

Research Article

Value of Ivabradine in Patients with Anterior ST-Elevation Myocardial Infarction: The VIVA-STEMI Study

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Abstract

Background: Role of ivabradine in patients with anterior wall ST-elevation myocardial infarction (STEMI) is unknown.

Methods: This is a two-center, randomized controlled, double-blinded trial, that included patients presenting with anterior wall STEMI and eligible for primary percutaneous coronary intervention (PPCI) from June 2016 through July 2018. After PPCI, patients were randomized (1:1) to receive bisoprolol plus ivabradine (ivabradine group) versus bisoprolol plus placebo (control group). Up-titration of ivabradine and/or bisoprolol was performed over a period of 6 weeks in all patients as tolerated. The primary outcome was

resting heart rate at 6 weeks. Other secondary clinical outcomes were studied.

Results: A total of 670 patients were included. Ivabradine was associated with a significant reduction in heart rate compared to placebo at 2 weeks (73.0 ± 2.8 vs 78.2 ± 1.75 bpm, respectively, $p < 0.001$), 4 weeks (67.1 ± 2.9 vs 73.3 ± 2.2 bpm, respectively, $p < 0.001$), and 6 weeks (62.3 ± 2.1 vs 66.9 ± 2.9 bpm respectively, $p = 0.001$). At 6 months, post-MI angina occurred in 30 (10.7%) versus 50 patients (17.6%) in ivabradine and control groups, respectively ($p = 0.022$). Heart Failure (HF) hospitalizations were less in ivabradine group (14.6% versus 23.2%, $p = 0.010$). At 12 months, there was a significant reduction in post-MI angina, and HF hospitalizations (16.7% versus

27.4%, $p=0.002$ and 21.7% versus 34.8%, $p=0.001$, in ivabradine and control groups, respectively).

Conclusions: Ivabradine, in addition to beta-blocker therapy, in patients with anterior STEMI was associated with superior heart rate control and clinical outcomes compared to placebo. Larger randomized controlled trials are encouraged to confirm role of ivabradine in these patients.

Keywords: Ivabradine; STEMI

Abbreviations: CAD-coronary artery disease; MACE-major adverse cardiac events; PCI-percutaneous coronary intervention; STEMI-ST-elevation myocardial infarction

1. Introduction

Coronary artery disease (CAD) remains a leading cause of death in many countries worldwide [1]. Multiple efforts aim at improving outcomes after myocardial infarction (MI) including revascularization and advancements in medical therapy. Among the determinants of outcomes after MI is the resting heart rate. Prior studies have shown that elevated heart rate (usually defined as higher than 75 beats per minute) at discharge and follow up are associated with worse outcomes and even increased mortality [2-4]. At the cellular level, elevated heart rate is associated with shortening of the length of cardiac cycle, minimizing diastolic perfusion time and thus worsening of the myocyte oxygen supply [2]. Such hemodynamic effects can also lead to impaired flow through collaterals resulting in a reduction of tissue perfusion in the jeopardized myocardial regions [3, 4] with potential impairment in contractility [4-6]. Ivabradine, a drug that selectively inhibits certain ion channel in the sinoatrial node (SAN) responsible for the pacemaker or “funny” (If) mixed sodium-potassium

current, leads to slowing of the sinus rate with no effect on myocardial inotropic function or coronary vasomotor tone [7]. The role of Ivabradine in stable CAD was studied in multiple randomized controlled trials (RCT) and have demonstrated an overall neutral effect on clinical outcomes. The data about the role of ivabradine after MI is more limited. In patients presenting with inferior wall MI, ivabradine was equally effective as metoprolol in a single-center study [8]. So far, the role of ivabradine after anterior wall ST-elevation myocardial infarction (STEMI) has not been studied. This randomized controlled trial aims at examining the role of Ivabradine in addition to conventional beta-blocker therapy in patients with anterior wall STEMI.

2. Methods

2.1 Inclusion criteria

This study was a two-center, prospective, double-blinded, randomized controlled study conducted from June 2016 through July 2018 at the tertiary Department of Cardiology, Ain Shams University and Al-Asafra Hospital, Egypt. The main inclusion criteria were patients between the age of 18 and 90 years presenting with anterior STEMI eligible for primary PCI. Exclusion criteria included patients with a) prior thrombolysis; b) bleeding gastric ulcer or severe gastritis within 6 months; c) bleeding diathesis (e.g. advanced liver disease); d) cardiogenic shock; and e) cardiac arrhythmias (e.g. atrial fibrillation).

2.2 Study design

After obtaining a written consent from the patients, eligible patients willing to take part in the study were assigned in a 1:1 ratio to receive one of two treatments; bisoprolol 2.5 mg once daily plus ivabradine 5 mg twice daily (ivabradine group) or bisoprolol 2.5 mg once daily plus placebo (control group). Medical therapy was advanced during

hospitalization then at 2-week intervals over the period of 6 weeks to the maximum tolerated doses aiming to reach a target heart rate of 60 beats per minute on a resting ECG. Figure 1 illustrates the study design. Randomization was performed before coronary

angiography using a computer-generated list of random numbers. All patients provided written informed consent before randomization. Both the patients and physicians performing the primary PCI and follow up were blinded to the treatment.

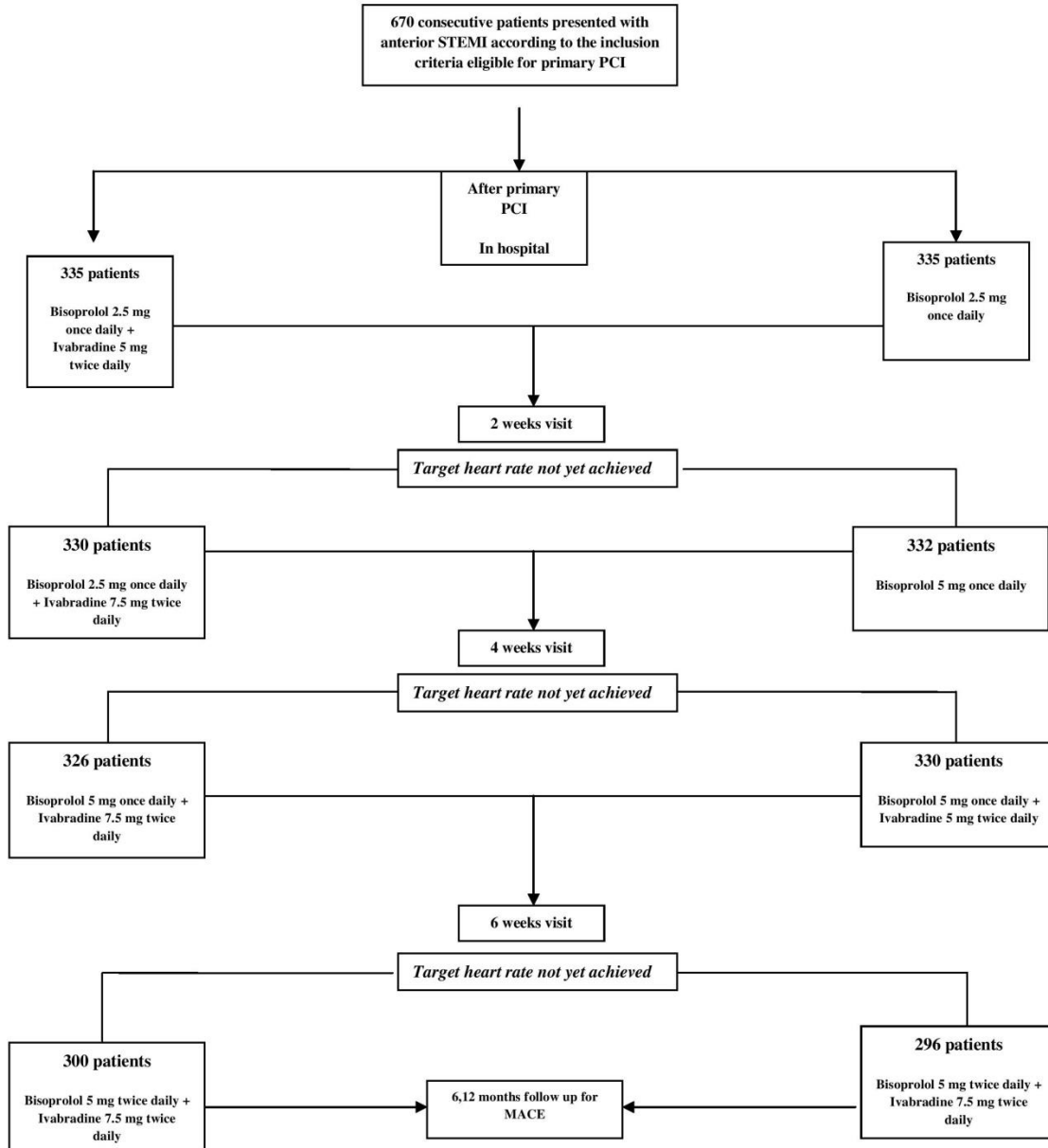


Figure 1: Study design.

2.3 Ethical committee approval

This study was performed according to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethical committees at both centers.

2.4 Patient and Public Involvement

Neither patients nor any public authority was involved in the study design or participated in any data collection or analysis. Patients were aware of the study after proper explanation of the protocol.

2.5 Endpoints

The primary endpoint was the resting heart rate at 6 weeks. Secondary endpoints included resting heart rate at 2 and 4 weeks, all-cause death, cardiovascular death, myocardial infarction (MI), target vessel revascularization, stroke, unstable (post-MI) angina, and heart failure hospitalization at 6 and 12 months after randomization. Clinical endpoints were defined according to guidelines [9].

2.6 Statistical analysis

Categorical variables are expressed as number and percentage of patients. Continuous data are reported as means and standard deviation as well as 95% confidence intervals when appropriate. Statistical analyses were performed with SPSS 18.0 (SPSS Inc., Chicago, Illinois).

3. Results

3.1 Baseline characteristics of the included cohort

A total of 670 patients met our inclusion criteria. The baseline characteristics were well balanced between the two treatment groups. The door-to-balloon time was similar between the ivabradine and placebo group (44.6 ± 22.7 mins vs. 53.7 ± 39.1 mins, $P=0.275$). No

significant difference was noted between both groups regarding baseline TIMI flow (0.2 ± 0.5 vs. 0.2 ± 0.4 respectively, $p=0.595$) or thrombus burden (4.5 ± 1.1 vs. 4.7 ± 0.8 respectively, $p=0.332$). Echocardiographic data at the time of discharge were also similar between both groups. Details of the baseline, procedural and echocardiographic criteria are summarized in Tables 1-3.

3.2 Primary outcome

In-hospital resting heart rate was similar between ivabradine and control groups, with a trend towards lower resting heart rate with ivabradine (79.6 ± 2.4 vs. 81.4 ± 1.6 bpm, respectively, $p=0.067$). There was a significant reduction in heart rate with ivabradine at 2 weeks (73.0 ± 2.8 vs. 78.2 ± 1.75 bpm respectively, $p<0.001$), 4 weeks (67.1 ± 2.9 vs. 73.3 ± 2.2 bpm respectively, $p<0.001$), and 6 weeks (62.3 ± 2.1 vs. 66.9 ± 2.88 bpm respectively, $p=0.001$). All patients tolerated the maximum doses of ivabradine in the study design. No significant bradycardia or arrhythmias were observed in either group.

3.3 Secondary outcomes

At 6 months, 30 patients (10.7%) in the ivabradine group versus 50 patients (17.6%) in the control group suffered from post-MI angina ($p=0.022$). Hospitalization due to heart failure was also significantly less in the ivabradine group (14.6% versus 23.2%, $p=0.010$). Similarly, at 12 months, there was a significant reduction in post-MI angina and hospitalization due to heart failure (16.7 % versus 27.4%, $p=0.002$ and 21.7% versus 34.8%, $p=0.001$, respectively) in the ivabradine versus control groups. Cardiac death and TVR were similar between both groups at 6 and 12 months follow up.

	Ivabradine group (n=335)	Control group (n=335)	P-Value
Male, n (%)	290 (86.7)	301 (90.0)	1.000
Age, years, mean \pm SD	55 \pm 9.2	57 \pm 11.6	0.672
Diabetes, n (%)	134 (40.0)	111 (33.3)	0.789
Insulin Therapy, n (%)	78 (23.3)	44 (13.3)	0.506
Hypertension, n (%)	123 (36.7)	123 (36.7)	1.000
Dyslipidemia, n (%)	44 (13.3)	22 (6.7)	0.671
Smoking, n (%)	223 (66.7)	257 (76.7)	0.567
Ex-smoking, n (%)	22 (6.7)	21 (6.7)	1.000
Family history, n (%)	33 (10)	33 (10)	1.000
Renal Impairment, n (%)	0 (0)	11 (3.3)	0.986

Table 1: Baseline characteristics.

	Ivabradine group (n=335)	Control Group (n=335)	P-Value
Duration from onset of pain till peak pain, min, mean \pm SD	195.0 \pm 203.3	204.2 \pm 181.5	0.854
Duration from peak pain till arrival to the ER, hours, mean \pm SD	3.8 \pm 2.8	4.2 \pm 3.2	0.293
Door to balloon time, min, mean \pm SD	44.6 \pm 22.7	53.7 \pm 39.1	0.275
Culprit vessel			
LAD, n (%)	324 (96.6)	335 (100)	0.975
Diagonal, n (%)	11 (3.3)	0 (0)	0.986
Site of occlusion			
Ostial, n (%)	22 (6.7)	0 (0)	0.492
Proximal third, n (%)	201 (60)	245 (73.3)	0.412
Mid-segment, n (%)	100 (30)	90 (26.7)	0.901
Distal third, n (%)	12 (3.3)	0 (0)	0.899
Baseline TIMI flow, mean \pm SD	0.2 \pm 0.5	0.2 \pm 0.4	0.595
Thrombus burden, mean \pm SD	4.5 \pm 1.1	4.7 \pm 0.8	0.332
Stent diameter, mean \pm SD	3.2 \pm 0.3	3.6 \pm 0.4	0.247
Stent length, mean \pm SD	20.2 \pm 3.1	21.4 \pm 3.4	0.061
Gb IIb/IIIa inhibitors, n (%)	0 (0)	0 (0)	
Stent postdilatation using non complaint balloon, n (%)	33 (10)	44 (13.3)	0.983

Table 2: Procedural data.

	Ivabradine group (n=335)	Control Group (n=335)	P-Value
LV end diastolic dimension, mm, mean ± SD	55.4 ± 4.3	54.4 ± 5.8	0.831
LV end systolic dimension, mm, mean ± SD	39.8 ± 5.1	40.8 ± 6.2	0.762
Left atrial dimension, mm, mean ± SD	36.0 ± 3.3	38.3 ± 6.3	0.807
EF by M-mode, %, mean ± SD	51.6 ± 8.6	49.7 ± 10.6	0.745
EF by 2D eyeballing, %, mean ± SD	47.7 ± 8.9	48.2 ± 8.7	0.899
EF by Simpson’s technique, %, mean ± SD	44.3 ± 7.5	43.6 ± 7.0	0.797
Pericardial effusion, n (%)	0 (0)	0 (0)	

EF= ejection fraction; LV= left ventricle

Table 3: Echocardiographic data.

In-hospital HR	Ivabradine group (n=335)	Control group (n=335)	P-Value
Day 1, bpm, mean ± SD	87.9 ± 2.46	87.7 ± 3.1	0.875
Day 2, bpm, mean ± SD	84.2 ± 2.85	84.8 ± 2.34	0.614
Day 3, bpm, mean ± SD	79.6 ± 2.4	81.4 ± 1.6	0.067
2 weeks visit	(n=330)	(n=332)	
HR at rest, bpm, mean ± SD	73.0 ± 2.8	78.2 ± 1.75	<0.001
Percentage achieving target HR, n (%)	67 (20.3)	58 (17.4)	0.709
4 weeks visit	(n=326)	(n=330)	
HR at rest, bpm, mean ± SD	67.1 ± 2.9	73.3 ± 2.2	<0.001
Percentage achieving target HR, n (%)	194 (59)	107 (32)	0.370
6 weeks visit	(n=300)	(n=296)	
HR at rest, bpm, mean ± SD	62.3 ± 2.1	66.9 ± 2.88	0.001
Percentage achieving target HR, n (%)	242 (80.6)	157 (53)	0.07

BPM= beats per minute; HR= heart rate

Table 4: Primary outcome of resting heart rate.

	Ivabradine group	Control Group	P-Value
	(n=335)	(n=335)	
In-hospital			-
Bleeding, n (%)	0 (0)	0 (0)	
Stroke, n (%)	0 (0)	0 (0)	-
Death, n (%)	0 (0)	0 (0)	-
Cardiac death, n (%)	0 (0)	0 (0)	-
ST-segment Re-elevation (MI) , n (%)	0 (0)	0 (0)	-
TLR, n (%)	0 (0)	0 (0)	-
TVR, n (%)	0 (0)	0 (0)	-
Total MACE, n (%)	0 (0)	0 (0)	-
Re-catheterization, n (%)	0 (0)	0 (0)	-
6 months follow up	(n=280)	(n=284)	
Stroke, n (%)	0 (0)	0 (0)	-
MI, n (%)	0 (0)	0 (0)	-
Death, n (%)	0 (0)	0 (0)	-
Cardiac death, n (%)	0 (0)	0 (0)	-
TLR, n (%)	0 (0)	0 (0)	-
TVR, n (%)	0 (0)	0 (0)	-
Post MI angina, n (%)	30 (10.7)	50 (17.6)	0.022
Hospitalization for HF, n (%)	41 (14.6)	66 (23.2)	0.010
12 months follow up	(n=262)	(n=276)	
Stroke, n (%)	0 (0)	0 (0)	-
MI, n (%)	0 (0)	0 (0)	-
Death, n (%)	0 (0)	0 (0)	-
Cardiac death, n (%)	3 (0.8)	5 (1.49)	0.725
TLR, n (%)	32 (11.4)	41 (14.4)	0.263
TVR, n (%)	32 (11.4)	41 (14.4)	0.263
Post MI angina, n (%)	47 (16.7)	78 (27.4)	0.002
Hospitalization for HF, n (%)	61 (21.7)	99 (34.8)	0.001

MI: myocardial infarction. TLR: target lesion revascularization. TVR: target vessel revascularization. MACE: major adverse cardiac events

Table 5: Secondary outcomes.

4. Discussion

In this prospective, randomized controlled, double-blinded study comparing ivabradine versus placebo in addition to beta-blocker after anterior wall STEMI, we report an important finding. Compared with placebo, the use of ivabradine in addition to bisoprolol was associated with better control of resting heart at 2, 4, and 6 weeks, and was further associated with a lower risk of hospitalization for unstable angina or heart failure at 6 and 12-month follow up. Normally, heart rate is determined by the rate of spontaneous diastolic depolarization in the SA node [10]. Spontaneous diastolic depolarization is influenced by a mixed sodium–potassium current (I_f) across f-channels. If channels are directly and selectively inhibited by ivabradine, which results in reduced diastolic depolarization rates and the slowing of heart rate [11-14]. The beneficial role of ivabradine in patients with stable CAD was inconsistent across multiple randomized controlled trials. The anti-ischemic effects of ivabradine were compared with atenolol in the INITIATIVE study [15]. After 16 weeks of treatment, patients receiving 7.5 mg twice daily of ivabradine and those receiving atenolol (100 mg/day) had comparable advantageous effects on the exercise time and the occurrence of angina attacks per week. In addition to ivabradine's non-inferiority in this study, data at 4 months of follow-up showed that all stress test variables, including time to limiting angina, time to angina onset and time to 1 mm ST-segment depression, were improved with ivabradine. Furthermore, Ivabradine was of value in patients with angina who had undergone coronary revascularization [16-18]. In a post hoc analysis from ADDITIONS [16] in 1193 patients with angina and history of PCI treated with ivabradine 5.0 mg or 7.5 mg twice daily for 4 months, the frequency of angina attacks was reduced from 1.9 ± 2.4 per week to 0.5 ± 1.5 per week and the

rate of nitrate utilization was reduced from 2.7 ± 3.7 per week to 1.0 ± 1.9 per week ($P < 0.0001$).

Lower resting heart rates was associated with improved outcomes after myocardial infarction. Despite that, the role of ivabradine in post-MI patients was even less studied, with some of the studies being on animal models [19]. A single-center study examined the role of ivabradine in patients with inferior wall STEMI and demonstrated its safety and efficacy when compared with metoprolol [8]. The current study is the first to challenge ivabradine vs placebo in addition to bisoprolol in patients with anterior wall STEMI and demonstrate the potential benefit of adding ivabradine in better controlling resting heart rate and lowering the risk of recurrent hospitalization for unstable angina or heart failure.

The role of beta-blocker therapy after MI cannot be underestimated, especially on the cardiac muscle performance, in addition to their mortality benefit. In patients where beta-blocker therapy is not enough to achieve target heart rates, ivabradine can play a beneficial role. It is important to note, however, that despite its role in reducing the risk of unstable angina and heart failure, that was not translated into a reduction in all-cause or cardiovascular mortality. Few explanations exist. First the sample size was relatively small, and the study was not powered to detect a difference in mortality. Second, the left ventricular systolic function, a major determinant of long-term mortality after STEMI, was comparable in both groups. Further studies are encouraged to examine the survival benefit of ivabradine in patients with anterior STEMI and heart failure.

We acknowledge some limitations in the current study. First, the majority of our patient population were of middle age, with single-vessel disease, and absence of

multiple comorbidities. This limits the extrapolation of our results to more elderly and sicker patients where aggressive heart rate control may be associated with side effects. Second, the mean left ventricular EF after STEMI was 40-50% range, which did not allow the study of ivabradine in patients with significant systolic dysfunction.

5. Conclusions

Ivabradine in addition to bisoprolol in anterior STEMI offers better control of heart rate with potential benefit in reducing risk of post MI angina and heart failure hospitalization. Studies including more diverse cohorts of patients with anterior STEMI are encouraged to confirm our results.

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