Risk Factors & Cardiovascular Disease

Expert Answers to Three Key Questions

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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.

Keywords: socioeconomic factor; socioeconomic condition; social gradient; coronary heart disease; cardiovascular disease

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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.[1-3] 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.[11] 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,[1] 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.[12] 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.[13] 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[2] 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.

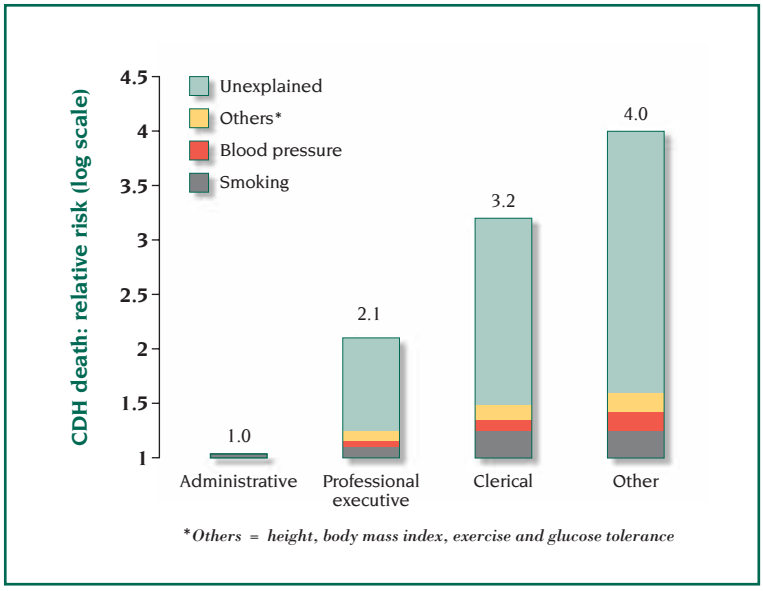

Figure 1. *Relative risk of death from coronary heart disease (CHD) among civil servants according to employment grade (proportions of differences explained by risk factors).*

Modified from reference 11: *van Rossum CT, Shipley MJ, van de Mheen H, Grobbee DE, Marmot MG. Employment grade differences in cause-specific mortality. A 25-year follow up of civil servants from the first Whitehall study.* J Epidemiol Community Health. *2000;54: 178-184. Copyright © BMJ Publishing Group Ltd.*

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.[14] 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.[15] 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.[16] When an association between a given exposure (eg, hypertension) and an outcome (CVD) is modified by a third variable (eg, 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 emotional support was associated with a composite measure of cardiovascular risk for low-income patients, but not for patients with higher incomes.[17] 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.[18] 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.

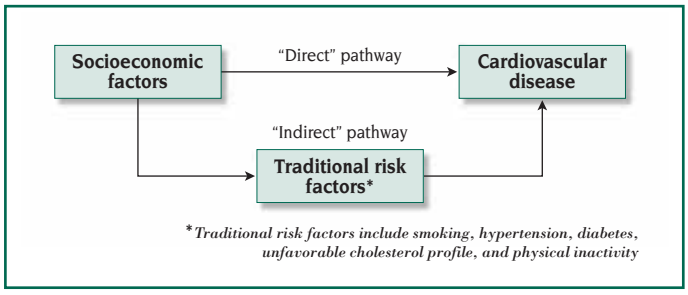

Figure 2. *Conceptual framework explaining the role of socioeconomic factors in the etiology of cardiovascular disease.*

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 affected 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.[19,20] 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.[21]

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.[22] 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.[23] One of the effects of globalization is what has been called the "coca-colonization" of living habits including increased consumption of fats and sweeteners.[24] 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[25] with the United States leading the change,[26] and exporting conditions such as obesity to less developed societies.[27]

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.[28] Furthermore, low social cohesion or social capital have been found to be predictors of coronary heart disease.[29] 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.[30] 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.[31]

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.[32] 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.

Socioeconomic factors and cardiovascular disease

The epidemiological transition of CVD from being a disease of the wealthy to one of the poor has been analyzed in the changes in the socioeconomic distribution of heart disease in developing and developed societies. In a research article, Chang et al[33] reported on the unadjusted odds ratios for stroke in different regions of the world and their association with secondary and low educational strata using high education as the reference group. The authors found an inverse association with education in Asia, Latin America, and Eastern Europe, with the effect being most pronounced in Eastern Europe and least apparent in Latin America. On the contrary, the association appeared to be positive in Africa.

In developing societies, the epidemic struck the more affluent sections of society first, but as the epidemic matured, the socioeconomic gradient reversed, with socioeconomically disadvantaged groups becoming increasingly vulnerable.[10] Higher risk for coronary heart diseases among advantaged groups have not been reported only in Africa, but also in Hong Kong,[34] Puerto Rico,[35] and Pakistan.[36] In the most affluent nations and former socialist countries, there has been a reversal in the association between coronary heart disease mortality and socioeconom-

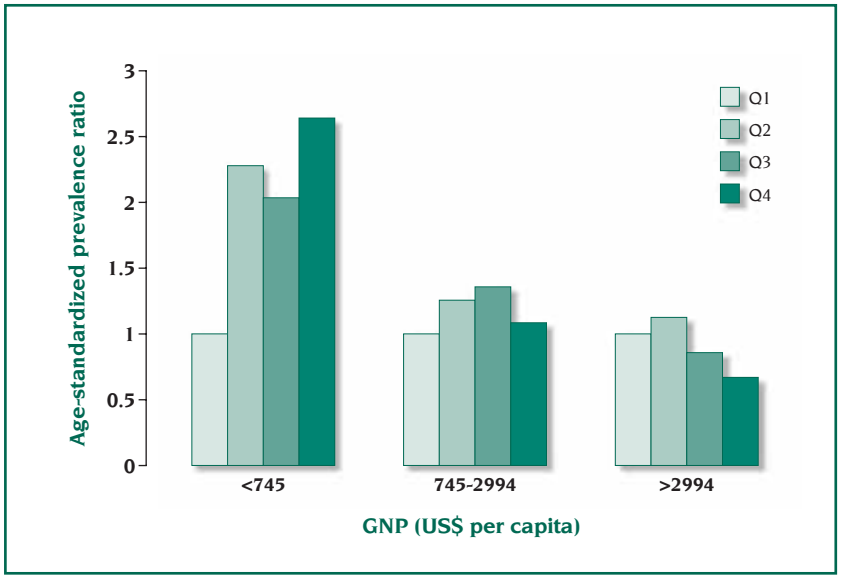

Figure 3. *Age-standardised prevalence ratio for women's obesity by quartiles (Q) of years of education in low, lower-middle, and upper-middle income economies (1992-2000).*

Modified from reference 39: *Monteiro CA, Conde WL, Lu B, Popkin BM. Obesity and inequities in health in the developing world.* Int J Obes. *2004:28:1181-1186. Copyright © Nature Publishing Group.*

ic position observed during the 20th century, with a widening mortality gap over time. The "switchover" has been documented in England and Wales[37] 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.[38]

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 developed and developing 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.

Figure 3 shows the age-standardized prevalence ratio for women's obesity by quartiles of years of education in low, lower-middle, and upper-middle income economies in 1992 to 2000.[39] Results indicate that belonging to the lower socioeconomic group is a protective factor against obesity in low-income economies (GNP below US$745 per capita), but is a risk factor for the disease in upper-middle-income economies (GNP ≥US$2995 per capita).

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[40] and area-level indicators.[41,42] 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.[43]

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[44,45] in southern European countries that are also characterized by lower rates of coronary heart disease compared to northern Europe, the US, and the UK.[46] 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[47] 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.[48] Changes in the distributions of CVD and traditional risk factors for CVD such as smoking, hypertension, diabetes, unfavorable cholesterol profile, and physical inactivity are inextricably 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.[47] 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,[48] 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 incompatible 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.

Keywords: heart rate; risk factor; cardiovascular event; atherosclerosis; arrhythmia; myocardial ischemia; epidemiology; coronary artery disease; heart failure; ivabradine

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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 arrhythmias.[13,14] 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

SELECTED ABBREVIATIONS AND ACRONYMS

AMI	acute myocardial infarction
BCAPS	Beta-blocker Cholesterol-lowering Asymptomatic Plaque Study
BEAUTIFUL	MorBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary artery disease and left ventricULar dysfunction
CAD	coronary artery disease
CIBIS	Cardiac Insufficiency BIsoprolol Study
COMET	Carvedilol Or Metoprolol Evaluation Trial
HR	heart rate
hr	hazard ratio
INITIATIVE	INternatIonal TrIal of the AnTianginal effects of IVabradinE compared to atenolol
PPS	Paris Prospective study
AMI	acute myocardial infarction
MERIT-HF	MEtoprolol controlled release Randomized Intervention Trial in Heart Failure
SHIFT	Systolic Heart failure treatment with I_f inhibitor ivabradinE Trial

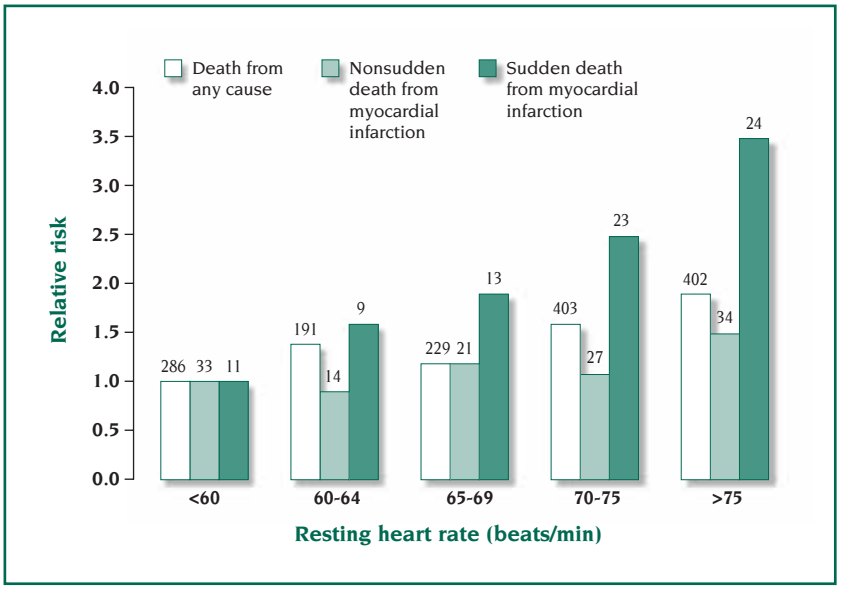

Figure 1. *Relative risks of death from any cause and of nonsudden and sudden death from myocardial infarction, according to the quintile of resting heart rate.*

Adapted from reference 2: *Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetiere P. Heart-rate profile during exercise as a predictor of sudden death.* N Engl J Med *2005; 352:1951-1958. Copyright © 2005, Massachusetts Medical Society.*

ages.[1] 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.[2] In those two studies, the relationship was much steeper for sudden cardiac death.[1,2] 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)*.[2] HR has also been shown to predict mortality in hypertensive populations[3,4] and in elderly patients.[4]

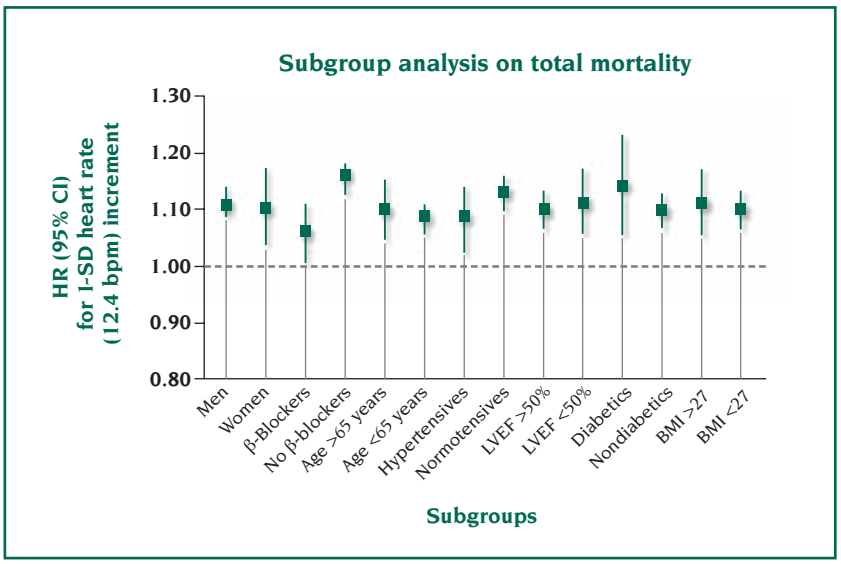

Figure 2. *Subgroup analyses on total mortality for a 1-SD increment in heart rate (12.4 bpm) in patients with suspected or proven CAD*

Abbreviations: *BMI, body mass index; LVEF, left ventricular ejection fraction.*
Adapted from reference 5: *Diaz A, Bourassa MG, Guertin MC, Tardif JC. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease.* Eur Heart J. *2005;26: 967-974. Copyright © 2005, Oxford University Press.*

In CHD patients, HR was a significant predictor of mortality at 30 days and 10 months after an acute coronary syndrome.[15] 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.[5] 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 (<62 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,[5] in contrast to some studies in the

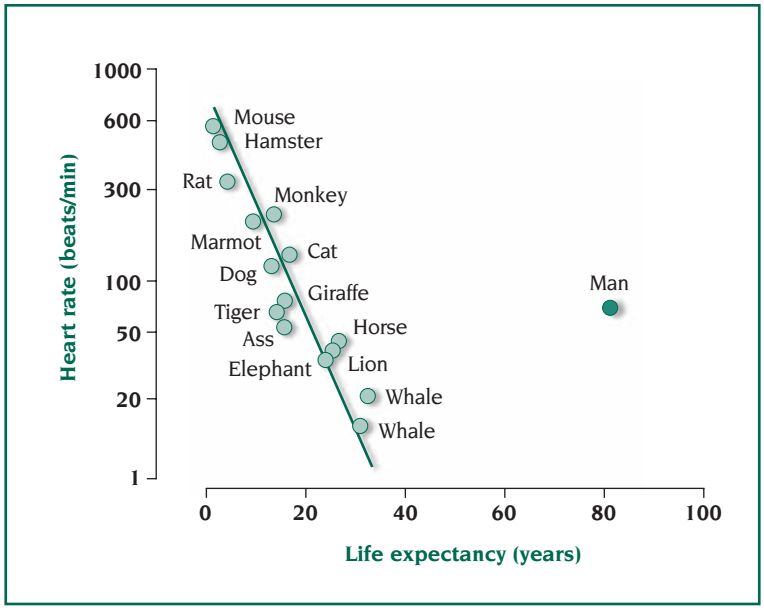

Figure 3. *Semilogarithmic relationship between resting heart rate and life expectancy in mammals.*

Adapted from reference 18: *Levine HJ. Rest heart rate and life expectancy.* J Am Coll Cardiol. *1997; 30:1104-1106. Copyright © 1997, Elsevier Biomedical.*

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 7.3×10^8 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

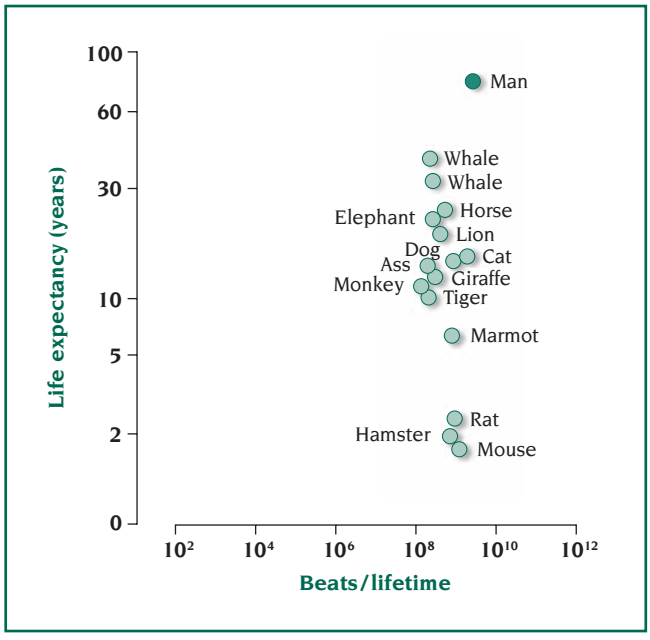

Figure 4. *Rela-tionship between life expectancy and total heart beats/lifetime.*

Adapted from reference 18: *Levine HJ. Rest heart rate and life expectancy.* J Am Coll Cardiol. *1997; 30:1104-1106. Copyright © 1997, Elsevier Biomedical.*

- Increased severity and progression of coronary atherosclerosis
- Lesser development of collaterals
- Increased risk of coronary plaque disruption
- Increased arterial rigidity
- Greater myocardial oxygen consumption (MVO_2)
- Decreased myocardial perfusion (shortening in the duration of diastole)
- Increased susceptibility to arrhythmias
- Marker of sympathetic overactivity
- Increased risk of left ventricular dysfunction

Table I. *Pathophysiological mechanisms relating an increased heart rate and cardiovascular disease.*

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.[7] 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.[8] A high HR has also been associated with an increased risk of coronary plaque disruption.[9] 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.[10] 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.[11] 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 (MVO_2) 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%.[12]

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.[1,2] A high HR is a major determinant of the occurrence of ventricular tachycardia or fibrillation during experimentally induced acute ischemia in dogs.[13] Decreased HR variability is also associated with an increased risk of malignant arrhythmias after an acute myocardial infarction (AMI).[14] 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.[20]

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.[21] 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.[22]

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

Kjekshus 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 β-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 *(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[25] and its benefits explain the wide use of β-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. β-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]

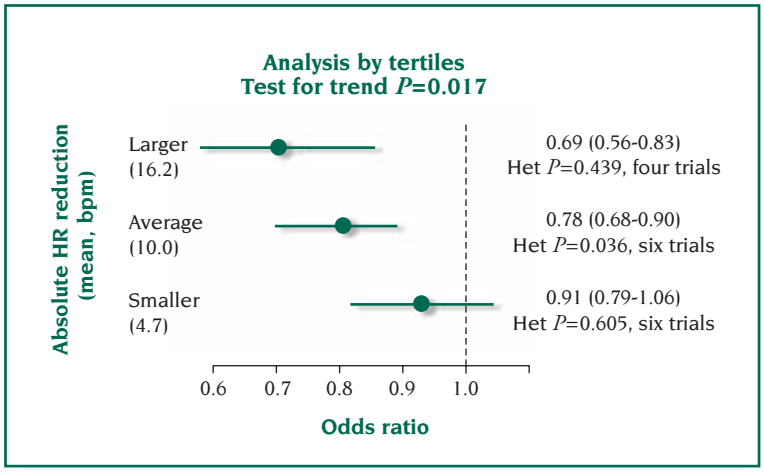

Figure 5. *Relationship between resting heart rate (HR) reduction (by tertiles) and all-cause mortality in post-myocardial infarction clinical trials. Odds ratios represented are comparing odds between the active treatment and placebo groups.*

Adapted from reference 24: *Cucherat M. Quantitative relationship between resting heart rate reduction and magnitude of clinical benefits in post-myocardial infarction: a meta-regression of randomized clinical trials.* Eur Heart J. *2007, 28, 3012–3019. Copyright © 2007, Oxford University Press.*

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 Na^+-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] Ivabradine 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.

Ivabradine and heart rate reduction

In a randomized, double-blinded, multicenter, multinational trial involving 360 patients randomized to placebo or to one of three dosages of active therapy (2.5, 5, or 10 mg twice daily), ivabradine consistently reduced HR at rest and during exercise.[34] The magnitude of HR reduction was slightly smaller than that obtained with therapeutic doses of β-blockers and greater than that with calcium channel antagonists like verapamil and diltiazem. HR reduction with ivabradine was dose-related and was observed across all dosages. Despite substantial HR lowering, ivabradine caused little change in blood pressure compared with placebo.

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.[34] 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)*.[35] 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 I_f 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.[36] 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.[37,38] 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.[39]

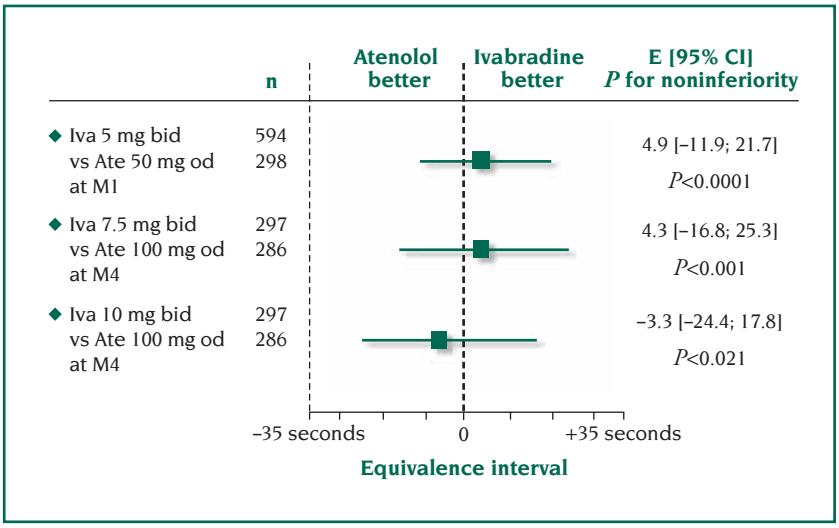

Figure 6. *Comparison of the effects of ivabradine and atenolol on time to 1-mm ST- segment depression at trough of drug activity.*

Adapted from reference 35: *Tardif JC, Ford I, Tendera M, et al; INITIATIVE Investigators. Efficacy of ivabradine, a new selective I_f inhibitor, compared with atenolol in patients with chronic stable angina.* Eur Heart J. *2005; 26: 2529-2536. Copyright © 2005, Oxford University Press.*

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 gradual in many epidemiological studies including those with very long follow-ups (more than 20 years). It is observed for all cardiovascular deaths, but stronger for sudden than nonsudden cardiovascular deaths. (ii) It has been reported in populations both without and with preexisting cardiovascular disease, and the association is stronger in men than in women in some studies. (iii) The relationship is biologically plausible and coherent as increasing HR is associated with many pathological processes in atherosclerosis and in cardiac susceptibility to arrhythmias. (iv) "Experimental" evidence includes animal and human studies that indicate that HR reduction (by sinus node ablation in animals or pharmacological treatment in animals and patients) protects against atherosclerosis progression, malignant arrhythmias, and heart failure mortality.

Is HR an independent risk factor for cardiovascular disease? Obviously HR increases with poor fitness and

with cardiac dysfunction, two conditions associated with an altered prognosis. The predictive value of HR, however, persists even after adjustment for physical activity,[3] exercise capacity,[2] cardiac function,[5] 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 pathophysiologic 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 with important prognostic implications to that of a risk factor will require formal demonstration that pure HR reduction will decrease cardiovascular event rates in a prospectively conducted clinical trial. This hypothesis is currently being tested with the I_f current inhibitor ivabradine, a pure HR-reducing agent, in two trials: BEAUTIFUL (MorBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary artery disease and left ventricULar dysfunction)[45] and SHIFT (Systolic Heart failure treatment with I_f inhibitor ivabradine Trial).[46]

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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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Cardiovascular disease (CVD) has traditionally been considered as a "man's disease," but this perception is changing as it is 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.[1] 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.[1] 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.[2] 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

ACE	angiotensin-converting enzyme
ARB	angiotensin receptor blocker
CAD	coronary artery disease
CHD	coronary heart disease
CVD	cardiovascular disease
DM	diabetes mellitus
HRT	hormone replacement therapy
IHD	ischemic heart disease
SCORE	Systematic COronary Risk Evaluation

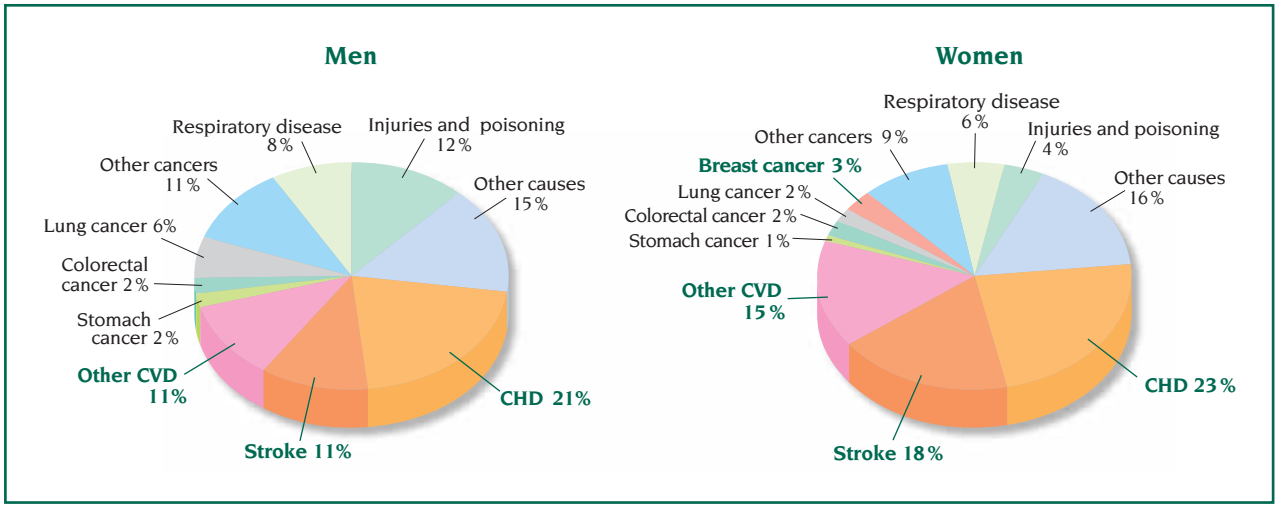

Figure 1. *Causes of death in Europe by gender. World Health Organization 2004.*

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 preeclampsia 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 al[6] 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, HbA_{1c} 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.[8] 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)*.[9]

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.[10] 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.[11] 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.[12,13] In the simvastatin arm of the Heart Protection Study (HPS),[12] 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.[13] 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.[14] 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.[15]

Lifestyle modification and pharmacotherapy are the therapeutic mainstays to decrease morbidity and mortality. 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.

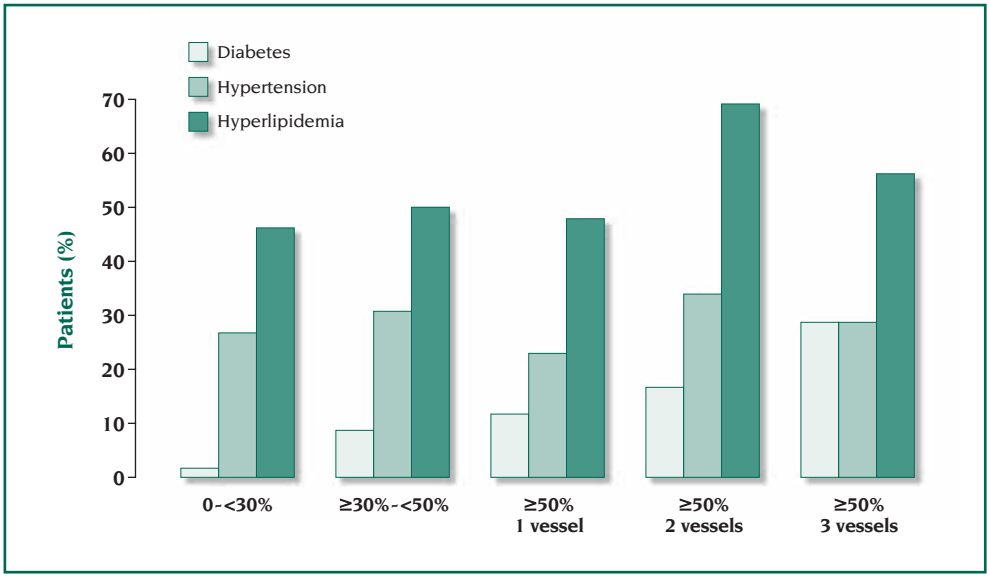

Figure 2. *Stockholm Female Coronary Risk Study. Coronary angiographic findings versus risk factors.*

Modified after reference 9: *Al-Khalili F, Svane B, Wamala SP, Orth-Gomér K, Rydén L, Schenck-Gustafsson K. Clinical importance of risk factors and exercise testing for prediction of significant coronary artery stenosis in women recovering from unstable coronary artery disease: the Stockholm Female Coronary Risk Study.* Am Heart J. *2000; 139: 971-978. Copyright © 2000, Elsevier BV.*

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.

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%.[16] 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.[17]

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.[2] 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.

Diabetes

Cardiovascular events are the leading cause of death especially in type 2 diabetes mellitus (DM).[18] 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).[19] 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.[2] In the Nurses' Health Study, women with diabetes alone had a coronary mortality 8.7 times higher than nondiabetics, and those who had in addition a known IHD history had a relative risk for fatal CAD of 25.8.[20] In the Copenhagen City Heart Study, over a 20-year period, the relative risk of new myocardial infarction in 7198 women was 1.5 to 4.5 among diabetics compared with nondiabetics.[21] Also, women with diabetes develop CVD at the same time in life as men, canceling out the 10-year protection effect afforded by female hormones. Women are equally susceptible to DM as men, and the incidence of this disease is increasing in both genders. The frequency and severity of atherosclerotic disease in diabetes has led the US National Cholesterol Education Project Adult Treatment Panel III (NCEP ATP III) to label DM as a CHD equivalent, justifying aggressive risk factor control.

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.[22] Based on the Nurses' Health Study, the recommended target BMI is 18.5-24.9 kg/m^2 with a waist circumference of <82 cm for women and <98 cm for men.[23]

Sedentariness, physical activity, and exercise

Blair et al observed in their prospective observational study that a lower fitness level was associated with 4.7-fold increased risk for CAD (0.44) and stroke (0.51), independent of other vascular risk factors.[24] 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.[25] 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.[26]

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. The left ventricle

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]

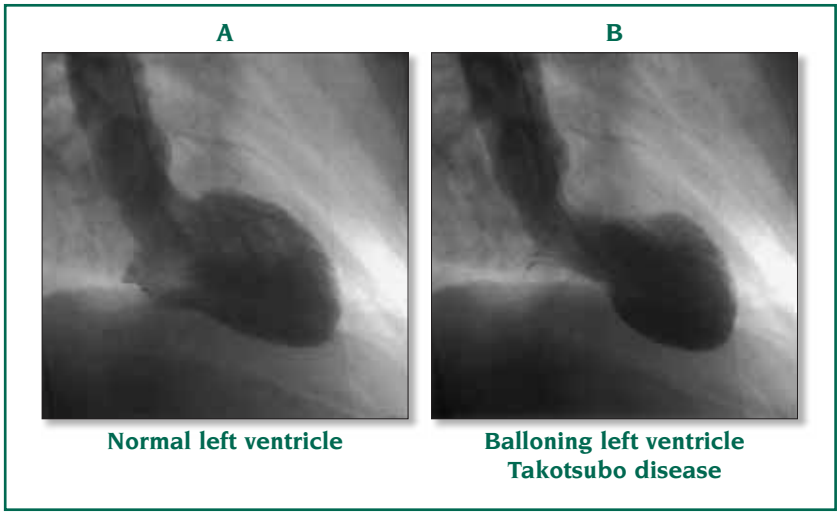

Figure 3. *Characteristic aspect of left ventricle in takotsubo disease. Karolinska University Hospital/ Photo by Karin Schenck-Gustafsson.*

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 then 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-

tical in men and women, but few gender-based analyses have been performed.

Female sex hormones

Female 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.[30] These recent findings contradict previous observational data suggesting a cardioprotective 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.

Figure 4. *"Go Red for Women" campaign. © American Heart Association/World Heart Federation.*

Campaigns like the World Heart Federation's (former AHA) "Go Red for Women" are very important to spread the knowledge about cardiovascular disease in women. This campaign is now running in 30 countries, and Sweden was one of the first in Europe to start, by holding it on Women's International Day (8 March 2006). It is now into its 3rd year *(Figure 4)*.

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