the heart itself. The work on congenital heart disease was carried out with a group of brilliant young surgeons.

At that time, we noticed that catheterization of the coronary sinus in man could be carried out at will. From then on our work was primarily concerned with the extraction and utilization of foodstuffs by the human heart and their contribution to its oxidative metabolism. We continued this work at the University of Alabama in Birmingham and found that the heart was, as Taegtmeyer expressed it, “an organ with metabolic flexibility.” It uses carbohydrates, fats, and amino acids according to their availability, and myocardial failure is not accompanied by changes in myocardial extraction of foodstuffs. We began to recognize that the heart is a metabolic organ rather than a mere pump, which regulates and is regulated by flow and pressure. Alabama was followed by Washington University in St Louis, by Wayne State University in Detroit, and finally by the Huntington Medical Research Institute in Pasadena. In Detroit we introduced coincidence counting in the determination of human coronary flow in situ.

I hope this incomplete tale has brought out some general facts about the progress of clinical and fundamental research. Yesterday’s research looks primitive and simple as compared to the present. But I would venture that our successors 50 years from now will look at today’s research with the same degree of condescension that we reserve for the work of our predecessors. Science and art are the children of the times during which they are created. The style of creation changes, but human nature changes little. There also should be close dialogue between research carried out at the bench and at the bedside. Research should, like Claude Lenfant expressed it, “gather from the tree of knowledge fruit for the solace and refreshment of mankind.”

**FURTHER READING**


Risk Factors & Cardiovascular Disease

Summaries of Ten Seminal Papers

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1. Selected major risk factors and global and regional burden of disease
M. Ezzati and others. Lancet. 2002


3. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study
S. Yusuf and others. Lancet. 2004

4. Risk of cardiovascular and all-cause mortality in individuals with diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance: the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab)
E. L. Barr and others. Circulation. 2007

5. Sick individuals and sick populations

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. Clinical reality of coronary prevention guidelines: a comparison of EUROASPIRE I and II in nine countries. EUROASPIRE I and II Group. European Action on Secondary Prevention by Intervention to Reduce Events
EUROASPIRE I and II Group. Lancet. 2001

8. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age
D. M. Lloyd-Jones and others. Circulation. 2006

9. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies
S. Lewington and others. Lancet. 2002

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

Selection of seminal papers by Guy G. De Backer, MD, PhD
Department of Public Health - Ghent University
University Hospital - Ghent - Belgium

Highlights of the years by Ian Mudway, MD
Lung Biology - Division of Life Sciences - Franklin Williams Building
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Here is the first large systematic attempt to identify risk factors for cardiovascular disease globally and regionally contributing to morbidity and mortality. Previous estimates had been unreliable, overly selective, limited to individual risk factors, and often restricted to a small number of settings, all of which obscured comparisons. Indeed they had been perfect so far as Governments and lobbyists were concerned. For 26 selected risk factors, the expert working groups undertook a comprehensive review of published work and other sources—eg, government reports and international databases—to obtain data on the prevalence of risk factor exposure and hazard size for 14 epidemiological regions of the world. The study did not use categorical attribution, but rather counterfactual attribution based on theoretical minimum exposure models. Population-attributable fractions were estimated by applying the potential impact fraction relation to the mortality and burden of disease estimates from the global burden of disease (GBD) database.

Childhood and maternal underweight (138 million disability-adjusted life years [DALY], 9.5%), unsafe sex (92 million DALY, 6.3%), high blood pressure (64 million DALY, 4.4%), tobacco (59 million DALY, 4.1%), and alcohol (58 million DALY, 4.0%) were the leading causes of global burden of disease. Mortality was dependent on blood pressure, tobacco, cholesterol, low weight, and unsafe sex. In contrast, morbidity was related to underweight, unsafe sex, blood pressure, tobacco and alcohol, then unsafe water. In developed countries, the principal risks associated with morbidity were tobacco, blood pressure, cholesterol, weight, low fruit intake, and physical inactivity—ie, the typical Western constellation. In low-mortality developing countries, underweight, unsafe sex, unsafe water, and indoor fire smoke were the principal risk factors. However, in higher-mortality developing countries, the burden changed to alcohol, blood pressure, tobacco, and underweight. The paper concluded that substantial proportions of global disease burden are attributable to these major risks, to an extent greater than previously estimated. Developing countries suffer most or all of this burden due to many of the leading risk factors. Strategies that target these known risks can provide substantial and underestimated public health gains.

Like all studies of this kind, this one’s quality is dependent on the underlying accuracy of the measurements, which was good for blood pressure, but variable for exercise. As this analysis uses DALY, mental illness due to alcohol counts significantly, but may not feature in certain societies like China or the Muslim world. Lastly, this study is cross-sectional and retrospective and so does not capture the evolution of risk, especially toward a more obese society.

For those in Western societies, the implications of the study are sobering: systolic blood pressure 115 mm Hg, total cholesterol 3.8 mmol/L, body mass index 21 kg/m², 600 g vegetables per day, <85 dB of noise, avoid sedentary jobs, 2.5 hours of exercise, no sex, no alcohol, and no illicit drugs. Given the differences between the factors driving mortality and morbidity, the implication of this study is striking.

Argentina faces a financial crisis after it defaults on a $805 million World Bank loan; former Italian Prime Minister Giulio Andreotti is convicted of complicity in the 1979 contract killing of journalist Mino Pecorelli; and Abdullah Gül is elected the new prime minister of Turkey.

I. Graham, D. Atar, K. Borch-Johnsen, et al; Representatives of Nine Societies and Invited Experts


The Fourth Joint task force recommendations cover 112 pages of text with a no less than 33-page summary. After stating that cardiovascular disease (CVD) is the major cause of premature death in Europe and that it is an important cause of disability and contributes substantially to the escalating costs of health care, the justification for another guideline follows. They start by stating that in the 2003 Guidelines a 10-year risk of CVD death of 5% or more was arbitrarily considered high risk, which implied a 95% chance of not dying from CVD within 10 years, which was less than impressive when counseling patients. In 2007, this becomes increased risk, possibly missing the point of negative predictive values in statistical medicine. In 2007, new sections on gender, heart rate, body mass index/waist circumference, other manifestations of CVD, and renal impairment were added. These guidelines aim to assist physicians and other health professionals in fulfilling their endeavor of achieving effective preventive measures in day-to-day clinical practice. Unfortunately, it is unlikely that the average patient will easily comprehend the guidelines. They advise that patients with multiple risk factors resulting in raised total CVD risk (>5% 10-year risk of CVD death, type 2 diabetes, and type 1 with microalbuminuria and those with markedly increased single risk factors with possible end-organ damage) should be treated, ie, 25% of the population. Risk is to be estimated by means of the Systematic CORonary Risk Evaluation (SCORE) tool, which is stated to be intuitive, multifactorial, flexible, objective, polylingual, and allows age discrimination—but which only defines mortality associated with the principal cardiovascular risk factors, but not the commoner and more relevant factor of morbidity that concerns all health services. Health is defined as having a healthy diet, not smoking, engaging in physical activity, body mass index <25 kg/m², blood pressure <140/90 mm Hg, total cholesterol < 5 mmol/L, low-density lipoprotein (LDL) cholesterol <3 mmol/L with a glucose <6 mmol/L. In high-risk subjects, once atherosclerosis has been dealt with, the next goal is reducing blood pressure to <130/80 mm Hg, total cholesterol to <4.5 mmol/L with an option of <4 mmol/L, LDL-cholesterol to <2.5 mmol/L with an option of <2 mmol/L, blood glucose to <6 mmol/L; and HbA1c to <6.5%—all if feasible. The Consensus finishes by stating that the European Health Charter advocates the development, promotion, and implementation of comprehensive health strategies, measures, and policies at European, national, regional, and local level, that promote cardiovascular health and prevent cardiovascular disease—quite an agenda!

2007

Viktor Zubkov is confirmed as the new Prime Minister of Russia; thousands are evacuated from San Bernardino and San Diego Counties in California due to raging wildfires; and melting sea ice in the Arctic Ocean opens up the Northwest Passage between Europe, Asia, and North America.
Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study

S. Yusuf, S. Hawken, S. Ounpuu, T. Dans, A. Avezum, F. Lanas, M. McQueen, A. Budaj, P. Pais, J. Varigos, L. Lisheng; INTERHEART Study Investigator

Lancet. 2004;364:937-952

In modern medicine bigger is always better. Case-control studies have always been easy to perform and provide valuable preliminary data that are later substantiated and improved through prospective cohort studies. One of the questions that had not been systematically addressed prior to InterHEART was that though more than 80% of the global burden of cardiovascular disease now occurs in low-income and middle-income countries, knowledge of the importance of risk factor profiles has largely been derived from developed countries. Therefore, whether classic cardiovascular risk factors have similar effects on the risk of coronary heart disease worldwide was unknown. InterHEART was a standardized case-control study of acute myocardial infarction in 52 countries, on all permanently inhabited continents. It recruited 15 152 cases and 14 820 controls and investigated the relationship of smoking, history of hypertension or diabetes, waist/hip ratio, dietary patterns, physical activity, consumption of alcohol, apolipoproteins (Apo), and psychosocial factors to myocardial infarction, but not, unfortunately, stroke or peripheral arterial disease. It calculated odds ratios with confidence intervals for the association of risk factors to myocardial infarction and also the population-attributable risks (PAR) that could be ascribed to each risk factor. Ranked in order raised ApoB/ApoA1 ratio (3.25 for extreme quintiles, PAR 49.2% for top four quintiles vs lowest quintile), smoking (odds ratio 2.87 for current vs never, PAR 35.7% for current and former vs never), psychosocial factors (2.67, PAR 32.5%), abdominal obesity (1.12 for extreme tertiles and 1.62 for middle vs lowest tertile, PAR 20.1% for top two tertiles vs lowest tertile), history of hypertension (1.91, PAR 17.9%), low daily consumption of fruits and vegetables (1.42, PAR 13.7% for lack of daily consumption), lack of regular physical activity (1.16, PAR 12.2%), diabetes (2.37, PAR 9.9%), and absence of alcohol consumption (1.10, PAR 6.7%), were all related to acute myocardial infarction ($P<0.0001$ for all risk factors and $P<0.03$ for alcohol). These associations were noted in men and women, old and young, and in all regions of the world. It concluded that abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruits, vegetables, and alcohol, and regular physical activity accounted for the vast majority of the risk of myocardial infarction worldwide in both sexes everywhere. The study suggests that approaches to prevention could be based on common principles worldwide and would likely prevent most premature cases of myocardial infarction. All bound within the ring of atherosclerosis, the nine Nazgul of risk factors accounted for 90% of the PAR in men and 94% in women. However, the unequal treatment of the various risk factors when analyzed dichotomously, by tertile or quintile, suggests that older data relying on dichotomous median analysis may still be correct in giving primary roles to smoking, hypertension, and diabetes. The prominence given to abdominal obesity for instance is difficult to reproduce in other studies and certainly did not show up clearly in prospective cohort studies such as Framingham even using body mass index as surrogate. InterHEART reinforces the idea that humans are all basically the same and all societies would benefit from the same interventions dedicated to life, liberty, and the pursuit of happiness.
Diabetes mellitus increases the risk of cardiovascular disease (CVD) and all-cause mortality. The relationship between milder elevations of blood glucose and mortality is less clear as it has not been so intensively studied due to the dichotomy bias often shown in epidemiological studies. This effect also applies to cigarettes. The Australian Diabetes, Obesity, and Lifestyle Study (AusDiab) study investigated whether impaired fasting glucose and impaired glucose tolerance, as well as diabetes mellitus, increase the risk of all-cause and CVD mortality. Between 1999 and 2000, glucose tolerance status was determined in 10,428 participants by the World Health Organization (WHO) criteria of 1999. Ninety-two percent of patients had type 2 diabetes. After a median follow-up of 5.2 years, 298 deaths had occurred (88 CVD deaths) at a rate of 5.5/1000 patient-years. Compared with those with normal glucose tolerance, the adjusted all-cause mortality odds ratios (ORs) and 95% confidence intervals (CIs) for previously known diabetes mellitus and newly diagnosed diabetes mellitus were 2.3 (1.6 to 3.2) and 1.3 (0.9 to 2.0), respectively. The risk of death was also increased in those with impaired fasting glucose (1.6 [1.0 to 2.4]) and impaired glucose tolerance (1.5 [1.1 to 2.0]). Sixty-five percent of all those who died of CVD had known diabetes mellitus, newly diagnosed diabetes mellitus, impaired fasting glucose, or impaired glucose tolerance at baseline. Known diabetes mellitus (2.6 [1.4 to 4.7]) and impaired fasting glucose (2.5 [1.2 to 5.1]) were independent predictors for CVD mortality after adjustment for age, sex, and other traditional CVD risk factors, but impaired glucose tolerance was not (1.2 [0.7 to 2.2]). The 172 non-CVD deaths comprised 59% neoplasia with 2.3 (1.5-3.6) for known diabetes, 1.0 (0.5-1.9) for new diabetes, 1.6 (1.1-2.3) for impaired glucose tolerance, and 1.3 (0.7-2.3) for impaired fasting glucose, showing the wider relationship of diabetes and morbidity. The AusDiab study confirmed the strong association between abnormal glucose metabolism and mortality, and it suggested that glucose contributes to a large proportion of total mortality in the general population. In contrast with the DECODE/DECODA studies (Diabetes Epidemiology Collaborative analysis of Diagnostic criteria in Europe/Asia) and other studies it did not show a relationship of impaired glucose tolerance with CVD, but the number of events was small in this group and the study may be subject to power limitations for subgroup analyses, especially as the authors admit the follow-up period was comparatively short. Other studies have taken a different approach—in EPIC-Norfolk (East-Anglian component of the European Prospective Investigation into Cancer), HbA1c found an exponential relationship to CD risk. Similarly, in this study, it might have been possible to integrate areas under the glucose tolerance curve if a more invasive sampling protocol had been used rather than a basic glucose tolerance test—in which case again it is likely that a log-linear relationship would have been found and the nonsense of dichotomizing glucose would have to be abandoned in cardiovascular risk calculation. The results of AusDiab combined with other studies suggest CVD and neoplasia prevention strategies based on intervention on risk factors for hyperglycemia and its progression may be warranted in people with all defined categories of abnormal glucose metabolism.

Risk of cardiovascular and all-cause mortality in individuals with diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance: the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab)


Circulation. 2007;116:151-157
Sick individuals and sick populations

G. Rose


Although, at first sight the republication in the same journal of an article first published 16 years ago might be labeled as autoplagiarism, this might also be seen as proof that classics never age. The article starts with the question: “why did this patient get this disease at this time?” It goes on to discuss the flawed concept of normal population ranges and of relative risk of disease. It then introduces the still heretical concept—at least to some of the tabloid newspapers—that association is not causation, by showing that water hardness is negatively associated with cardiovascular disease in Scotland (r=–0.67). It notes incidentally that universally present risk factors are the hardest to identify as they have no influence on the distribution of disease, which is the basis of all epidemiological research—the Rumsfeldian “unknown unknown”. The paper then discusses the differences between the “causes of cases” and “causes of incidence.” To highlight how normal distributions can be shifted by environmental factors—eg, blood pressure in rural Kenya and UK civil servants—it not only shows that genes often matter little to overall human health, but a lot to individuals—as any one who has inherited male pattern baldness knows all too well. By demonstrating this again for cholesterol and showing how individuals vary with respect to population means, it shows that the determinants of incidence are not the same as the causes of cases, so giving the lie to protocol-based medicine everywhere.

The paper then reviews approaches to prevention. The “high-risk” strategy is appropriate for individuals, motivating for both patient and doctor, cost-effective, individually beneficial, and in health economic terms totally useless. However high-risk strategies are also costly in terms of screening, essentially palliative and temporary, limited to individuals, and often behaviorally inappropriate. It notes that “a large number of people at a small risk give rise to more cases of disease than a small number who are at high risk,” using Down’s syndrome as an example where screening under age 30 is not performed, but where most cases occur. In contrast, population-based strategies are radical, have large potential health economic benefits, and are behaviorally appropriate. Thus, reducing fat and carbohydrate intakes, smoking cessation, and all the other Government-sponsored initiatives will do the country good however dull and worthy they seem. Yet these initiatives are of small benefit to individuals (the prevention paradox), poor motivators of subjects and physicians, and give rise to an obsession with low-incidence complications, which seem to highlight adverse benefit-risk ratios that allow the scientific ignorance of the media to have a field day. There are not many articles that ought to be compulsory reading for all doctors in training—or even, if nominally trained, as continuing professional development—this is one.
Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project


*Eur Heart J.* 2003;24:987-1003

One of the things about The European–American cultural wars is the competition it engenders. Thus to counter Boeing set up Airbus. The Systematic Coronary Risk Evaluation (SCORE) project is the European version of this vision applied to the field of cardiovascular risk calculation. It was initiated to develop a risk scoring system for use in the clinical management of cardiovascular risk in European clinical practice as all previous risk calculation systems were based on the Caucasian (European–derived) population of the Massachusetts town of Framingham, which, though dated, seems to still work with a little realignment. The project assembled a pool of datasets from 12 European cohort studies of various vintages and regionalities, mainly, but not exclusively, carried out in general population settings. These studies totaled 205 178 individuals (88 080 women and 117 098 men) and represented 2.7 million person-years of follow-up. During the period of observation, there were 7934 cardiovascular deaths, of which 5652 were deaths from coronary heart disease. Ten-year risk of fatal cardiovascular disease was calculated using a Weibull model in which age was used as a measure of exposure time to risk rather than as a risk factor. Separate estimation equations were calculated for coronary heart disease and for noncoronary cardiovascular disease. Unfortunately, due to limitations of data quality and inconsistent coding, only fatal events could be determined with any accuracy though everyone knows death certificate causes of death leave a lot to be desired and show retrospection bias. Thus the advantage of Framingham in giving clinically useful morbidity data was lost in the endeavor of creating a comprehensive tool for all of Europe. Furthermore, due to marked and inexplicable discrepancies within the continent, separate risk models had to be calculated for high-risk and low-risk regions of Europe. In addition, again due to inadequate data collection, two parallel estimation models were developed, one based on total cholesterol and the other on total cholesterol/high-density lipoprotein (HDL) cholesterol ratio, so that the final tool would agree with the bulk of previous scientific and epidemiological data that HDL cholesterol was an important protective factor against cardiovascular disease. The risk estimations were displayed graphically in simple risk charts rather than using a points scoring system as advocated in the USA. A validation study was conducted of the predictive value of the risk charts by applying them to persons aged 45-64, generating areas under ROC curves ranging from 0.71 to 0.84, similar to those found in the Framingham risk calculation variants. The final conclusion claims the SCORE risk estimation system offers direct estimation of total fatal cardiovascular risk in a format suited to the constraints of clinical practice.

The sluice gates on the Three Gorges Dam in China are closed, beginning the filling of the reservoir of the world’s largest hydroelectric project; archeologists announce that the mummy of Queen Nefertiti may have been found in the Valley of the Kings; and three 160 000-year-old human skulls are unearthed in Ethiopia, lending support to the “out of Africa” single origin theory of human evolution.
Clinical reality of coronary prevention guidelines: a comparison of EUROASPIRE I and II in nine countries. EUROASPIRE I and II Group. European Action on Secondary Prevention by Intervention to Reduce Events

EUROASPIRE I and II Group; European Action on Secondary Prevention by Intervention to Reduce Events

Lancet. 2001;357:995-1001

I

t is all very well having guidelines, but are they being implemented? Patients with coronary heart disease (CHD) are supposedly the top priority for preventive cardiology. The first EUROASPIRE survey (EUROpean Action on Secondary Prevention by Intervention to Reduce Events) among patients with established CHD in nine countries in 1995-96 showed substantial potential for risk reduction as most therapies were greatly underused and many risk factors undertreated.

In the best tradition of medical audit, a second survey (EUROASPIRE II) was carried out in 1999-2000 in the same countries to see whether preventive cardiology had improved since the first.

EUROASPIRE II compared the proportion of patients in both studies who achieved the lifestyle, risk factor, and therapeutic goals recommended by the Joint European Societies II report on coronary prevention. The surveys were undertaken in the same selected geographical areas and supposedly representative hospitals in the Czech Republic, Finland, France, Germany, Hungary, Italy, the Netherlands, Slovenia, and Spain. Consecutive patients (men and women ≤70 years of age) were identified after coronary artery bypass graft or percutaneous transluminal coronary angioplasty, or a hospital admission with acute myocardial infarction or ischemia, and were interviewed at least 6 months later. The first audit surveyed 3569 patients and, in the second, 3379 patients were interviewed. The prevalence of smoking remained almost unchanged at 19.4% vs 20.8%. The prevalence of obesity (body mass index ≥30 kg/m²) had increased substantially from 25.3% to 32.8%. The proportion with high blood pressure (≥140/90 mm Hg) was virtually the same (55.4% vs 53.9%), whereas the prevalence of high total cholesterol concentrations (≥5.0 mmol/L) decreased substantially from 86.2% to 58.8%. Aspirin or other antiplatelet therapy was as widely used in the second survey as in the first (83.9% overall), and reported use of β-blockers (53.7% → 66.4%), angiotensin-converting enzyme (ACE) inhibitors (29.5% → 42.7%), and hypoglycemic therapies (10.4% → 15.0%), and especially lipid-lowering drugs (32.0 → 62.9%), increased. In parallel, there were reductions in calcium channel blockers (36.3% → 25.9%).

The least surprising finding was the lack of change. This is a recurring feature of audit. Adverse lifestyle habits continued much as before with the same attachment to old addictions and new trends among European CHD patients to develop new addictions to sugar and saturated fat aided, no doubt, by fast-food outlets. Medical practitioners, all of whom had successfully seized upon the use of aspirin seemed reluctant to adopt the increasing portfolio of antihypertensive agents, either because of doubts bout their efficacy or their increasingly complex vocabulary. However, in the case of statins there was rapid consensus. They did not look beyond the first inadequate licensed doses as most CHD patients were still not achieving the undemanding cholesterol goal <5 mmol/L. The auditors conclude there is a collective failure of medical practice in Europe to achieve the substantial potential among patients with CHD to reduce the risk of recurrent disease and death. Among all the complexity of risk factors and medications lies a simple and exceptionally effective formula: aspirin + β-blocker + ACE inhibitor + statin.

2001

Julia Roberts is awarded the Oscar for best actress for her performance in Erin Brockovich; the Universal Studios Japan theme park opens in Osaka; and Robert Ludlum, author of 29 spy novels, including The Bourne Identity, The Bourne Supremacy, and The Bourne Ultimatum, dies
Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age


Circulation. 2006;113:791-798

This paper begins with the depressing message that despite 40 years of intervention cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide. Lifetime risk estimates have been used to change behavior in breast cancer (1 in 8 women at age 40) by encouraging participation in screening programs, yet the lifetime risk approach to atherosclerotic CVD has not previously been attempted, and the effect of risk factor burden on lifetime risk was unknown. This analysis included all Framingham Heart Study participants who were free of CVD (myocardial infarction, coronary insufficiency, angina, stroke, claudication) at 50 years of age. Lifetime risks up to age 95 were estimated for men and women, with non-cardiovascular death as the alternate end point.

The study followed up 3564 men and 4362 women for 111 777 person-years, during which time 1757 had CVD events and 1641 died of other causes. All data were used from examination periods as close to age 50 as possible except for high-density lipoprotein (HDL) cholesterol, which was only measured from 1971, and here data were used from age 40. At 50 years of age, lifetime risks were 52 (95% confidence interval [CI], 49% to 54%) for men and 39 (37%-41%) for women, with median survivals of 30 and 36 years, respectively. For hard end points, the risks were 41 (39%-44%) and 29 (27%-31%) for each sex respectively. This compares with lifetime risk for breast cancer of 12.5%, prostate cancer 19%, lung cancer 8% in men and 6% in women, and colorectal cancer of 6%, and yet cancer is commonly seen as the greater threat to life. With more adverse levels of single risk factors, lifetime risks increased and median survivals decreased. Presence of ≥2 major risk factors compared with those with optimal levels massively increased lifetime risks (13-fold in men [69% vs 5%], and 6-fold in women [50% vs 8%] and decreased survival (28 vs >39 years in men, 31 vs >39 years in women). Lifetime risks were greatest in patients with diabetes (67% men, 57% women) only analyzed up to age 75 due to reduced survival. Despite its trendiness, only small effects were seen with obesity alone. Risk was similar for smokers and non-smokers, but smokers had earlier events doubling their rate of disease by age 70 and had a 5-year shorter survival, but also confounded analysis due to other smoking-related causes of death. Absence of established risk factors at age 50 years was associated with very low lifetime risk for CVD and markedly increased survival. Therefore, optimizing risk factor profiles in middle age would seem to offer the potential to deliver exceptional health benefits 25 years later. However, this runs counter to the trend in society as the number of risk factor-free individuals in the USA declined from 42% to 36% from 1991-2001 mostly due to increased obesity and its metabolic consequences.

The results of the Framingham lifetime analysis should promote efforts aimed at preventing development of risk factors in young individuals. Given the high lifetime risks and lower survival in those with intermediate or high risk factor burden at 50 years of age, these data may be useful in communicating risks and supporting intensive preventive therapy based on the use of global risk estimates rather than unifactorial approaches and the great significance of even minor lifestyle changes made early enough.

Chad and Sudan sign the Tripoli Agreement, ending the Chadian-Sudanese conflict; Social networking site Facebook is opened to the public; and An ancient Egyptian sun temple is discovered beneath a flea market in the Ein Shams suburb of Cairo
The fashion these days is to integrate studies and meta-analyze them by pooling the results and not necessarily the original data. Among others, this approach is cheap and does not require massive program grants for original research. Yet despite its perceived simplicity, to get round the limitations of the data sets and publication bias involves complex statistical techniques.

This study assessed the age-specific relevance of blood pressure to cause-specific mortality using a collaborative meta-analysis of individual participant data from the separate prospective studies. The source information was obtained on each of one million adults with no previous vascular disease recorded at baseline in 61 prospective observational studies of blood pressure and mortality all with >5000 years of person-years follow-up from the age range 40 to 89 years. To avoid reverse causality, patients with established atherosclerotic disease were excluded. Meta-analysis was performed using “time-dependent” correction for regression dilution, ie, variation at baseline that would tend to minimize observed effects to derive related mortality during each decade of age at death to the estimated usual blood pressure at the start of that decade. Hazard ratios were derived from 5 age ranges and 10 categories of blood pressure after adjustment for sex, study and correction within each 5-year period within the study.

During 12.7 million person-years at risk, there were about 56,000 vascular deaths (12,000 stroke, 34,000 ischemic heart disease [IHD], 10,000 other vascular) and 66,000 other deaths at ages 40-89 years. Within each decade of age at death, the proportional difference in the risk of vascular death associated with a given absolute difference in usual blood pressure is about the same down to at least 115 mm Hg usual systolic blood pressure (SBP) and 75 mm Hg usual diastolic blood pressure (DBP), below which there were very little data. At ages 40 to 69 years, each difference of 20 mm Hg usual SBP (or, approximately equivalently, 10 mm Hg usual DBP) is associated with a more than twofold difference in the stroke death rate, and with twofold differences in the death rates from IHD and from other vascular causes as plotted as a series of log-linear graphs though maybe a curvilinear relationship would also fit the datasets. All of these proportional differences in vascular mortality are about half as extreme at ages 80 to 89 years as at ages 40 to 49 years, but the annual absolute differences in risk are greater in old age. The age-specific associations are similar for men and women, and for cerebral hemorrhage and cerebral ischemia. For predicting vascular mortality from a single blood pressure measurement, the average of SBP and DBP was considered slightly more informative than either alone, and pulse pressure was much less informative.

The meta-analysis concluded that throughout middle and old age, usual blood pressure is strongly and directly related to vascular (and overall) mortality, without any evidence of a threshold down to at least 115/75 mm Hg. A 10/5 mm Hg reduction in long-term blood pressure would result in a 40% reduction in stroke or 30% in ischemic heart disease, but even a 2/1 mm Hg reduction would reduce stroke mortality by 10% and ischemic heart disease by 7%, so throw away the salt now or should we meta-analyze that as well first?

Researchers at the Information Technology Center at the University of Tokyo calculate π to 1.24 trillion digits, setting a new world record; Congo’s government, rebels, and opposition parties sign a peace accord to end 4 years of civil war; and the Supreme Court of Canada rules that the Harvard mouse is not patentable, as in its view a higher life form does not fall within the definition of an invention.
An updated coronary risk profile. A statement for health professionals

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

Circulation. 1991;83:356-362

No one ever reads obscure journals, especially in the days of impact factors, citation indices, h-scores, and other publication metrics. This paper updates the famous cardiovascular disease risk profiles paper published in the *American Heart Journal* in 1991 (12: 293-8)—or 1990 if you do not read beyond the typographical error in the abstract, which is still used as the basis of all Framingham study-derived risk calculators. It is based on the Framingham cohort of 1968-1975 aged >50 years combined 12 years follow-up of the Framingham Offspring cohort aged 30-74 years. It gathers the classic risk factors of age, sex, dichotomous smoking status, total and high-density lipoprotein (HDL) cholesterol, blood pressure, and dichotomizes diabetes and ECG—left ventricular hypertrophy. It hints at incomplete data coverage for both diabetes and left ventricular hypertrophy, but 87% of HDL cholesterol was available. Diabetes was diagnosed on the basis of insulin/oral hypoglycemic therapy or single fasting glucose >140 mg/dL (7.8 mmol/L). The final study included 5573 participants (2590 men and 2983 women), and follow-up was for 12 years. The combined end point was coronary heart disease including all versions of angina (stable and unstable), myocardial infarction, and sudden death.

The paper then gives the detailed method necessary to calculate cardiovascular risk including coefficients with a worked example. It is thus the antithesis of black box models such as either the neural net calculation of the Munster Heart Study or the unpublished equations underlying the modern QRISK score currently much in favor in the UK. The quirks required to improve the data fit are interesting: natural log transformation of all continuous data; use of quadratic age term for women (possibly to get round the risk increase around menopause), but which serves to increase early as opposed to late risk; the inclusion of the ratio of the combined total-HDL-cholesterol ratio removes age interaction terms associated with each individually in previous models and finally that now men and women have similar biological behavior in this model especially as regards smoking with diabetes. In addition, left ventricular hypertrophy, which is usually deleted from modern risk estimation, turns out to be a strong risk factor, but with a large confidence interval due to a low incidence at baseline. Though mentioned as significant omissions, both family history of early coronary heart disease and obesity are discussed, but not included, in the risk calculation system as no method was devised to allow quantification of intensity of family history and obesity turned out only to be a cardiovascular risk factor over longer periods than 10 years. Many guideline committees have proceeded to include these in the risk calculation by adding arbitrary fiddle factors that are usually very poorly justified.

For those not able to calculate risks using a computer or spreadsheet, a superficially simpler points scoring system is included to derive 5- and 10-year prospective risks of events. This has been the US system ever since though the Europeans and British have tended to prefer glossy graphs as they are easier to read, but with the disadvantage of requiring multiple versions—at least until recently when the diabetes-related graphs and charts were abolished on the basis of cardiovascular risk equivalence.

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1991

Soviet forces move in Vilnius in an attempt to prevent Lithuanian independence; US serial killer Aileen Wuornos confesses to the murders of six men; and Operation Desert Storm begins with air strikes against Iraq.
Risk Factors & Cardiovascular Disease

Bibliography of One Hundred Key Papers

selected by Guy G. De Backer, MD, PhD
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University Hospital - Ghent - BELGIUM - e-mail: guy.debacker@ugent.be


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