Heart rate: from risk marker to risk factor

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Several risk factors for the development of coronary heart disease and related mortality have been identified to facilitate detection of patients at high risk and to guide prevention of the disease and its sequelae. This presentation will suggest that heart rate, easily measured clinically, is evolving from its demonstrated status as a risk marker of mortality and morbidity in various populations, to become a risk factor in patients with established coronary artery disease. Substantial epidemiological data support the predictive value of resting heart rate for total mortality and cardiovascular mortality. Indeed, this relationship was found in the general population and in hypertensive patients as well as in patients with clinically evident coronary artery disease (including those with stable angina and prior myocardial infarction). Several criteria commonly used to assess the validity of epidemiological associations (such as those involving blood cholesterol concentrations and development of coronary artery disease) have been applied to resting heart rate. The relationships between resting heart rate and the development of coronary artery disease, as well as all-cause and cardiovascular mortality, were found to be strong, graded and independent of other factors such as blood pressure and physical activity. The ongoing BEAUTIFUL and SHIFT trials will assess the therapeutic value of pure heart rate reduction in populations with coronary artery disease with and without heart failure (as well, in SHIFT, in patients with heart failure in the absence of coronary disease), thus providing the necessary evidence to support risk factor status for heart rate in this population.

Keywords
Heart rate; Risk factor; Cardiovascular mortality

Introduction

Coronary artery disease (CAD) is a highly prevalent condition with life-threatening sequelae. The disease affects a large portion of the general population over 60 years of age. According to the Framingham Heart Study, lifetime risk of coronary heart disease for individuals aged 40 is 48% for men and 31% for women. Therefore, coronary heart disease represents an important public health problem, costly for society and responsible for relatively high mortality and morbidity in the affected patients. An obvious medical need, therefore, is guidance in efforts at disease prevention aided by identifying markers to detect individuals likely to develop CAD and its clinical sequelae. Observational studies as well as randomized trials have contributed to current understanding of risk markers and to the identification of those which can be modified with clinical benefit, so-called ‘risk factors’. The major risk markers for CAD and the first identified, aside from sex and age, were total cholesterol, systolic and diastolic blood pressures, smoking, and diabetes. Other, less predictive, risk markers included obesity, physical inactivity, and family history of coronary heart disease (particularly in young individuals). Among more recently recognized markers of CAD risk, metabolic syndrome and resting heart rate have been acknowledged. This review aims to present and assess the evidence now accumulating in support of the evolution of heart rate, an easily measured clinical parameter, from risk marker to risk factor for mortality and morbidity from CAD.
Difference between risk marker and risk factor

Both risk markers and risk factors are identified from correlations between the presence of the factor and subsequent development of the disease. A risk marker can be considered a risk factor if intervention to modulate this factor results in parallel modulation of risk, provided that the analysis demonstrating this risk modulation accounts for possible confounding factors. For example, systemic arterial hypertension is well established as a risk factor for CAD and its sequelae and for stroke, not only because it identifies patients at risk for cardiovascular events but because many studies, with many different agents, have demonstrated that, in hypertensive persons, risk is reduced when the blood pressure is reduced.5–12

The demonstration of the benefits of blood pressure reduction with many different agents is important: some antihypertensives, including the angiotensin-converting enzyme (ACE) inhibitors, ramipril (in HOPE, the Heart Outcomes Prevention Evaluation) and perindopril (in EUROPA, European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease), and the angiotensin receptor blocker (ARB), telmisartan (in ONTARGET, The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) appear to reduce events by pharmacological effects that add to the benefits of antihypertensive action.5,6,13 Several criteria have been developed to validate a risk marker as a risk factor, as detailed in what follows.

Resting heart rate and cardiovascular mortality

Several epidemiological studies support resting heart rate as a predictor (risk marker) of total mortality and of cardiovascular mortality. The Chicago Peoples Gas Company Study (including 1233 men followed up for 15 years), the Chicago Western Electric Company study (including 1899 men followed up for 17 years), and the Chicago Heart Association Detection Project (including 5784 men followed up for 5 years), reported together in 1980, were among the earliest to demonstrate the prognostic importance of resting heart rate for all-cause mortality in large populations.14 Indeed, multivariate analysis using age, blood pressure, total blood cholesterol, smoking, and body weight as covariates found heart rate to be an independent predictor of both sudden cardiac death and non-cardiovascular mortality in two of the three cohorts studied. As illustrated in Figure 1, the Framingham study, reporting a 30-year follow-up in 1987, demonstrated a significant relationship, in both men and women, between heart rate, cardiovascular mortality, coronary heart disease, and sudden coronary death.15 Paralleling these findings, a study of 19,386 ‘white collar’ employees in France, followed up over 20 years, found that resting heart rate significantly predicted non-cardiovascular mortality in both men and women.16 In men, the risk of cardiovascular death was lowest among those with heart rate < 60 bpm; in comparison with this group, relative risks among men with resting heart rate 60–80 bpm, 81–100 bpm, and >100 bpm were 1.35, 1.44, and 2.18, respectively (all statistically significant). Cardiovascular deaths were primarily and predominantly due to coronary events, and not to cerebrovascular accidents. In men, the predictive value of heart rate was independent of age, hypertension, total cholesterol, body mass index, smoking, and exercise activity. In women, heart rate did not influence cardiovascular mortality. Other parallel results were reported from the MATISS Project, which included 2533 men aged 40–69. During 24,457 subject-years of follow-up, heart rate independently predicted total mortality, cardiovascular mortality, and non-cardiovascular mortality.17 In another French cohort, including 5713 asymptomatic working men between the age of 42 and 53 at study entry, 23-year follow-up demonstrated a significant association between resting heart rate and both sudden and myocardial infarction-related death.18 As seen in Figure 2, in this study, resting heart rate > 75 bpm defined a relative risk of 3.92 for sudden death compared with heart rate < 60 bpm. Finally, in a study preliminarily reported at the 2006 Annual Scientific Session of the European Society of Cardiology, the same group showed a correlation between resting heart rate and overall mortality and, additionally, that changes in

Figure 1 Resting heart rate and all-cause mortality in the Framingham Study. From Kannel et al.15 with permission. The Framingham study, with a follow-up of 30 years, demonstrated that in both sexes at all ages, all-cause mortality increased progressively and significantly (P < 0.01), in relation to heart rate.

Figure 2 Resting heart rate and mortality in the general population. From Jouven et al.18 with permission.
resting heart rate during a 5-year interval also influenced mortality rates. Those subjects who decreased their heart rate by more than 7 bpm had a lower mortality than those whose heart rate remained relatively stable or those whose heart rate increased >7 bpm.19

Resting heart rate and mortality in arterial hypertension

Heart rate is an independent predictor of total and cardiovascular death in subjects with arterial hypertension. The Framingham Study evaluated 4530 subjects aged 35–74 with systolic blood pressure ≥140 mmHg or diastolic ≥90 mmHg and who were not on antihypertensive medication. Biennial mortality rates were determined using pooled logistic regression.20 A heart rate increment of 40 bpm from the group mean was associated with odds ratios for total mortality of 2.18 (1.68, 2.83 CI: 95%) for men and 2.14 (1.59, 2.88 CI: 95%) for women; for cardiovascular mortality, odds ratios were 1.68 (1.19, 2.37) for men and 1.70 (1.08, 2.67) for women. Figure 3 shows the relation between heart rate and mortality in men.

Resting heart rate in patients with coronary artery disease

The most common manifestation of CAD is stable angina pectoris. Angina occurs when myocardial oxygen demand exceeds oxygen supply, usually resulting from coronary artery narrowing caused by atherosclerotic lesions (and, far less commonly, by coronary artery spasm). Increases in heart rate are well established as precipitators of ischaemia, both by increasing myocardial oxygen demand and by limiting supply.21 In addition, among patients with established CAD, heart rate is directly related to the likelihood of sudden arterial occlusion.22 Thus, it is not surprising that, in an analysis of a registry of 24,913 patients with suspected or proven CAD referred for coronary angiography and followed for an average of 14.1 years in the Coronary Artery Surgery (CASS) Study, Diaz et al.23 found resting heart rate to be an independent predictor of total and cardiovascular mortality in men and women. As pointed out by Palatini,24 the relatively better prognosis observed in patients with lower resting heart rates may not be ascribed solely to beta-blocker therapy, independent of heart rate, because the effect of heart rate also was found among patients not taking beta-blockers. The predictive value of heart rate was independent of the effects of hypertension, diabetes, and smoking. Importantly, the relation between heart rate and cardiovascular mortality also was independent of ejection fraction and of the number of diseased coronary vessels. In addition, patients with heart rate ≥83 bpm had a higher risk of hospital admission for cardiovascular cause than those with a heart rate ≤62 bpm.

In a parallel study aimed to assess the post-acute and early chronic period after myocardial infarction, Hjalmarson et al.25 evaluated 1807 patients to define the relation between heart rate, in hospital and after discharge, and total mortality from day 2 to 1 year post-infarction. Both in-hospital mortality and post-discharge mortality were directly related to heart rate on hospital admission. As seen in Figure 4, total mortality was 15% for patients with admission heart rate between 50 and 60 bpm, 41% for those with heart rates >90 bpm, and 48% if heart rate was ≥110 bpm. Mortality from hospital discharge to 1 year was also related to maximal heart rate observed in the coronary care unit and to heart rate at discharge. In patients with severe heart failure, cumulative mortality was high (60–68%) regardless of heart rate on admission. Nonetheless, in patients with moderate heart failure (grade 2 pulmonary venous congestion), cumulative mortality when admission heart rate was >90 bpm was more than twice that when admission heart rate was <90 bpm (39 vs. 18%). A similar trend was observed in patients with mild or no heart failure (18 vs. 10%).

In another study of 8915 patients first seen when acutely ill with myocardial infarction and treated with a fibrinolytic drug as part of the GISSI-2 study, Zuanetti et al.26 found that in-hospital mortality increased progressively with increasing heart rate (7.1% for heart rate <60 bpm to 23.4% for heart rate >100 bpm). Heart rate was available at discharge in 7831 patients

![Figure 3](https://academic.oup.com/eurheartjsupp/article-abstract/10/suppl_F/F2/371147/10?sec=abstract)

**Figure 3** Resting heart rate and all-cause mortality in men with hypertension. From Gilman et al.20 with permission. Analysis from the Framingham Study, involving 2037 men with hypertension, demonstrates the univariate (adjusted for age) relationship between heart rate and death from all causes, cardiovascular disease, and coronary heart disease.

![Figure 4](https://academic.oup.com/eurheartjsupp/article-abstract/10/suppl_F/F2/371147/10?sec=abstract)

**Figure 4** Total mortality from day 2 to 1 year related to admission heart rate in patients with and without heart failure. From Hjalmarson et al.25 with permission.
in whom 6-month mortality was directly related to discharge heart rate (from 0.8% for heart rates < 60 bpm to 14.3% for heart rates > 100 bpm). On multivariate analysis the predictive value of heart rate for mortality was independent of other factors assessed. In CIBIS II, a study of the impact of the beta blocker, bisoprolol, on outcome in patients with chronic heart failure, a relation was also found between pre-therapy heart rate and heart rate reduction during the trial vs. clinical outcome: multivariate analysis indicated that baseline heart rate and heart rate reductions both were significantly and independently related to survival and to hospitalization for worsening heart failure.\(^2^7\)

In the placebo group, the lowest baseline heart rates and the largest heart rate reduction were associated with the best survival and with a reduction of hospital admissions. Bisoprolol further improved survival at any level of baseline heart rate or heart rate reduction.

**Criteria for validating heart rate as a risk factor**

Several criteria are used to assess the validity of epidemiological associations in CAD.\(^2^8\) **Plausibility**, based on current understanding of pathophysiology, provides a basis for concluding that a relation is consistent with the associated disease, in this case, CAD. **Strength** is determined by the relative risk of developing an outcome with the factor vs. the risk without. **Gradation of effect**, analogous to a dose–response curve in pharmacology, is defined by the quantitative impact of a change in the magnitude of the factor or the duration of exposure to the factor vs. the outcome of interest. The clearer the gradation of effect, the more likely the factor is, indeed, a beneficially modifiable risk factor. **Consistency** is the demonstration of the association between factor and outcome in a variety of populations, for example, cohorts involving various age spectra, both genders, and different ethnic groups. Perhaps most importantly, if the factor is modifiable by currently available strategies, diminution of the factor should beneficially modify the outcome. **Table 1** applies these criteria to the example of blood cholesterol, and also to resting heart rate, the latter in relation to all-cause mortality and cardiovascular mortality. In theory, heart rate reduction should reduce mortality, particularly cardiovascular mortality, for patients with CAD and, most especially, for those suffering acute myocardial infarction. Consistent with this hypothesis, in a review of results of beta-blocker trials for acute infarction, Kjekshus et al.\(^2^9\) observed a relation between the reduction in resting heart rate and the reduction in mortality. However, as yet, data are not available based on randomized clinical trials designed specifically to test the hypothesis that heart rate lowering improves survival after infarction or in any other population with CAD. In part, this deficiency relates to the lack, until recently, of drugs that can selectively and specifically lower heart rate without other apparent cardiovascular effects. The recent availability of ivabradine, an \(I_{	ext{i}}\) current inhibitor that is the first pure heart-rate lowering agent approved in Europe (for treatment of patients with chronic stable angina pectoris), has facilitated assessment of the impact of heart-rate lowering, alone, on outcome in patients with CAD. The BEAUTIFUL study (morBidity–mortality Evaluation of the \(I_{	ext{i}}\) inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) to be fully analysed and reported at the 2008 Annual Scientific Session of the European Society of Cardiology, and the ongoing Systolic Heart failure treatment with \(I_{	ext{i}}\) inhibitor ivabradine Trial (SHIFT) study, now ongoing and slated for completion in 2010, employ ivabradine to test the heart-rate lowering hypothesis. BEAUTIFUL is a 10 900-patient, multinational, randomized, placebo-controlled mortality trial in patients with chronic stable CAD plus left ventricular dysfunction.\(^3^0\) SHIFT is a 5500-patient trial assessing the impact of pure heart rate reduction on mortality and heart failure hospitalizations in patients with chronic stable heart failure due to either primary myocardial disease or CAD.

**Table 1** Heart rate as a risk factor: weight of evidence

<table>
<thead>
<tr>
<th>Criteria for assessing the clinical validity of epidemiological associations in coronary artery disease</th>
<th>Cholesterol</th>
<th>Heart rate</th>
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<tbody>
<tr>
<td>Plausibility</td>
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<td>Strength</td>
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Conclusions

Several observational studies, registries, and trials have identified heart rate as a risk marker for cardiovascular mortality, independent of other risk markers, including currently validated risk factors. Resting heart rate has been directly related to all-cause mortality, cardiovascular mortality, and development of cardiovascular disease in the general population, in hypertensive patients, and in patients with CAD. These findings, as well as the suggestive data of Kjekshus et al.\(^2^9\) from cross-sectional analysis of post-myocardial infarction trials, strongly suggest the potential benefit of heart rate reduction in patients with CAD, demonstration of which would validate heart rate as a risk factor. Thus far, the relation between heart rate and outcome has been found plausible,\(^2^1,2^2,3^1\) and strong, graded, and independent of other factors including blood pressure and physical activity.\(^1^4–1^8\) With BEAUTIFUL and SHIFT, all criteria accepted for validation of a risk factor will be assessable. From the currently available data, it is likely that heart rate will join the list of such risk factors for CAD, thus...
importantly altering management strategies for patients with CAD.

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References