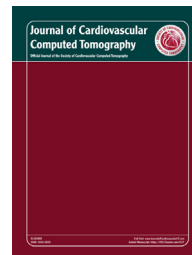




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## Original Research Article

# Comparison of different strategies of ivabradine premedication for heart rate reduction before coronary computed tomography angiography

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## ARTICLE INFO

## Article history:

Received 2 August 2013

Received in revised form

31 October 2013

Accepted 16 December 2013

## Keywords:

Ivabradine

Coronary CT

Safety

Multidetector CT

Different strategies

Single dose versus multiple dose

## ABSTRACT

**Objective:** The aim of this study was to assess the effectiveness and safety of different strategies of ivabradine therapy by comparing the effects on heart rate (HR), blood pressure (BP), and image quality of coronary CT angiography (CTA).

**Methods:** A total of 192 consecutive patients were randomly assigned to 3 groups of oral premedication with ivabradine 15 mg (single dose), 10 mg (single dose), and 5 mg twice daily for 5 days, prospectively. Patients using HR-lowering drugs and patients with  $\beta$ -blockade contraindication were excluded. The target HR was 65 beats/min. In addition 5 to 10 mg of intravenous metoprolol was administered to the patients at the CT unit, if required. The systolic and diastolic blood BP values and the HRs were recorded. Image quality was assessed for 8 of 15 coronary segments with a 4-point grading scale. Results were compared with the Kruskal-Wallis test, one-way ANOVA, and  $\chi^2$  test.

**Results:** Reductions in mean HR after the treatment were  $18 \pm 6$ ,  $14 \pm 4$ , and  $17 \pm 7$  beats/min for groups 1, 2, and 3, respectively. With the total additional therapies, 81.3%, 67.2%, and 84.3% of the patients achieved HR < 65 beats/min in groups 1, 2, and 3, respectively. The mean BP values before coronary CTA were not significantly changed except for patients in group 2. Unacceptable (score 0) image quality was obtained in only 4.5%, 10.2%, and 4.2% of all the coronary segments, in groups 1, 2, and 3, respectively.

**Conclusions:** Our study indicates that coronary CTA with premedication with oral ivabradine in all 3 strategies is safe and effective in reducing HR, in particular with a  $\beta$ -blockade

**Conflict of interest:** The authors report no conflict of interest.

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<http://dx.doi.org/10.1016/j.jcct.2013.12.005>

combination. All 3 ivabradine regimes may be an alternative strategy for HR lowering in patients undergoing coronary CTA. Ivabradine 15 mg (single dose) and ivabradine 5 mg twice daily for 5 days are superior to the ivabradine 10-mg single-dose regime for HR lowering without adjunctive intravenous  $\beta$ -blocker usage.

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## 1. Introduction

Coronary CT angiography (CTA) has significantly increased our ability to image the heart and coronary arteries non-invasively<sup>1</sup> to provide a high negative predictive value, ranging from 93% to 100%.<sup>2–5</sup> Importantly, to achieve accurate results, sufficient image quality which depends on a low and stable heart rate (HR) is mandatory. Despite significant technical developments, such as using 64-, 128-, and 320-row coronary CTA, HR control is still an important factor in optimizing the image quality of coronary CTA.<sup>6</sup> Thus, to achieve HR reduction,  $\beta$ -blocking medication or calcium antagonists are routinely administered before coronary CTA examinations.

In recent studies, a substantial portion of patients who require HR reduction have contraindications to  $\beta$ -blockers.<sup>6,7</sup> In some patients  $\beta$ -blockade therapy can not sufficiently decrease the HR. Target HR was achieved in only 35% of the patients receiving a  $\beta$ -blocker before coronary CTA.<sup>7</sup> Calcium channel blockers (diltiazem and verapamil) can be used when  $\beta$ -blockers are contraindicated.<sup>8</sup> However, the reduction rate efficiency of these drugs has been disappointing.<sup>9</sup> Thus, a need exists for alternative HR-lowering premedication. Ivabradine is a promising HR-lowering agent that reduces the heart's natural pacemaker activity by inhibiting the funny ion channel. Ivabradine lowers HR at concentrations that do not affect other cardiac ionic currents.<sup>10</sup> As a result, this novel drug has no other direct cardiovascular effects.<sup>11</sup> Recently, some studies reported that ivabradine is as effective as  $\beta$ -blocker therapy for the HR-lowering premedication, without major side effects.<sup>12,13</sup> Pichler et al<sup>13</sup> reported that, in patients who received the ivabradine in combination with the  $\beta$ -blocker therapy, significantly stronger HR reduction was achieved, whereas the decrease in systolic blood pressure (BP) was less, compared with ivabradine-only and metoprolol-only groups. In addition, Adile et al<sup>14</sup> reported that HR reduction was significantly greater in patients treated with ivabradine than in patients receiving oral  $\beta$ -blocker therapy. But as far as we know, to date no study compares the efficacy of different strategies of ivabradine premedication.

The aim of this study was to assess the effectiveness and safety of different strategies of ivabradine therapy by comparing the effects on HR, BP, and image quality of coronary CTA.

## 2. Methods

### 2.1. Study population

A total of 192 consecutive patients with suspected coronary artery disease were randomly assigned to 3 groups, as oral premedication with ivabradine 15 mg (single dose), 10 mg

(single dose), and 5 mg twice daily for 5 days. The study is planned as a prospective study. Patient characteristics are summarized in Table 1. The patients were all in sinus rhythm. The general exclusion criteria for this study were HR < 70 beats/min (admission HR), systolic BP < 100 mm Hg, diastolic BP < 70 mm Hg, atrial fibrillation, second- or third-degree atrioventricular block, history of coronary stents or previous bypass surgery, impaired renal function (creatinine > 1.5 mg/dL) or left ventricular ejection fraction < 30%, and a known allergy to iodinated contrast media. The patients with long-term  $\beta$ -blocker or calcium channel blocker therapy were excluded to avoid the summation of HR-reducing effect. We also exclude patients with contraindications to  $\beta$ -blocker therapy (severe aortic stenosis, asthma, severe chronic obstructive pulmonary disease with significant bronchospasm, severe peripheral vascular disease, and overt heart failure). The reason for the latter criteria is the potential risk of not reducing the HR efficiently for some of the ivabradine regimes without  $\beta$ -blocker adjunctive therapy. For this reason we preferred the strategy of including  $\beta$ -blockers as an adjunctive therapy in the present study. A total of 283 patients were referred for coronary CTA over a period of 5 months. Thirty-three (11.6%) were excluded because of the general exclusion criteria described earlier. Thirty-five of the remaining patients (12.3%) had  $\beta$ -blocker or calcium channel blocker medication, and 23 (8.1%) patients were excluded because of the contraindications to  $\beta$ -blocker therapy. Subsequently, the remaining 192 patients were randomly assigned to 3 groups consequently according to their HR at the time of admission (Fig. 1). The study was approved by the institutional ethics committee, and written informed consent was obtained from all subjects before the study.

### 2.2. Patient preparation and HR control

All patients were first assessed during an outpatient visit by a cardiologist, and each patient's history, risk factors, demographics, current medical treatment, and indication for

**Table 1 – Patient characteristics by premedication groups.**

Variables	Group 1 (15 mg)	Group 2 (10 mg)	Group 3 (5 mg $\times$ 2)	P
Age, y, mean $\pm$ SD	50 $\pm$ 8	51 $\pm$ 8	51 $\pm$ 9	.88
Male sex, n (%)	40 (62.5)	45 (70.3)	35 (54.7)	.19
BMI, mean $\pm$ SD	28 $\pm$ 2	29 $\pm$ 3	29 $\pm$ 2	.34
DM, n (%)	13 (14.1)	8 (12.5)	16 (25)	.19
HL, n (%)	27 (42.2)	22 (34.4)	26 (40.6)	.63
HBP, n (%)	32 (50)	27 (42.2)	35 (54.7)	.36

BMI, body mass index; DM, diabetes mellitus; HL, hyperlipidemia; HBP, high blood pressure.

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