Efficacy of Ivabradine versus β -Blockers for Heart Rate Reduction during Computed Tomography Coronary Angiography: A Meta-Analysis of Randomized Controlled Trials

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Key Words

Ivabradine · Computed tomography coronary angiography · β -Blockers · Randomized controlled trials

Abstract

Objective: To quantify the efficacy of pretreatment with ivabradine compared to β -blockers before computed tomography coronary angiography (CTCA) via a meta-analysis of clinical randomized controlled trial data. **Methods:** We conducted a search for randomized controlled trials of pretreatment with ivabradine compared to β -blockers before CTCA in Medline, PubMed, Embase, SCI/SSCI/A&HCI, SAS Publishers, Web of Science, and the Cochrane Central Register. The Jadad quality score of the included studies, and the mean difference (MD) in heart rate reduction, were indicators of efficacy. RevMan 5.2 and Stata 12.0 software were used for the meta-analysis. **Results:** Eight studies involving a total of 1,324 patients were included in the final analysis. The results showed that ivabradine was significantly more effective at improving the heart rate of patients achieving the target heart rate (<65 bpm) during CTCA (OR 5.02; 95% CI 3.16–7.98, $p < 0.00001$, $I^2 = 20\%$). A comparison of efficacy between ivabradine and β -blockers showed a statistically significant effect of ivabradine on heart rate reduction during

CTCA (MD -4.39 ; 95% CI -4.80 to -3.99 , $p < 0.00001$, $I^2 = 0\%$). Ivabradine also led to a significant reduction in heart rate prior to CTCA (MD -5.33 ; 95% CI -10.26 to -0.39 , $p = 0.03$, $I^2 = 92\%$). In terms of the total reduction in heart rate during CTCA, significant differences were noted between the ivabradine group and the β -blocker group (MD 2.64; 95% CI 1.25–4.02, $p = 0.0002$, $I^2 = 0\%$). The mean percentage reduction in heart rate in the ivabradine group was significantly higher than that in the β -blocker group (MD 7.18; 95% CI 5.64–8.72, $p < 0.00001$, $I^2 = 43\%$). Ivabradine had no significant effect on either systolic blood pressure (BP) (MD 11.41; 95% CI 6.43–16.40, $p < 0.00001$, $I^2 = 85\%$) or diastolic BP (MD 1.79; 95% CI -0.00 to 3.58, $p = 0.05$, $I^2 = 56\%$). **Conclusion:** Compared to β -blockers for heart rate reduction, ivabradine is a potentially attractive alternative for patients undergoing CTCA.

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Introduction

A low and stable heart rate (HR) is an important prerequisite for the achievement of optimal image quality and diagnostic accuracy with computed tomography coronary angiography (CTCA). Accordingly, to minimize

Table 1. Quality features and study characteristics of the 8 reports included in the meta-analysis

Study	Randomized patients (ivabradine/ β -blockers/ placebo), n	Intervention	Design	Time before CTAT	Baseline HR ($\pm$ SD) in the ivabradine/ control group, bpm	Target HR, bpm
Çelik et al. [1]	120 (60/60)	Ivabradine 15 mg/day, β -blockers 5–10 mg/day	Cluster randomized controlled trial	2 h	80 $\pm$ 7 81 $\pm$ 7	<65
Guaricci et al. [2]	90 (30/31/29)	Ivabradine 5 mg b.i.d., β -blockers 50 mg b.i.d., placebo	Randomized controlled	5 days	73 $\pm$ 9 74 $\pm$ 11 72 $\pm$ 10	<65
Adile et al. [3]	100 (50/50)	Ivabradine 5 mg b.i.d., β -blockers 50 mg b.i.d.	Randomized controlled	2 days	90.02 $\pm$ 7.02 91.92 $\pm$ 5.75	<65
Guaricci et al. [4]	183 (48/48/38/49)	Ivabradine 5 mg q.d., ivabradine 7.5 mg q.d., β -blockers unclear, placebo	Randomized controlled trial	5 days	73.2 $\pm$ 9.2 76.3 $\pm$ 7.7 70.5 $\pm$ 9.4 71.3 $\pm$ 9.2	<60
Pichler et al. [5]	120 (60/60)	Ivabradine 15 mg q.d., β -blockers 50 mg q.d.	Randomized controlled trial	2 h	76 $\pm$ 11 76 $\pm$ 8	<65
Bayraktutan et al. [6]	110 (56/54)	Ivabradine 5 mg b.i.d., β -blockers 5 mg/ml	Randomized controlled trial	3 days	75 $\pm$ 4.8 73 $\pm$ 5.8	<65
Adile et al. [7]	200 (100/100)	Ivabradine 5 mg b.i.d., β -blockers 50 mg b.i.d.	Randomized controlled trial	2 days	Unclear	<65
Patel et al. [8]	100 (58/42)	Ivabradine unclear, β -blockers unclear	Randomized controlled trial	1–2 days	75 $\pm$ 7 77 $\pm$ 10	<65

coronary artery motion artifacts and optimize the image quality, an HR of 60–65 bpm is required, whereas an increase in HR is associated with an almost linear deterioration of image quality and diagnostic accuracy. β -Blockers and calcium channel blockers are the fundamental drugs used for HR reduction, but their negative inotropic and dromotropic effects limit their application in patients with hypotension, asthma, and peripheral vascular disease since some patients seemly cannot tolerate the side effects. The pacemaker current (I_f) channel is a hyperpolarization-activated cyclic nucleotide-gated channel, and ivabradine is the first sinoatrial node I_f current inhibitor that is different from traditional HR-reducing agents. Ivabradine reduces the HR without affecting cardiac contractility, ventricular repolarization, blood pressure (BP), or atrioventricular conduction. Ivabradine is undoubtedly a potentially attractive alternative for inappropriate sinus tachycardia, stable angina, heart failure, and other cardiovascular diseases, and it has good prospects for clinical application. A number of studies [1–10] have

shown that ivabradine plays an important role in HR reduction in CTCA, particularly in terms of quantification of the efficacy of pretreatment with ivabradine before CTCA. We therefore examined whether there was a significant difference via meta-analysis.

Methods

Search Strategy

We searched for randomized controlled trials of pretreatment with ivabradine before CTCA from 2000 to the year of reporting. Medline, PubMed, Embase, SCI/SSCI/A&HCI, SAS Publishers, Web of Science, and the Cochrane Central Register were searched using the following key words: ivabradine, computed tomography coronary angiography, β -blockers, randomized controlled trials, CTCA, RCTs, and HR.

Inclusion Criteria

We only considered randomized control trials, and detailed information about random sequence generation, allocation concealment, and blinding was not considered. Patients undergoing

Fig. 1. Forest plot of ivabradine vs. HR improvement (bpm) in patients achieving the target HR during CTCA.

CTCA comprised the research object. The observation group was treated with ivabradine, and the control group was given β -blockers.

Exclusion Criteria

Nonrandomized controlled trials, studies with incomplete information, and repeatedly published literature were excluded. All patients were in normal sinus rhythm. Patients with atrial fibrillation, a pacemaker, second- and third-degree atrioventricular block, New York Heart Association class III–IV, impaired renal function, a known allergy to iodinated contrast media, pregnancy, an unstable clinical condition, thyroid disease, a baseline HR <60 bpm, a left ventricular ejection fraction <30%, a BP <100/70 mm Hg, known arrhythmias, retinal disease, or chronic obstructive pulmonary disease were excluded.

Literature Screening

Two reviewers set the inclusion and exclusion criteria, evaluated all of the literature, and discussed in cases of disagreement; whenever there was similar or repeated literature, only studies with high-quality and complete data were chosen.

Quality Evaluation

The Jadad scoring method was used to assess the quality of the literature in terms of the following 3 aspects: randomization, blinding or lack thereof, and loss to follow-up and exit.

Synthesis of Data and Summary Measures

Standardized mean differences (MD) for continuous variables, and risk ratios (RR) and odds ratios (OR) for dichotomous end points, were reported with 95% CI. Data were pooled together with random-effects models using the inverse-variance method. Heterogeneity across studies was tested using the I^2 statistic; a random-effects model was used in cases of significant heterogeneity ($I^2 > 50\%$), and a fixed-effects model was used with for I^2 statistics <50%. To evaluate the presence of publication bias, the funnel plot was inspected. All analyses were performed using RevMan 5.2 software and Stata 12.0.

Results

The characteristics of the trials and the baseline characteristics of the patients are shown in table 1. Finally, 8 studies [1–8] were included in our meta-analysis. The experimental group was treated with ivabradine, and the control group was given β -blockers.

Ivabradine was significantly more effective at improving the HR of patients achieving the target HR (<65 bpm) during CTCA (OR 5.02; 95% CI 3.16–7.98, $p < 0.00001$, $I^2 = 20\%$) (fig. 1).

Ivabradine led to a significant reduction in HR prior to CTCA (MD -5.33 ; 95% CI -10.26 to -0.39 , $p = 0.03$, $I^2 = 92\%$), as reported by 6 studies (fig. 3).

In all 8 studies on ivabradine treatment, the HR during CTCA was lower in patients receiving ivabradine than in those receiving β -blockers (MD -4.39 ; 95% CI -4.80 to -3.99 , $p < 0.00001$, $I^2 = 0\%$) (fig. 2).

Three studies reported significant differences in the total HR reduction between the ivabradine group and the β -blocker group (MD 2.64; 95% CI 1.25–4.02, $p = 0.0002$, $I^2 = 0\%$) (fig. 4).

The mean percentage reduction in HR was also significantly greater in patients treated with ivabradine compared to those treated with β -blockers (MD 7.18; 95% CI 5.64–8.72, $p < 0.00001$, $I^2 = 43\%$) (fig. 5).

Ivabradine had no significant effect on either systolic or diastolic BP. In contrast to its significantly better HR-lowering properties compared to β -blockers, there was no significant effect of ivabradine on the systolic (MD 11.41; 95% CI 6.43–16.40, $p < 0.00001$, $I^2 = 85\%$; fig. 6) or diastolic blood pressure (MD 1.79; 95% CI -0.00 to 3.58, $p = 0.05$, $I^2 = 56\%$; fig. 7).

Fig. 2. Forest plot of ivabradine vs. β -blockers. HR reduction (bpm) during CTCA.

Fig. 3. Forest plot of ivabradine vs. β -blockers. HR reduction (bpm) prior to CTCA.

Fig. 4. Forest plot of ivabradine vs. β -blockers. Total HR reduction (bpm) during CTCA.

Fig. 5. Forest plot of ivabradine vs. β -blockers. Mean percentage reduction in HR during CTCA.

Fig. 6. Forest plot of the effect of ivabradine vs. β -blockers on the systolic BP.

Fig. 7. Forest plot of the effect of ivabradine vs. β -blockers on the diastolic BP.

Table 2. Egger's test

Standard effect	Coefficient	Standard error	t	p > t	95% CI
Slope	-0.2659048	1.550033	-0.17	0.869	-4.058699 to 3.52689
Bias	-3.436225	7.204586	-0.48	0.650	-21.06521 to 14.19276

Fig. 8. Funnel plot of ivabradine versus β -blockers, with pseudo 95% confidence limits, for HR reduction during CTCA. SE = Standard error. **Fig. 9.** Egger's publication bias plot. Ivabradine vs. β -blockers for HR reduction during CTCA.

Publication Bias

Publication bias was assessed graphically using a funnel plot. Even though only 8 studies were included in this analysis, the results illustrate that the funnel plot was roughly symmetrical (fig. 8). Egger's test ($p > 0.05$) and Egger's publication bias plot (fig. 9) suggested no significant publication bias in this study (table 2).

Sensitivity Analysis

Stata 12.0 was used for the sensitivity analysis (fig. 10).

Discussion

This is the first study to evaluate the benefits of ivabradine in patients undergoing CTCA using a meta-analysis. Multiple previous studies have demonstrated an inverse relationship between HR and the image quality of CTCA [11, 12]. The pooled results from 8 randomized controlled trials suggest that, compared to β -blockers, ivabradine can significantly reduce the HR both during and prior to CTCA. Ivabradine is also more effective at improving the rate of patients achieving the target HR during

Fig. 10. Funnel plot sensitivity analysis of ivabradine vs. β -blockers for HR reduction during CTCA.

CTCA. HR is a well-established risk factor for major adverse cardiac events. Our meta-analysis indicated that ivabradine could decrease the HR both during and prior to CTCA compared to β -blockers. More impressively, in contrast to its significantly better HR-lowering properties

compared to those of β -blockers, ivabradine had no significant effect on either systolic or diastolic BP, making it more suitable for patients with hypotension, chronic obstructive pulmonary disease, or peripheral vascular disease. Lambrechtsen and Egstrup [12] showed that ivabradine administered orally 2 and 16 h before CTCA examinations resulted in a significantly lower HR before CTCA, making it more convenient than the use of intravenous short-acting β -blockers immediately before the examination. As the use of intravenous short-acting β -blockers is time consuming, such pretreatment will save time when preparing the patient for CTCA acquisition. Despite the routine use of β -blockers prior to CTCA studies, it is not uncommon to have patients with HR persistently above the target range of 65 bpm despite the use of oral as well as intravenous β -blockers [13–15]. The use of β -blockers is also contraindicated in many diseases, and thus CTCA with oral ivabradine premedication is a feasible, safer, and more effective way to reduce the HR to generate images of diagnostically acceptable quality in almost all coronary segments in comparison to β -blockers. Ma et al. [16] reported that ivabradine improved myocardial performance, left ventricular function and ventricular remodeling, and even survival in rodent heart failure, including ventricular fibrillation, myocardial infarction, stable angina, and hypertension-induced cardiomyopathy.

A novel drug, ivabradine was found to be safe and effective as an HR-reducing agent. Ivabradine is a pure HR-lowering agent that acts via selective and specific inhibition of the cardiac pacemaker I_f current, which controls the spontaneous diastolic depolarization in the sinus node and regulates the HR. The cardiac effects are specific to the sinus node, with no effect on intra-atrial, atrio-ventricular, or intraventricular conduction times, myocardial contractility, or ventricular repolarization. The coronary blood flow velocity increases after ivabradine treatment because the diastolic period is prolonged. In addition, enhanced diastolic relaxation may possibly increase the early diastolic coronary blood flow via a suction effect [17]. Its side effects are infrequent and mostly restricted to dose-related visual disturbances. Therefore, ivabradine is suitable for a wide range of patients, including those individuals for whom other HR-lowering agents may be contraindicated [1].

In conclusion, we performed a meta-analysis of the available data to define the conditions and circumstances in which ivabradine may be a promising choice for patients undergoing CTCA, especially those who cannot tolerate β -blockers due to their side effects. Ivabradine had no significant effect on either systolic or diastolic BP.

Compared to the currently used drugs for HR reduction, it is a potentially attractive alternative for patients undergoing CTCA, with less serious adverse effects. Thus, ivabradine can successfully substitute β -blockers, particularly in patients with contraindications for β -blockers. Further unified protocols and well-designed prospective randomized controlled trials on this topic using larger sample sizes are still needed.

Limitations

Ivabradine plays an extremely important role in patients undergoing CTCA, especially those who cannot tolerate β -blockers and or calcium channel blockers due to their side effects. However, our meta-analysis has several potential limitations that should be taken into account. First, we analyzed different types of β -blockers; their characteristics are different and their effects may be unequal. Second, in the randomized controlled trials, the baseline HR of the patients was not based on a unified level. Third, the randomized controlled trials included in our study were very few, i.e. only 8, involving a total of 1,324 patients included in the final analysis, and the randomized controlled trials were all completed in Western countries, so there may have been regional differences in patients. These factors may have had an impact on our results. Further and more specific studies are warranted to address these issue.

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