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Review

# Effect of ivabradine on central aortic blood pressure in patients with stable coronary artery disease: What do we know?

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ABSTRACT

Treatment of hypertensive patients with beta-blockers decreases central blood pressure (CBP) less than other antihypertensive drugs, which is believed to account for their lesser cardiovascular protection in this setting. Some authors have suggested that decreasing heart rate (HR) with beta-blockers would increase CBP. In contrast to beta-blockers, the anti-anginal agent ivabradine reduces HR without other hemodynamic effects, and represents an attractive tool for exploring the direct relationship between HR and CBP. Here, we review the available clinical data assessing the effect of selective HR reduction with ivabradine on CBP in patients with stable coronary artery disease (CAD). We collected data from five studies which report either increase, decrease, or neutral effects of ivabradine on CBP. Further studies are needed to clarify the exact role of ivabradine on CBP. However, as supported by its pharmacodynamic effect in patients with stable CAD, available evidence to date suggests that ivabradine does not negatively impact CBP when associated with beta-blocker. HR reduction with both beta-blockers and ivabradine remains well-established treatments for the symptomatic treatment of angina patients.



The CAFÉ (Conduit Artery Function Evaluation) study reported that beta-blockers were associated with a lower reduction in central blood pressure (CBP) when compared with other antihypertensive agents, despite similar reduction in peripheral blood pressure [1]. This finding is believed to account for the lesser cardiovascular protection of beta-blockers in hypertensive patients [2]. Some authors have speculated that the main culprit for this effect was heart rate (HR) reduction, which would lead to an increase in wave reflection and hence negatively impact CBP [3,4]. The anti-anginal agent ivabradine reduces HR but, in contrast to beta-blockers, has no other hemodynamic effects. Ivabradine acts by selective and specific inhibition of the cardiac pacemaker current $I_f$ that controls the spontaneous diastolic depolarization in the sinus node and regulates heart rate. Because it specifically targets the sinus node, ivabradine has no effect on myocardial contractility or peripheral blood pressure. Thus, ivabradine represents an attractive tool for exploring the direct relationship between HR and CBP. Here, we review the available clinical data assessing the effect of selective HR reduction with ivabradine on CBP in patients with stable coronary artery disease (CAD). In all, five studies have explored the effect of ivabradine on CBP in CAD patients, 2 reporting a neutral effect, 2 reporting a decrease, and one reporting an increase (Table 1).

Two clinical trials showed a lack of effect of ivabradine on CBP indices [5,6]. In one randomized controlled study, 12 patients with stable CAD received ivabradine or placebo administered in two successive 3-week periods according to a randomized, double-blind, cross-over design [5]. Importantly, all patients were receiving background beta-blocker therapy during the trial. Thus, this data reflects real-life situation, as ivabradine is frequently prescribed in association with a beta-blocker in patients with CAD. CBP parameters were recorded by applanation tonometry (SphygmoCor®) at baseline and at the end of each treatment period. When compared with placebo, ivabradine had no significant impact on aortic systolic blood pressure ($-4.0 \pm 9.6$ mm Hg with ivabradine versus $+2.4 \pm 12.0$ mm Hg with placebo, $p = 0.13$) and on central pulse pressure ($+3.8 \pm 9.4$ mm Hg with ivabradine versus $+2.9 \pm 7.8$ mm Hg with placebo, $p = 0.78$). Similarly, augmentation index was not modified by ivabradine treatment ($-0.8 \pm 10.0\%$ with ivabradine versus $+0.3 \pm 7.6\%$ with placebo, $p = 0.87$).

A similar neutral effect of ivabradine on CBP was reported in a second study in which 30 patients with stable angina were enrolled [6]. Here, again, patients received stable background beta-blocker therapy during the study (bisoprolol), making the data relevant to clinical practice. CBP parameters were evaluated by applanation tonometry (SphygmoCor®) at baseline, 3 h after intake of a single dose of ivabradine, and after 1 and 2 months of chronic treatment with ivabradine. HR was reduced by both acute ($-8.2$ bpm, $p < 0.01$) and chronic ($-13.3$ bpm at 1 month, $p < 0.001$, and $-16.4$ bpm at

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**Table 1**
Effect of ivabradine on central blood pressure parameters in patients with coronary artery disease.

| Study | Patients | Study duration | Design | Doses | Beta-blocker background therapy | Methods for CBP measurement | Heart rate | Central systolic blood pressure | Central pulse pressure | Augmentation index | Overall impact of ivabradine on CBP |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ivabradine used on top of beta-blocker | | | | | | | | | | | |
| Dillinger et al. [5] | N = 12<br>Stable CAD ± hypertension | 3 weeks | RCT (control: placebo)<br>Cross-over, double-blind, multicenter | I: 7.5 mg bid | Stable background therapy[a] | Applanation tonometry | I: −15.8 bpm<br>P: 0.3 bpm | I: −4.0 mm Hg<br>P: 2.4 mm Hg | I: 3.8 mm Hg<br>P: 2.9 mm Hg | I: −0.8%<br>P: 0.3% | Neutral |
| Lopatin et al. [6] | N = 30<br>Stable CAD ± hypertension | 1 day | Single-arm, open-label, single center | I: 5 mg | B: 5 mg/day | Applanation tonometry | −8.2 bpm | −2.1 mm Hg | −0.6 mm Hg | −0.9% (−4.3%[b]) | Neutral |
| | | 1 month | Single-arm, open-label, single center | I: 11.5 mg/day[c] | B: 5 mg/day | Applanation tonometry | −13.3 bpm | −1.8 mm Hg | 0.9 mm Hg | 0.7% (−5.8%[b]) | Neutral |
| | | 2 months | Single-arm, open-label, single centre | I: 11.5 mg/day[c] | B: 5 mg/day | Applanation tonometry | −16.4 bpm | −2.3 mm Hg | 0.4 mm Hg | 1.2% (−6.7%[b]) | Neutral |
| Amosova et al. [8] | N = 85<br>Hypertensive, stable CAD | 6 months | RCT (control: bisoprolol)<br>Parallel, single-blind, single center | I: 12.7 mg/day[c]<br>B: 10 mg/day | B: 5 mg/day | Applanation tonometry | −11.4 bpm<br>−15.9 bpm | B + I: −15.5 mm Hg<br>B: −6.4 mm Hg | B + I: −13.5 mm Hg<br>B: −5.2 mm Hg | B + I: −4.5%<br>B: 1.5% | Decrease |
| Ivabradine used alone (no beta-blocker background therapy) | | | | | | | | | | | |
| Shavarov et al. [7] | N = 31<br>Hypertensive, stable angina | 6 weeks | RCT (control: atenolol)<br>Parallel, open-label, single center | I: 14.4 mg/day[c]<br>A: 137.5 mg/day[c] | - | Applanation tonometry | I: −20 bpm<br>A: −20 bpm | I: −6.9 mm Hg<br>A: −8.0 mm Hg | I: −4.0 mm Hg<br>A: 5.0 mm Hg | I: −13.5%[b]<br>A: −2%[b] | Decrease |
| Rimoldi et al. [9] | N = 46<br>Stable CAD ± hypertension | 6 months | RCT (control: placebo)<br>Parallel, singe-blind, single center | I: 5 mg uptitrated to 7.5 mg bid | – | Left heart catheterization | I: −9 bpm<br>P: −1 bpm | I: +11 mm Hg<br>P: −3 mm Hg | I: 8 mm Hg<br>P: 0 mm Hg | –<br>– | Increase |

Values are mean differences from baseline to study end.
A = atenolol; B = bisoprolol; B + I = bisoprolol + ivabradine combination; CAD = coronary artery disease; CBP = central blood pressure; I = ivabradine; P = placebo; RCT = randomized controlled trial.
[a] 7 patients were receiving bisoprolol, 2 patients acebutolol, 2 patients carvedilol, and 1 patient atenolol for >3 months before start of the study.
[b] AIx@75 (augmentation index normalized for a heart rate of 75 bpm).
[c] Mean dose.