Slowing heart rate with ivabradine: new treatment options

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The burden of coronary artery disease (CAD) remains high and is the main cause of death and a major cause of morbidity. The treatment of patients with symptomatic CAD is aimed at preventing myocardial infarction and death, and reducing the symptoms of angina and occurrence of myocardial ischaemia. Significant evidence shows that elevated heart rate plays an important role in triggering ischaemic events in patients with CAD and is an important predictor of cardiovascular morbidity and mortality. Ivabradine is a potent anti-anginal agent which works by specifically lowering heart rate. Its antianginal and anti-ischaemic efficacy has been established in a number of randomized placebo-controlled trials, ivabradine being non-inferior to beta-blockers and to calcium antagonists. These trials have also shown that ivabradine is well tolerated and can be safely combined with other cardiovascular agents. The ASSOCIATE study showed that ivabradine provides significant heart rate reduction and improvement in all exercise test criteria in patients with stable angina receiving the beta-blocker atenolol. In addition to its effects on myocardial ischemia and anginal symptoms, ivabradine has the potential to improve clinical outcomes in patients with limiting angina or in patients with a heart rate above 70 b.p.m. as suggested in the BEAUTIFUL trial. In summary, ivabradine is a potent anti-anginal agent, which can be used alone (when beta-blockers are contraindicated or not tolerated) or in combination with beta-blockers, with excellent tolerability.

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Coronary artery disease (CAD) is the single most common cause of death in Europe, with over one in five men and women dying from the disease, accounting for 1.92 million deaths each year.1 The treatment of patients with symptomatic CAD is directed towards preventing myocardial infarction and death and reducing the symptoms of angina and occurrence of myocardial ischaemia. Significant evidence shows that elevated heart rate plays an important role in triggering ischaemic events in patients with CAD and is an important predictor of cardiovascular morbidity and mortality.

Elevated heart rate is a major determinant of myocardial ischaemia in patients with angina

Myocardial ischaemia develops when coronary blood flow becomes inadequate to meet myocardial oxygen demand (Figure 1). The main clinical symptom of myocardial ischaemia is angina pectoris. In the heart, an increase in oxygen demand (e.g. during physical exercise or emotional stress) must be met by a proportional increase in coronary blood flow. However, in patients with CAD, myocardial blood flow is compromised as a result of atherosclerotic narrowing of the coronary arteries, and may not be able to meet the metabolic demands of the myocardial tissue. This transient imbalance is known as ‘demand ischaemia’ and is responsible for most episodes of chronic stable angina. ‘Supply ischaemia’ is caused by an acute reduction in oxygen supply as a consequence of increased coronary vascular tone (coronary vasospasm), or as a result of marked reduction or cessation of coronary flow such as that caused by unstable plaque or coronary occlusion following plaque rupture. In general, supply ischaemia of the myocardium results in acute coronary syndromes (unstable angina or myocardial infarction). Anginal symptoms can be a manifestation of either supply or demand ischaemia. Other changes indicative
of myocardial ischaemia include electrocardiogram (ECG) changes (such as ST-segment deviation) without clinical symptoms and global and regional impairment of ventricular function.

Heart rate influences both myocardial oxygen demand and supply and is therefore a key determinant of ischaemia. In patients with reduced coronary blood flow as a result of CAD, an elevated resting heart rate or a rise in heart rate due to a triggering factor such as stress increases the heart’s oxygen requirement. At the same time, an increased heart rate reduces diastolic perfusion time and decreases the heart’s oxygen supply. An increase in heart rate therefore acts on both sides of the supply and demand equation to deprive the heart of oxygen. In patients with stable CAD, most ischaemic episodes are preceded by an increase in heart rate. Ischaemic episodes are also related to the diurnal variation in heart rate, with a marked increase in the early morning hours. Furthermore, the likelihood of developing myocardial ischaemia is proportional to the baseline heart rate; patients with a mean heart rate of 60 b.p.m. have levels of ischaemia that are at least two-fold less than those of patients with a mean heart rate of 90 b.p.m. (Figure 2).

An elevated resting heart rate is a risk factor in patients with acute and stable coronary artery disease

A compelling body of epidemiological evidence demonstrates that elevated resting heart rate increases the risk of all-cause mortality and cardiovascular mortality in patients with CAD. These data have been derived from analyses of large registries of patients undergoing coronary arteriography for CAD, observational studies, and post hoc analyses of randomized controlled trials conducted in patients with CAD. The prognostic value of elevated heart rate has been demonstrated both in patients with acute and stable CAD.

Prognostic value of elevated heart rate in patients with acute coronary artery disease

It is widely accepted that overall heart rate in patients experiencing a myocardial infarction is higher than that of matched controls such that resting heart rate is included in several risk prediction scores for patients with acute coronary syndromes, e.g. the Global Registry of Acute Coronary Events (GRACE) and Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin (epitifibatide) Therapy (PURSUIT) scores. In patients with acute coronary events, heart rate on admission has a J-curve distribution with an increased event rate at very low and high heart rates even after controlling for baseline variables. Furthermore, a sustained elevated heart rate following myocardial infarction is associated with higher mortality, and has been shown to be a better predictor of both all-cause and cardiovascular mortality than left ventricular ejection fraction in this patient group.

The first study that evaluated the role of heart rate in the acute coronary setting was that of Hjalmarson et al. They examined heart rate at admission and on hospital discharge for 1807 patients admitted with an acute myocardial infarction. Both in-hospital and post-discharge mortality increased with increasing admission heart rate. Total mortality was 15% for patients with an admission heart rate between 50 and 60 b.p.m., 41% for heart rates >90 b.p.m., and 48% for heart rates of 110 b.p.m. or more. In patients with severe heart failure, cumulative mortality was high regardless of the level of admission heart rate. However, in patients with mild-to-moderate heart failure, cumulative mortality for patients with admission heart rates of 90 b.p.m. or more was at least twice that of patients with admission heart rates of <90 b.p.m.

Since then, a number of other studies have demonstrated the predictive power of elevated heart rate in patients with acute coronary syndromes. In a retrospective analysis of the Global Utilization of Streptokinase and t-PA (alteplase) for Occluded Coronary Arteries (GUSTO-I) clinical trial database, heart rate was the most powerful independent ECG predictor of 30-day mortality. A recent analysis of the CRUSADE data has demonstrated the
The prognostic value of heart rate for in-hospital mortality in a contemporary population of patients with acute coronary syndromes. Compared with a reference group of patients with heart rates of 60–69 b.p.m., patients with higher heart rates and very low heart rates (≤50 b.p.m.) had higher mortality and adverse outcomes, although this analysis was limited to in-hospital outcomes. An analysis from the GISSI-3 database has extended this observation to long-term outcomes using data from the 8915 patients with acute myocardial infarction and ECG recordings at hospital entry and discharge. The GISSI-3 researchers demonstrated a 10-fold increase in mortality at 6 months in patients with a heart rate above 100 b.p.m. when compared with those with a baseline heart rate below 60 b.p.m.

Prognostic value of elevated heart rate in patients with stable coronary artery disease

Over several decades, numerous and large-scale studies have consistently demonstrated the significant power of elevated resting heart rate in predicting cardiovascular risk in patients with stable CAD. We conducted one of the largest of these studies, using the Coronary Artery Surgery Study (CASS) registry, which included 24,913 patients with suspected or proven CAD. In this population, a baseline heart rate of 83 b.p.m. or more significantly increased the risk of all-cause and cardiovascular mortality by 32 and 31%, respectively, compared with a baseline heart rate of ≤63 b.p.m. over 14.7 years of follow-up. The results remained highly significant when controlling for age, sex, body mass index, smoking, hypertension, diabetes, the extent of CAD, the magnitude of left ventricular dysfunction, the level of physical activity, or use of β-blockers, indicating that high resting heart rate is an independent predictor of mortality in patients with CAD.

More recently, the INVEST trial investigators evaluated associations between baseline and follow-up resting heart rates and adverse outcomes in elderly patients with hypertension and chronic CAD. In this population, high baseline as well as high and very low follow-up resting heart rates were associated with increased risk of adverse outcomes regardless of treatment strategy and underlying comorbidity such as diabetes or prior myocardial infarction. This increased risk was observed at heart rates as low as 75 b.p.m.

An analysis of the placebo arm of the morBidity–mortality EvAluAtion of the If inhibitor ivabradine in patients with coronary disease and left-ventricular dysfunction (BEAUTIFUL) trial provided an exceptional
opportunity to prospectively test the predictive value of resting heart rate in patients with stable CAD.\textsuperscript{14} \textsc{beautiful} is therefore the first prospective study to assess whether stable coronary patients with a heart rate of \( \geq 70 \text{ b.p.m.} \) have a higher risk of cardiovascular events. After adjustment for baseline characteristics, patients with heart rates of 70 b.p.m. or more had a 34\% increased risk for cardiovascular death (\( P = 0.0041 \)), 53\% increased risk of admission to hospital for heart failure (\( P < 0.0001 \)), 46\% increased risk of admission to hospital for myocardial infarction (\( P = 0.0066 \)), and 38\% increased risk of coronary revascularization compared with those with lower heart rates (\( P = 0.037 \)) (Figure 4). For every increase of 5 b.p.m., there were increases in cardiovascular death of 8\% (\( P = 0.0005 \)), admission to hospital for heart failure of 16\% (\( P < 0.0001 \)), admission to hospital for myocardial infarction of 7\% (\( P = 0.052 \)), and coronary revascularization of 8\% (\( P = 0.034 \)). Importantly, in this prospective study, the strong prognostic value of elevated heart rate was observed on top of a high level of background treatment, including \( \beta \)-blockers.

In a \textit{post hoc} analysis of the Treating to New Targets (TNT) trial, the effect of resting heart rate on major cardiovascular events was assessed in 9580 patients with stable CAD over a median follow-up of 4.9 years.\textsuperscript{24} The rate of major cardiovascular events was 11.9\% in those with a baseline heart rate of 70 b.p.m. or more versus 8.8\% in those with a baseline heart rate \(< 70 \text{ b.p.m.} \). In this analysis, every 10 b.p.m. increase in resting heart rate was associated with an 8\% increase in major cardiovascular events. In particular, a resting heart rate of \( \geq 70 \text{ b.p.m.} \) was associated with a 40\% increased risk of all-cause mortality and more than doubled the risk of heart failure hospitalization, but not the risk of stroke or myocardial infarction.\textsuperscript{24}

The most recent data, as yet only published in abstract form, come from the ONGoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) Trial Programme, which includes the ONTARGET and Telmisartan Randomized Assessment study in ACE-I intolerant subjects with cardiovascular disease (TRANSCEND) trials. In this most recent analysis, patients were receiving contemporary medical care including statins.\textsuperscript{15} The ONTARGET trial compared the efficacy of ramipril and of telmisartan versus the combination of the two agents for prevention of cardiovascular morbidity and mortality in a population at high risk of cardiovascular disease due to a history of CAD, stroke, peripheral vascular disease, or diabetes mellitus type 1 or 2 with end-organ damage. In the same type of patients, TRANSCEND compared the efficacy of telmisartan with placebo in patients intolerant to angiotensin-converting enzyme inhibitors. The combined ONTARGET and TRANSCEND analysis included a total of 31 531 patients. Investigators evaluated the association between resting heart rate and a combined endpoint of cardiovascular mortality, myocardial infarction, stroke, and heart failure hospitalizations, as well as the prespecified secondary endpoint of all-cause mortality. According to reported preliminary data, patients with a heart rate of more than 70 b.p.m. had a 23\% increased risk of major vascular events compared with those with a heart rate of 70 b.p.m. or less (\( P < 0.0001 \)). A heart rate over 70 b.p.m. was independently associated with increased cardiovascular mortality (\( P < 0.0001 \)), all-cause death (\( P < 0.0001 \)), and hospitalization for heart failure (\( P < 0.0001 \)). The results remained significant after adjustment for all comorbid risk factors as well as for \( \beta \)-blocker and calcium channel blocker use.

The investigators also examined the data by quintiles, separating the patients into groups based on baseline heart rate. Compared with patients with the lowest heart rate (58 b.p.m. or less), those with the highest heart rate (\( > 78 \text{ b.p.m.} \)) had a 77\% increased risk of cardiovascular disease mortality and a 65\% increased risk of all-cause mortality.

### Controlling heart rate in daily clinical practice in patients with angina and patients with stable coronary artery disease

Of the current agents used to treat angina, three classes of medications have heart rate-lowering actions: \( \beta \)-blockers, non-dihydropyridine calcium channel blockers, and the \( I_{1} \) current inhibitor ivabradine. Although not pure heart rate-lowering agents, a number of studies have suggested that the impact on mortality outcomes of \( \beta \)-blockers and some calcium channel blockers after myocardial infarction is related to resting heart rate reduction. These results have been summarized in a meta-analysis, which identified 14 trials with \( \beta \)-blockers and 3 trials with calcium channel blockers with mortality outcomes post-myocardial infarction and documented changes in resting heart rate.\textsuperscript{25} A statistically significant relationship was found between resting heart rate reduction and reduction in cardiac mortality (\( P < 0.001 \)), all-cause mortality (\( P = 0.008 \)), sudden death (\( P = 0.015 \)), and recurrence of non-fatal myocardial infarction (\( P = 0.024 \)). Each 10 b.p.m. reduction in heart rate was estimated to reduce the relative risk of cardiac death by 30\%. However, there are side effects and limitations associated with the use of both classes of drugs, some of which are related to their haemodynamic impact.\textsuperscript{26} \( \beta \)-Blockers have well-known side effects including fatigue, depression, worsening of airways disease, hypotension, erectile dysfunction, and symptomatic deterioration in peripheral vascular disease. Also, calcium channel blockers are contraindicated in patients with significant left ventricular systolic impairment.

A novel option is pure heart rate reduction with the selective \( I_{1} \) current inhibitor ivabradine. This agent has no effects on vasoconstriction or myocardial contractility and is approved for the treatment of chronic stable angina in patients with normal sinus rhythm, who have a contraindication or intolerance to \( \beta \)-blockers or in combination with \( \beta \)-blockers in patients inadequately controlled with an optimal \( \beta \)-blocker dose and whose heart rate is \( > 60 \text{ b.p.m.} \). Ivabradine has been directly compared with atenolol and amlodipine in several trials and has been
shown to be non-inferior to these agents for the treatment of chronic stable angina.27,28 We have also shown that ivabradine reduces angina and myocardial ischaemia in patients not adequately controlled by a β-blocker.29 Ivabradine may also have an impact on coronary outcomes, since a subgroup analysis of the BEAUTIFUL trial demonstrated 36 and 30% reductions in relative risk of hospitalization for fatal and non-fatal myocardial infarction and coronary revascularization, respectively, in patients with a heart rate of 70 b.p.m. or more treated with this medication.30 Ivabradine therefore has a role in the management of patients with stable angina, particularly when β-blockers are contraindicated or poorly tolerated, or in addition to other antianginal drugs when control of symptoms is insufficient.

Heart rate reduction is a well-established strategy for ischaemia/angina prevention in patients with angina pectoris. Furthermore, a solid body of evidence provides clear proof of a continuous increase in cardiovascular risk for heart rate values above 70 b.p.m. in patients with stable CAD. However, despite the established importance of heart rate in CAD, the results of the most recent European Heart Survey suggest that heart rate is inadequately controlled in patients in clinical practice.31 The survey examined resting heart rate in 3779 patients presenting with stable angina in relation to prior and subsequent pharmacological treatment, comorbid conditions, and clinical outcome. Mean baseline heart rate was 73 b.p.m. and 52.3% of patients had a baseline heart rate of more than 70 b.p.m., yet over half of the patients were not receiving heart rate-lowering therapy at baseline. These data highlight the lack of attention paid to heart rate in clinical practice and, as a consequence, the missed therapeutic opportunity for coronary patients.

Based on a large body of epidemiological and clinical evidence, heart rate should be used for risk assessment and to guide optimum medical treatment in coronary patients. Selective heart rate lowering with ivabradine has been shown to reduce angina and myocardial ischaemia in patients with stable CAD and also has the potential to improve hard cardiovascular outcomes.

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