


Lowering Heart Rate Post Revascularization: Angina and Quality of Life Improvement

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Coronary artery disease (CAD) is responsible for 38% of cardiovascular (CV) deaths in women and 46% in men.¹ Stable angina pectoris, the principle manifestation of CAD, affects close to 15% of the population aged 65 to 84 years.² The chronicity and the frequency of symptoms have a direct effect on quality of life (QOL); realization of subpar health conditions promotes a vicious circle of stressful stimuli that, in turn, can promote angina attacks.³ Given our aging population and the increasingly good prognosis of patients with stable CAD, this group of patients is growing.

Elevated heart rate (HR) may be implicated in coronary atherosclerosis and subsequently to myocardial ischemia and angina in an independent manner.⁴ Suggested mechanisms include an increase in the magnitude and frequency of the mechanical stress imposed on the arterial wall, shortening of the atheroprotective diastolic period, and prolongation of endothelial exposure to atherogenic local hemodynamic factors.^{5,6} The atherogenic microenvironment modulated by increased HR, in conjunction with the effect of systemic risk factors, promotes plaque formation and progression in atherosclerosis-prone regions.⁷ Reducing HR could potentially restrain the process of atherosclerosis which clearly relates to ischemia and, thus, angina.⁸ Ivabradine is a selective, pure HR-lowering agent that inhibits the *I_f* current in the sinoatrial node.⁹ Several studies have shown ivabradine to be noninferior to first-line antianginal agents, such as beta-blockers and calcium channel blockers, and superior to placebo.¹⁰⁻¹³ Ivabradine has a class IIa (level of evidence B) indication for the symptomatic treatment of chronic stable angina in patients intolerant to or inadequately controlled by beta-blockers.²

In this issue of *Angiology*, Zarifis et al¹⁴ evaluated the potential antianginal effect of ivabradine when coadministered with beta-blockers in 926 patients with chronic stable angina and history of coronary revascularization (coronary artery bypass graft or percutaneous coronary intervention) in a time period of 4 months. Evaluation was performed via 1 objective marker (resting HR at baseline and at 3 follow-up time points) and 2 subjective, patient-dependent markers, namely, the Canadian Cardiology Society (CCS) angina classification and QOL in means of the EuroQol-5 Dimension (EQ-5D) questionnaire.¹⁵ The authors¹⁴ showed that blocking the *I_f* channels and reducing HR, with the addition of ivabradine to beta-blockers therapy, decreased the number of angina events, from 2.2 ±

2.3 (median: 2.0, minimum: 0.0, maximum: 21.0, range: 21.0) to 0.3 ± 0.6 (median: 0.0, minimum: 0.0, maximum: 7.0, range: 7.0) times/week, $P < .001$, and nitrates consumption from 1.5 ± 2.2 (median: 1.0, minimum: 0.0, maximum: 20.0, range: 20.0) to 0.1 ± 0.4 (median: 0.0, minimum: 0.0, maximum: 5.0, range: 5.0) times/week, $P < .001$, and increased the percentage of patients classified as CCS class I (from 36.1% to 83.1%, $P < .001$). There was an overall improvement of QOL in the magnitude of previously reported larger scale ivabradine studies.¹⁶ Another key point of the study is the high compliance with ivabradine treatment, in a noninstitutional environment, thus reflecting routine clinical practice. This could explain the efficacy in reducing angina attacks.

The antianginal effects of ivabradine are dose dependent.¹⁷ Notably, in the current study,¹⁴ only ~50% of the patients received the recommended full dose of ivabradine (7.5 mg twice daily). The mean HR achieved was 63.9 bpm at the last visit, still above the recommended target resting HR for patients with stable angina. The higher the HR at baseline, the greater the HR reduction at follow-up; this effect was not related to beta-blocker dosage. Beta-blockers were mostly not at target dose, an observation in line with a recent study by Goldberger et al,¹⁸ examining dosages of beta-blockers and survival after myocardial infarction.¹⁹ Beta-antagonists may be administered at lower doses than those that have shown efficacy in randomized clinical trials. Similarly, previous studies combining ivabradine with beta-blockers did not achieve the recommended daily dose of ivabradine.^{16,20} Titration to maximum suggested dosages might not be achieved. Aside from medical grounds, this can be attributed to physician reluctance or patient inertia.

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Although Fox et al in the SIGNIFY (study assessing the morbidity-mortality benefits of the If inhibitor ivabradine in patients with coronary artery disease) study,²¹ to date the largest randomized double-blind, placebo control trial of ivabradine added to standard background therapy, failed to show that outcomes improve in patients with CAD without clinical heart failure, patients with no angina or CCS class I at baseline were the ones who demonstrated symptomatic improvement. Interestingly, primary end points of CV death and nonfatal myocardial infarction in SIGNIFY were increased by 18% in patients with activity-limiting angina. Although the latter has been attributed to higher ivabradine doses and concurrent use of nondihydropyridine calcium channel blockers, the exact mechanism remains elusive.²² The present study¹⁴ did not report major CV events following ivabradine administration in patients with stable CAD post revascularization.

The study by Zarifis et al,¹⁴ despite the lack of a control group evaluating the potential placebo effect of ivabradine and the relatively short duration of 4 months, showed significant improvements in QOL, an effect also evident by the close to triple the number of patients reclassified to CCS class I compared to baseline. Although the authors¹⁴ focused mainly on a relatively homogeneous population of patients, representative of routine clinical management in private cardiology offices, their results are likely generalizable to a broad spectrum of post revascularization patients with stable angina. The health-care system in Greece and more specifically the fact that cardiologists are commonly the primary care physician of the cardiac patient allows for advanced understanding of a patient-centered approach.

In light of evidence accumulated over the last years from trials on the effect of ivabradine on CV outcomes conjoined with the remarkable results that a subcategory of the treated population might develop more adverse cardiac events, it still remains elusive which patient with CV patient will benefit the most by the addition of ivabradine.²²⁻²⁴ Implementing and removing novel regimens from therapeutic schemes should be considered on a per-patient basis. Most and foremost before treating first (*primum succurrere*) and before doing no harm (*primum no nocere*), we ought to seek and understand the rationale (*primum scire*) of any treatment. Further, we should aim to shed light on the pathobiological mechanisms of angina that govern each patient population.

Declaration of Conflicting Interests

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