Korean Circ J. 2020 Sep;50(9):787-790
https://doi.org/10.4070/kcj.2020.0266
pISSN 1738-5520·eISSN 1738-5555

kcj
Korean Circulation Journal

Editorial

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Ivabradine for the Therapy of Chronic Stable Angina Pectoris

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▸ See the article "Ivabradine for the Therapy of Chronic Stable Angina Pectoris: a Systematic Review and Meta-Analysis" in volume 50 on page 773.

OPEN ACCESS

Received: Jun 23, 2020
Accepted: Jul 6, 2020

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Conflict of Interest
The author has no financial conflicts of interest.

The contents of the report are the author's own views and do not necessarily reflect the views of the *Korean Circulation Journal*.

Heart rate is one of the main determinants of myocardial oxygen demand and its increase can contribute to the development of myocardial ischemia and angina as a result of increased myocardial oxygen demand and a reduction in diastolic perfusion time. Therefore, heart rate reduction is an important treatment strategy for improving both symptoms of myocardial ischemia and quality of life (QOL) in chronic stable angina patients. In 1964, propranolol was firstly introduced as the clinically available beta blocker for the management of chronic stable angina, and calcium channel blockers became available in 1975. These 2 drugs have been classified as being first line for the control of heart rate and symptomatic relief of angina in recent guidelines.[1] Ivabradine selectively inhibits a cyclic nucleotide-gated transmembrane channel to generate a slow, inward-depolarizing mixed sodium-potassium current, referred to as the pacemaker or "funny" current (If) in sinoatrial nodal tissue, which leads to a decrease in the slope of diastolic depolarization of the pacemaker action potential and consequently the heart rate.[2] It causes a dose-dependent reduction in heart rate without affecting myocardial inotropic function, coronary vasomotor tone or systemic vascular resistance. Its mechanism of action is so distinct from that of other negative chronotropic agents that its role has been tested in several small and large studies and approved in specific condition including systolic left ventricular failure and chronic stable angina. Ivabradine therapeutically works in the dose between 2.5 and 7.5 mg administered twice daily and undergoes extensive first-pass hepatic metabolism by the cytochrome P450 enzyme CYP3A4, implicating its several drug-drug interactions. In relation to side effect, ivabradine can increase the incidence of atrial fibrillation and should be cautious in subjects with known atrial or ventricular arrhythmias. Additionally, attention must be paid when ivabradine is used with other negative chronotropic drugs so as to avoid excessive bradycardia.

Ivabradine has been evaluated in a couple of multicenter, randomized studies as an anti-ischemic drug in chronic stable angina patients, based on its negative chronotropic property. In these studies, ivabradine as monotherapy has shown the beneficial effects on the exercise stress testing variables such as total exercise duration and angina attack in a dose dependent fashion. It increased time to 1-mm ST segment depression by 32.0 and 44.1 second in a dose of 2.5 mg and 5 mg twice daily respectively compared with 9.0 second with placebo (p=0.016 for 5 mg twice daily dose vs. placebo) and time to limiting angina by 22.5 second and 27.2 second (vs. 12.7 second in placebo) with significant decrease in resting and exercise heart rate.[3] Ivabradine also proved the non-inferiority to atenolol or amlodipine in terms of total exercise duration and angina attack frequency in stable angina patients.[4][5]

In Antianginal efficacy and Safety of the aSsociation Of the If Current Inhibitor ivAbradine with a beTablockEr study, the addition of ivabradine to beta blocker in chronic stable angina pectoris patients gave better control of heart rate and improved all exercise test variables including total exercise duration and time to angina onset, compared with beta blocker alone.[6] This beneficial effect of ivabradine combined with beta blocker in stable angina was also demonstrated in prActical Daily efficacy anD safety of procoralan In combinaTION with beta blockerS study, which showed that this combination not only reduced heart rate, number of angina attacks, and nitrate consumption, but also improved the QOL in patients with stable angina pectoris.[7] Pooled analysis from both 3 observational clinical studies including 8,555 stable angina patients and 5 randomized, double-blind, parallel-group studies in 2,425 patients demonstrated that ivabradine reduced the frequency of angina attacks and nitrate consumption, irrespective of age, comorbidities, and the use of beta blocker. However, ivabradine surprisingly failed to demonstrate the positive results in 2 recent prospective, randomized, double-blind, placebo-controlled trials, the morBidity-mortality EvAlUaTion of the If inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction (BEAUTIFUL) and Study assessInG the morbidity-mortality beNefits of the If inhibitor ivabradine in patients with coronarY artery disease (SIGNIFY) trials. In BEAUTIFUL trial, 10,917 stable coronary artery disease patients with left-ventricular ejection fraction of less than 40% were randomized to 5 mg ivabradine, with the intention of increasing to the target dose of 7.5 mg twice a day, or matched placebo, in addition to guideline-directed medication (87% of patients on beta blocker).[8] Unfortunately, this study demonstrated that there was no improvement in the primary composite endpoint of cardiovascular death, hospitalization for acute myocardial infarction (MI), or hospitalization for new or worsening heart failure (hazard ratio [HR], 1.00; 95% confidence interval [CI], 0.91, 1.1; p=0.94). The absence of benefit of ivabradine treatment could have resulted from insufficient reduction in heart rate (6 beats per minute, bpm) or from very low baseline heart rates (71.6 bpm). In a pre-specified subgroup with heart rate of 70 bpm or greater, although there was no difference in the primary composite endpoint, ivabradine reduced the incidence of hospitalization for fatal and non-fatal MI (0.64; 95% CI, 0.49, 0.84; p=0.001) and coronary revascularization (0.70; 95% CI, 0.52, 0.93; p=0.016). These observations are consistent with previous reports that heart rate was detrimental only at 75 bpm or above. This would suggest that lowering heart rate in patients with coronary artery disease and high baseline heart rate is mostly effective on coronary endpoints. In a post hoc analysis of patients with activity-limiting angina, ivabradine was associated with a 24% reduction in the primary endpoint, mainly driven by 42% reduction in hospitalization for MI. These benefit of ivabradine were augmented in a subgroup of patients with heart rate of 70 bpm or more (73% reduction in hospitalization for MI and 59% reduction in coronary revascularization). Following this trial, the SIGNIFY intended to investigate the role of ivabradine added to standard anti-anginal therapy in 19,102 stable coronary artery disease patients with a heart rate of 70 bpm or more without clinical heart failure.[9] Despite a reduction in heart rate by 10 bpm during a median follow-up of 27.8 months, ivabradine did not improve the primary composite endpoint of cardiovascular death or nonfatal MI (6.8% vs. 6.4%; HR, 1.08; 95% CI, 0.96, 1.20; p=0.20). In a pre-specified subgroup analysis, there was a signal for an increase in the risk of cardiovascular events among 12,049 patients with activity-limiting angina (class ≥ II on the Canadian Cardiovascular Society [CCS] scale), but not among patients without angina or those who had angina of class I (p=0.02 for interaction). There are a couple of plausible explanations for the lack of a benefit in SIGNIFY. In the study, higher dosing regimen of ivabradine 10 mg twice daily than clinically recommended maximum doses being 7.5 mg twice daily decreased heart rate too much, which could be associated with a J-shaped curve for the relationship

https://doi.org/10.4070/kcj.2020.0266

between heart rate and clinical outcomes. Ivabradine also may have unintended effects that negate the potential benefits of the other heart rate lowering agents. Although there was not enough data and some had neutral or negative results, recent European Society of Cardiology and European Medicines Agency guidelines recommended the use of ivabradine as a second-line drug for chronic coronary syndrome patients whose angina is insufficiently controlled on short-acting nitrates, beta-blockers, or calcium-channel blockers. But, to reduce the risk of serious bradycardia, they gave the following recommendations: dosage of 5 to 7.5 mg twice daily, no combination with verapamil or diltiazem (inhibitors of cytochrome P450 P3A4), and sole use in angina patients in sinus rhythm with a heart rate ≥70 bpm who remain symptomatic despite anti-anginal therapy.

Kalvelage et al.[10] have identified randomized controlled trials (RCTs) that compared ivabradine versus placebo/standard therapy (ST) or other anti-anginal drugs, and systematically evaluated the existing evidences of ivabradine in chronic stable angina pectoris to provide the optimal care and supplement the current guidelines for the use of ivabradine in stable angina patients. A total of 16,039 patients (8,553 patients in ivabradine, 6,904 patients in placebo or ST, 582 patients in other anti-anginal drugs such as atenolol or ranolazine) in 11 RCTs were assessed with an average follow-up time of 6.4±8.6 months. Compared to placebo/ST, there were significant beneficial effects of ivabradine on the frequency of hospitalization in only one small cohort study (n=90; HR, 0.19; 95% CI, 0.04, −0.92; p=0.04), but no effects on cardiovascular mortality in one study (n=12,049; HR, 1.10; 95% CI, 0.94, 1.28; p=0.25). Meta-analysis of 2 studies demonstrated that ivabradine has no statistically significant effect on the frequency of angina pectoris episodes (n=168; weighted mean difference, −1.06; 95% CI, −2.74, 0.61; p=0.21). Five studies examined the exercise capacity and consistently showed a significant advantage of ivabradine over placebo or ST. However, a comparative meta-analysis of these data is not possible due to heterogeneity of outcome definition and measurement. Regarding individual QOL, ivabradine improved both the Seattle Angina Questionnaire score and the European QOL visual analogue scale significantly, compared with placebo (p<0.001), but showed worse results than ranolazine in very small cohort of patients. There was no significant difference between ivabradine and atenolol in terms of exercise capacity.

There are several limitations of the current study. First, nearly half of included studies (5 studies) had very small case numbers (average number of 30 per group). Therefore, the Grading of Recommendations Assessment, Development and Evaluation system recommended by Cochrane to evaluate the quality of evidence level was very low with publication bias or unclear risk of bias. In addition, most analysis comparing ivabradine with placebo/ST or with other agents were done in only one or 2 RCTs because there was only one study for each outcome or heterogeneity of outcome definition and measurement among RCTs. The negative effect of ivabradine in the subgroup of patients with CCS class II or higher from SIGNIFY study currently provides the strong evidence leading to a critical consideration for the use of ivabradine in this patient population. Although 2 other studies have been also included besides SIGNIFY study to re-evaluate the negative results of SIGNIFY study in the group of patients with CCS class II or higher, none of both studies measured the combined outcome of cardiovascular death and non-fatal MI. Furthermore, none of both performed a pre-defined subgroup analysis for the CCS class. Therefore, the negative results of SIGNIFY for the patients with CCS class II or higher cannot be supplemented. Finally, some data with respect to randomization and blinding were missing, so that an adequate assessment of a possible bias was not feasible for all included studies.

https://doi.org/10.4070/kcj.2020.0266

In conclusion, ivabradine has a unique electrophysiological effects, characterized by its negative chronotropic effect on the sinoatrial node and consequent favorable safety profile. Contemporary guidelines still recommend its use for the management of chronic stable angina as class IIa with level of evidence B. Further research will be needed to clarify if ivabradine will have different effects in specific subgroups.

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