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The Efficacy of Oral Ivabradine in Acute Phase in Non ST-segment Elevation Myocardial Infarction (NSTEMI) Post PCI: A Pilot Study

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The Efficacy of Oral Ivabradine in Acute Phase in Non ST-segment Elevation Myocardial Infarction (NSTEMI) Post PCI: A Pilot Study

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Abstract

Background: An elevated heart rate is a major risk factor for cardiovascular mortality and morbidity. This study aims to evaluate the beneficial effect of heart rate reduction of oral ivabradine in patients presenting with non ST-segment elevation myocardial infarction (NSTEMI) during acute stage post percutaneous coronary intervention.

Results: A total of 100 patients admitted to the emergency department, National Heart Institute, Cairo, Egypt, were randomized into two groups as follows: Group A: 50 patients with NSTEMI treated with ivabradine (5 mg twice daily) in addition to the conventional treatment; Group B: 50 patients with NSTEMI treated with the conventional treatment only. Demographic data, detailed history, clinical examination, chest pain onset, blood pressure, heart rate (HR), temperature and respiratory rate, electrocardiogram (ECG) as well as echocardiography and laboratory investigations were recorded. Patients were monitored for a period of 3–5 days (acute stage).

There was a significant difference between both groups regarding reduction of heart rate on discharge in patients presenting with NSTEMI ($P < 0.05$). However, there was no significant differences in mortality, heart failure (HF), cardiogenic shock, arrhythmia and any mechanical complications in the acute stage.

Conclusion: Ivabradine significantly reduced heart rate in patients with NSTEMI without affecting blood pressure or hemodynamics; however, this did not show a significant impact on major adverse cardiac events (MACE) during short-term follow up in the Coronary Care Unit (CCU) ([Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04285736) NCT04285736).

Keywords: Ivabradine, Non-ST elevated myocardial, Infarction, Heart rate, Major adverse cardiac events

1. Introduction

Ivabradine is an agent that acts by suppressing the heart rate and is used for symptomatic relief. Ivabradine acts by inhibiting the *IF* channel. This is the funny current or pacemaker current channels in the sinoatrial (SA) node; *F* is for “funny” so called due to its unusual properties compared with other current systems. Ivabradine is free from other cardiovascular adverse effects such as negative inotropy and increased intra-atrial, atrioventricular, and intraventricular

conduction. Unlike β blockers, ivabradine has no effect on vascular demand [1–4]. However, it has a favorable influence on stroke volume and myocardial oxygen rate-reduction. Also, it does not affect cardiac output, has no influence on stroke volume and blood pressure, either at rest or during exercise. [1,3–5].

Ivabradine was approved by the European Medicines Agency [EMA] in 2005 [1]. It is used for the symptomatic treatment of stable angina pectoris in patients with normal sinus rhythm. It is used for those who have a contraindication or cannot tolerate β blockers. It has been shown to be non-inferior to

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the β blocker atenolol for this indication and amlodipine apart from angina. It is also being used off-label in the treatment of inappropriate sinus tachycardia [3]. It has been recommended in the 2016 ACC/AHA (American College of Cardiology/American Heart Association) guidelines for the management of heart failure to reduce HF hospitalization for patients with symptomatic (NYHA class II–III) stable chronic heart failure with reduced ejection fraction (HFrEF) (LVEF $\leq 35\%$) who are receiving GDEM (Guideline – Directed Evaluation and Management), including a β blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest [4,6–9].

Heart rate reduction is beneficial for ischemic cardiovascular events, so its reduction may improve atherosclerosis, decrease myocardial oxygen demand, decrease risk of plaque rupture and by prolonging diastolic time and enabling coronary vasodilation, it increases myocardial oxygen supply as well [1,3,4]. Also, heart rate reduction may reduce cardiovascular mortality and morbidity [10]. However, there are no sufficient studies in NSTEMI patients regarding the effect of heart rate reduction by ivabradine post PCI.

Therefore, our aim is to study the heart rate reduction effect of oral ivabradine in patients presenting with non-ST-segment elevation myocardial infarction (NSTEMI) during acute stage following percutaneous coronary intervention (PCI).

2. Materials and methods

2.1. Study design

This was an interventional randomized parallel study.

This study was performed in the National Heart Institute (NHI), (Cairo, Egypt), from December 2014 till May 2016 on 100 patients admitted to the emergency department of NHI with acute NSTEMI. An informed consent was signed by all patients upon admission after reading and clarification of the aim and any potential hazard of the study. The study protocol was approved by the Research Ethics Committee, Faculty of Pharmacy, Cairo University.

Approval number CL (1200). This study was performed according to the Declaration of Helsinki [11].

2.2. Patients

A total of 100 patients were recruited according to the following criteria: Patients with NSTEMI with normal sinus rhythm and heart rate (HR) more than 70 beats per minute (bpm) and systolic blood

pressure (SBP) > 90 mm Hg undergoing PCI were included. The patients were excluded if they needed urgent cardiac surgery, IV inotropic agents or had a HR less than 60 bpm without any medication. Patients with liver impairment and decompensated heart failure were not admitted to the department where the study was performed and thus were automatically excluded.

The patients were randomized by randomly assigning each patient a number from 1 to 100 and dividing into odd and even numbers. Fifty patients with even numbers received ivabradine and fifty patients with odd numbers did not receive ivabradine. The intervention group (Group A) was treated with ivabradine (5 mg twice daily) before PCI once the patient was admitted in addition to the conventional treatment. The control group (Group B) was treated with the conventional treatment only.

All Patients received the following conventional anti-ischemic measures according to guidelines: aspirin 150 mg once daily after meal, clopidogrel 75 mg once daily, atorvastatin 40 mg once after dinner. ACEI: captopril 25 mg adjusted according to blood pressure, β blocker: cardio-selective bisoprolol 5 mg dose adjusted according to blood pressure and heart rate and parenteral anticoagulant: enoxaparin 1 mg/kg twice daily, unless contraindicated and adjusted when necessary. Oral ranitidine was given as 150 mg twice daily or IV ranitidine three times a day and diluted with normal saline. Any additional medications needed for patient co-morbidities were administered, with ensuring that no drug-interactions occurred. Patients were monitored for a period of 3–5 days during their stay in the CCU unit (acute stage) for the following outcomes:

- Primary outcome: heart rate reduction, mortality, heart failure (HF, defined as EF $< 40\%$), cardiogenic shock, arrhythmia, any mechanical complication diagnosed by echocardiography (acute mitral regurge, ventricular septal rupture, ventricular wall rupture ventricular aneurysm and ventricular pseudoaneurysm).
- Secondary outcome: side effects of ivabradine.

The following baseline data were collected as well: demographic data, detailed history and clinical examination, risk factors, medication history, any possible drug interactions with ivabradine, onset of chest pain, ejection fraction [EF] on admission, troponin (TnI), creatine kinase [CK], and its isoenzyme MB [CK-MB], serum creatinine, creatinine clearance [CrCl], serum sodium, serum potassium, echocardiography [ECHO], electrocardiogram [ECG], alanine aminotransferase [ALT], aspartate

Table 1. Baseline demographic, clinical and laboratory data of patients. Data expressed as numbers (percentages) or mean $\pm$ standard deviation.

Patient characteristic	Group A (n = 50)	Group B (n = 50)	P value
Male (n, %)	40, (80)	37, (74)	P > 0.05*
Age (years)	59.50 $\pm$ 7.75	60.88 $\pm$ 8.71	P > 0.05#
BMI (kg/m)	24.23 $\pm$ 3.45	21.64 $\pm$ 2.50	P > 0.05#
Onset of chest pain before admission (hours)	9.62 $\pm$ 4.8	8.08 $\pm$ 4.94	P > 0.05#
Heart rate on admission (beats per minute)	84.16 $\pm$ 10.090	81.74 $\pm$ 9.514	P > 0.05#
Temperature ($^{\circ}$ C)	37.98 $\pm$ 6.45	36.68 $\pm$ 1.49	P > 0.05#
Respiratory rate (number per minute)	18.70 $\pm$ 1.92	19.12 $\pm$ 2.01	P > 0.05#
EF on admission (%)	58.12 $\pm$ 9.94	56.12 $\pm$ 10.77	P > 0.05#
Positive Troponin (n, %)	50 (100)	50 (100)	
CK-MB (mcg/L)	65.48 $\pm$ 25.52	71.200 $\pm$ 30.95	P > 0.05#
Total CK (mcg/L)	319.22 $\pm$ 167.49	714.64 $\pm$ 702.64	P > 0.05#
Serum creatinine (mg/dL)	1.12 $\pm$ 0.32	0.95 $\pm$ 0.14	P > 0.05#
CrCl (mL/min)	84.32 $\pm$ 7.26	85.18 $\pm$ 7.63	P > 0.05#
AST (IU/L)	34.18 $\pm$ 10.71	38.12 $\pm$ 17.6	P > 0.05#
ALT (IU/L)	41.82 $\pm$ 14.07	44.20 $\pm$ 24.25	P > 0.05#
Sodium (mEq/L)	138.20 $\pm$ 5.44	139.90 $\pm$ 4.60	P > 0.05#
Potassium (mEq/L)	3.97 $\pm$ 0.44	3.95 $\pm$ 0.30	P > 0.05#
Hemoglobin (gm/dL)	11.27 $\pm$ 1.92	12.05 $\pm$ 1.79	P > 0.05#
WBC (cells per cubic millimeter)	9930 $\pm$ 2.74	10 240 $\pm$ 2.70	P > 0.05#
Platelets (cells per microliter)	244 580 $\pm$ 81.13	228 520 $\pm$ 33.56	P > 0.05#
Smoking (n, %)	21, (42)	27, (54)	P > 0.05*
Hypertension ^a (n, %)	30, (60)	25, (50)	P > 0.05*
Diabetes Mellitus (DM) ^b (n, %)	18, (36)	26, (52)	P > 0.05*
Previous IHD (n, %)	21, (42)	21, (42)	P > 0.05*
Stroke (n, %)	3, (6)	3, (6)	P > 0.05*
Family history of CAD (n, %)	17, (34)	10, (20)	P > 0.05*
Antidiabetics	18	26	P > 0.05*
Anti-arrhythmics	0	3	P > 0.05*
Antibiotics	4	4	P > 0.05*
Diuretics	4	5	P > 0.05*
Acetylcysteine	1	2	P > 0.05*
Potassium Chloride	1	3	P > 0.05*
Nitrates	5	5	P > 0.05*

BMI, body mass index; HR, heart rate; EF, Ejection Fraction; SBP, systolic blood pressure; DPB, diastolic blood pressure; CK-MB, Creatine kinase-MB; CK, Creatine kinase; CrCl, Creatinine clearance; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TLC, Total Leucocyte Count; IHD, ischemic heart disease; CAD, coronary artery disease.

P < 0.05 = significant, P > 0.05 = non-significant, * Chi square test, # independent *t*-test.

^a Hypertension defined as blood pressure above 140/90 mmHg [12].

^b Diabetes mellitus defined as random plasma glucose $\geq$ 11.1 mmol/l (200 mg/dl) [13].

aminotransferase [AST], white blood cell [WBC], red blood cell [RBC], hemoglobin [Hb] and platelet counts [PLT]. HR was measured every 2 h daily and ECG was done every 8 h daily. Echocardiography was done upon admission and discharge.

A checklist of ivabradine side effects was translated into Arabic (allergy, bradycardia, AV block, visual disturbance, headache, GIT disturbance, breathing difficulties, cold symptoms, confusion and depression) to check whether the patients suffered from any side effects. It was filled during discharge by the attending physician or the investigator.

2.3. Statistical analysis

Statistical analysis was performed using Statistical Packages of Social Science (SPSS 17.0)

software. Continuous variables were expressed as mean $\pm$ standard deviation and compared using unpaired *t*-test. Categorical variables were reported as frequency (percentages) and compared by Chi square test. Paired *t*-test was used to compare between heart rate at admission and discharge in group A. Statistical significance was defined as P < 0.05.

3. Results

There were no significant differences between the two groups in demographic characteristics, baseline laboratory data as well as comorbidities, and medications administered upon admission (Table 1). The average stay in the CCU for patients in both groups was 4 days (range 3–5 days).

Table 2. Primary and secondary outcomes. Data expressed as number of patients (percentages) or mean $\pm$ standard deviation.

Outcome	Group A (n = 50)	Group B (n = 50)	P-value
HR on discharge (beats per minute)	70.58 $\pm$ 9.41	78.7806 $\pm$ 13.8	0.001 [#]
ST segment depression on admission	40 (80)	28 (76)	P > 0.05*
ST segment depression on discharge	36 (72)	33(66)	P > 0.05*
Inverted T wave on Discharge	19 (38)	14 (28)	P > 0.05*
Heart failure (HF)	2 (4)	2 (4)	P > 0.05*
Arrhythmia	0 (0)	1 (2)	P > 0.05*
Cardiogenic shock	2 (4)	1 (2)	P > 0.05*
Mechanical complication	1 (6)	2 (0)	P > 0.05*
Wall motion abnormality	23 (46)	21 (42)	P > 0.05*
Mortality rate	1 (2)	0 (0)	P > 0.05*

P < 0.05 = significant, P > 0.05 = non-significant, * Chi Square test, # independent *t*-test.

HR on discharge: Heart rate; HF: Heart failure; HF:Ejection fraction less than 40% which is determined routinely by echocardiography.

Table 2 compares HR on discharge, incidence of abnormal ECG, presence of depressed ST segment and inverted T wave in both groups. HR was significantly lower in the ivabradine group upon discharge. Ivabradine was associated with significant reduction of heart rate from admission to discharge as well (P < 0.05). For patients not taking ivabradine there was no significant difference from admission to discharge (P = 0.23). Tachycardia defined as heart rate greater than 100 beats per minute was noted in 3 patients in each group at baseline. At the end of the study only 1 patient in group 1 had tachycardia and 2 patients in group 2. (P = 0.56)

All patients were troponin positive with abnormal ECG on admission and discharge. Eighty percent showed ST depression on admission and 72% showed ST depression on discharge. Also, 58% showed inverted T wave on discharge. Comparison of cardiac adverse events showed an incidence of 4% with HF in each group, 2% arrhythmia, in group B, 4% cardiogenic shock in group A and 2% in group B, 6% mechanical complications, and 2% mortality rate (one patient in group A) during the study period with no significant difference between the two groups (Table 2).

Ivabradine side effects occurred in only 9 patients (18%). Two patients suffered from bradycardia (HR < 60 bpm), two complained of visual disturbances, two complained of breathing difficulties and one complained of headache.

4. Discussion

Ivabradine is studied extensively worldwide in clinical studies and the outcomes of these studies will define the real role of pure heart-rate control in cardiovascular medicine [3,4].

To the best of our knowledge this is the first study to evaluate the efficacy of oral ivabradine as an add-on to the background therapy in patients presenting with non ST-segment elevation myocardial infarction (NSTEMI) following percutaneous coronary intervention (PCI) during the acute stage.

There was a significant difference between both groups regarding reduction of heart rate on discharge in patients presenting with NSTEMI (P < 0.05), as well as significant reduction of heart rate from admission to discharge (P < 0.05). Heart rate reduction has become an essential therapeutic strategy as shown in international guidelines [14–16]. This may improve oxygen consumption and reduce myocardial perfusion time in the ischemic heart. Therefore, heart rate control decreases risk of adverse cardiac events, mortality, hospitalization for myocardial infarction, and heart failure [1,3]. It is also known that elevated heart rate is an important determinant of myocardial ischemia and is an established risk factor in cardiovascular disease [1,3].

When IV ivabradine was studied in the acute phase post PCI in STEMI patients (VIVIFY trial) (The eValuation of the IntraVenous If inhibitor ivabradine after ST-segment elevation myocardial infarction trial) [17] heart rate was reduced over 8 h, with a faster and more marked decrease with ivabradine versus placebo. However, heart rate was similar in both groups after treatment discontinuation. There was no difference in cardiac biomarkers as well (creatinine kinase (CK-MB), troponin T and troponin I). Even though left ventricular ejection fraction was similar in both groups, left ventricular end-diastolic volume and left ventricular end-systolic volume were lower in the ivabradine group.

The efficacy of ivabradine in two different populations was studied; BEAUTIFUL (morbidity-mortality Evaluation of the If inhibitor ivabradine in

patients with coronary disease and left-ventricular dysfunction) [6,18] in 10917 patient for a period of 19 months and the Systolic Heart failure treatment with the If inhibitor ivabradine Trial (SHIFT) [4] in 6505 patients with left ventricular ejection fraction of 35% or lower for 12–48 months. In the BEAUTIFUL trial [6,18], heart rate reduction was significant however, no significant reduction of the primary composite end point of cardiovascular death, admission to hospital for acute MI and admission to hospital for heart failure or cardiac death was reported overall. However, a subgroup analysis of patients in the same trial showed reduced risk [6]. In the SHIFT trial [4] ivabradine was shown to significantly reduce heart rate and major adverse cardiac events as well.

In our study, there was no significant statistical difference between both groups regarding the development of total major adverse cardiac events in the CCU. The possible explanation for this difference in results is differences in the underlying diseases in response to reduction of HR as this may reduce some adverse outcomes markedly in patients with CAD as in BEAUTIFUL or in patients with HF as in SHIFT trial more than in patients with NSTEMI. In addition, both trials studied a large number of patients for a minimum of 12 months whereas our study followed up a small number of NSTEMI patients in the acute stage only post PCI.

5. Conclusion

Ivabradine in addition to standard therapy, significantly reduces heart rate in patients with NSTEMI after PCI. However, this did not show a significant impact on major adverse cardiac events (MACE) during follow up from CCU admission to discharge. Therefore, ivabradine is recommended to be added to anti-ischemic measures in case of in case of ACS or when uptitration of β -blocker is not possible.

Study limitations

Sample size was small as well as duration of the study was limited. Questionnaire was restricted to side effects upon discharge. Not all patients were capable of giving proper medication history prior to admission.

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References

- [1] Deedwania P. Selective and specific inhibition of if with ivabradine for the treatment of coronary artery disease or heart failure. *Drugs* 2013;73(14):1569–86.
- [2] Rudd N, Subiakto I, Asrar M, Mutha V, Van Gaal WJ. Use of ivabradine and atorvastatin in emergent orthopedic lower limb surgery and computed tomography coronary plaque imaging and novel biomarkers of cardiovascular stress and lipid metabolism for the study and prevention of perioperative myocardial infarct. *Trials* 2014;15:352.
- [3] Scicchitano P, Cortese F, Ricci G, Moncelli M, Iacoviello M, Zito A, et al. Ivabradine, coronary artery disease, and heart failure: beyond rhythm control. *Drug Des Dev Ther* 2014; 689–700.
- [4] Tavazzi L, Borer JS, Swedberg K, Böhm M, Ford I, Komajda M. Rationale and design of a randomized, double-blind, placebo-controlled outcome trial of ivabradine in chronic heart failure: the Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial (SHIFT). *Eur J Heart Fail* 2009;12(1):75–81.
- [5] Marquis-Gravel G, Tardif Ivabradine JC. The evidence of its therapeutic impact in angina. *Core Evid* 2008;3(1):1–12.
- [6] Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R. Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized, controlled BEAUTIFUL trial. *Eur Heart J* 2009;30(19):2337–45.
- [7] Fox K, Komajda M, Ford I, Robertson M, Bo M, Borer JS, et al. Effect of ivabradine in patients with left-ventricular systolic dysfunction: a pooled analysis of individual patient data from the BEAUTIFUL and SHIFT trials. *Eur Heart J* 2013;34:2263–70.
- [8] Kim Y, Boucher M, Argáez C, Issues C. Emerging IN. I funny channel inhibitors: an emerging option for heart failure. *CADTH* 2017;151:1–14.
- [9] Jessup M, Bozkurt B, Butler J, Casey DE, Masoudi FA, Colvin MM, et al. Correction to: 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the (2013) ACC/AHA guideline for the management of heart failure: a report of the ACC foundation/AHA. *Circulation* 2016;134(13):e282–93.
- [10] Fasullo S, Cannizzaro S, Maringhini G, Ganci F, Giambanco F, Vitale G, et al. Comparison of ivabradine versus metoprolol in early phases of reperfused anterior myocardial infarction with impaired left ventricular function: preliminary findings [Internet] *J Card Fail* 2009;15(10):856–63. <https://doi.org/10.1016/j.cardfail.2009.05.013>. Available from: .
- [11] World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *J Am Med Assoc* 2013;310(20):2191–4. 27.
- [12] Williams B, Mancia G, Spiering W, Rosei EA, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension the task force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). *Eur Heart J* 2018;39:3021–104.
- [13] Kerner W, Brückel J. Definition, classification and diagnosis of diabetes mellitus. *Exp Clin Endocrinol Diabetes* 2014; 122(7):384–6.
- [14] Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease. *Circulation* 2012;126(25): 3097–137.
- [15] Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;34(38): 2949–3003.

- [16] Voors AA, Seferovic P, Kolh P, Orn S, Avraamides P, Jaarsma T, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure (2012): the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the heart failure association (HFA) of the ESC. *Eur Heart J* 2012;33(14): 1787–847.
- [17] Steg PG, Lopez-de-Sà E, Schiele F, Hamon M, Meinertz T, Goicolea J, et al. Safety of intravenous ivabradine in acute ST-segment elevation myocardial infarction patients treated with primary percutaneous coronary intervention: a randomized, placebo-controlled, double-blind, pilot study, the European Society of Cardiology. *Eur Heart J: Acute Cardiovasc Care* 2013;2(3):270–9.
- [18] Fox K, Ford I, Steg PG, Tendera M, Ferrari R, Investigators B, et al. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;372:807–16.