IJPSR (2016), Vol. 7, Issue 4 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 25 October, 2015; received in revised form, 03 December, 2015; accepted, 22 January, 2016; published 01 April, 2016

A CLINICAL STUDY EVALUATING THE EFFECT OF IVABRADINE ON INFLAMMATION IN PATIENTS WITH NON ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROMES

M. Adel *, S. Mansour, N. A. Sabri, O. A. Badary and M. Ayman Saleh

Department of Clinical Pharmacy, Faculty of Pharmacy, Ain Shams University, Egypt.

Key words:

Ivabradine – Heart Rate – High Sensitivity C-Reactive Protein -Acute Coronary Syndromes – Atherosclerosis

Correspondence to Author:
M. Adel

Department of Clinical Pharmacy, Faculty of Pharmacy, Ain Shams University, Egypt

E-mail: adoula_2002@yahoo.com

ABSTRACT: There is a strong association between elevated heart rate (HR), systemic inflammation and atherosclerosis. We assumed that HR lowering by ivabradine might decrease inflammation in patients with non ST-segment elevation acute coronary syndromes (NSTE-ACS). Objective: Study the effects of ivabradine add on treatment on High sensitivity C-reactive protein (hsCRP) levels in patients with NSTE-ACS. **Methods:** This prospective, randomized, controlled, study recruited NSTE-ACS patients with HR ≥70beats per minutes. Each patient was randomly assigned to either control or ivabradine groups. The difference between the two groups was the addition of ivabradine (up to 7.5 mg bid) to the standard treatment of NSTE-ACS patients for 30 days in the ivabradine group. Levels of hsCRP were evaluated before and after the study period. The primary outcome was the difference between the two groups inhsCRP reduction. **Results:** We enrolled 45 patients, twenty three of which received ivabradine. The decrease (%) in HR after treatment was significantly larger inivabradine group than in control group (23.8 (7.3 – 31) vs 4.7 (0 - 22.5) %, p = 0.014). The decrease in HR was positively correlated to hsCRP reduction, r = 0.445, p = 0.003. No significant difference between ivabradine and control groups in hsCRP reduction (80 (38 - 90.6) vs 61.3 (24 - 76.4) %, P = 0.057). Ivabradine was well-tolerated. **Conclusion:** Ivabradine effectively and safely decreased HR in NSTE-ACS patients. Reduction in HR was associated with hsCRP reduction. Larger studies are required to better demonstrate the anti-inflammatory effects of ivabradine in ACS.

INTRODUCTION: The principal cause of acute coronary syndromes (ACS) in more than 90% of patients is the rupture of an atheromatous plaque. Endothelial dysfunction, inflammation, and the formation of fatty streaks are the core contributors to atherosclerotic plaquesformation.[1]

Heart rate is an independent risk predictor of the onset of acute coronary events. Many epidemiological and clinical studies aimed to explore the association between resting HR and outcomes in healthy and cardiovascular disease patients.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.7(4).1441-49

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.7 (4).1441-49

Elevated resting HR multiplies risk and interferes at all phases of the cardiovascular disease spectrum, initiating from endothelial dysfunction and passing through atherosclerotic lesion formation and plaque rupture to end-stage cardiovascular disease.[2]

In animal studies, sustained elevation of HR was associated with vascular oxidative stress, endothelial dysfunction, acceleration of atherogenesis, and vascular stiffness. Experimental data also suggested that a reduction in HR can delay the progression of coronary atherosclerosis. [3]

Clinical studies revealed a relation between accelerated resting HR, systemic inflammation and markers of endothelial dysfunction.[4, 5] Perski et al., have found a strong positive relationship between higher HR and the extent of atherosclerotic coronary lesions in young patients with myocardial

infarction. [6] A higher HR may itself directly induce an inflammatory response through an increased frequency of mechanical stress on the vascular endothelium.[7]

Ivabradine, an I(f) current inhibitor, induces a sustained and dose-dependent HR reduction at rest and during exercise, with no relevant effects on contractility, blood pressure or atrioventricular conduction. Treatment with ivabradine reduced vascular oxidative stress and inflammation, restored endothelial function, and augmented vascular compliance in ApoE deficientmice.[2]

The anti-anginal and anti-ischemic efficacy of ivabradine–in monotherapy or in combination with a β-blocker–has been demonstrated by several clinical trials. [8-10] As a consequence, the substance evolved as an alternative strategy particularly for patients in whom the use of β-blockers is contraindicated, intolerable or patients who remain symptomatic despite β -blockade.

In Europe, It is approved and indicated for the symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm who cannot take β-blockers. It is also indicated in combination with β-blockers in heart failure patients with left ventricular dysfunction inadequately controlled by β-blockers alone and whose HR exceeds 70 beats per minute. In the United States, Food and Drug Administration approved Ivabradine use only in heart failure. [11, 12]

C-reactive protein (CRP) is a sensitive marker of inflammation. Increased levels of high-sensitivity C-reactive protein (hsCRP) are associated with endothelial dysfunction; reflect subclinical inflammatory states such as vascular inflammation, and predict future cardiovascular risk.[3, 13]

Three population-based studies reported a positive correlation between increased resting HR and markers of inflammation (C-reactive protein, IL-6, white blood cell count, and fibrinogen) in apparently healthy subjects.[14-16]

In patients with ACS, higher hsCRP levels are associated with adverse outcomes and subsequent vascular events. [17] Clinical studies showed that the achieved level of hsCRP after ACS treatment is an independent predictor of consequent outcomes. Accordingly additional interventions aiming at lowering CRP in post-ACS may provide additive benefit in this high-risk subgroup of patients.[18]

Since increased HR may contribute to endothelial dysfunction by up-regulation of inflammatory cytokines, we expect that HR lowering by ivabradine will decrease inflammation in patients with ACS. The primary purpose of this study is to examine the effect of HR lowering by ivabradine on hsCRP levels in patients with NSTE-ACS.

MATERIALS AND METHODS:

The current study is a prospective, randomized, controlled, study. It was carried out in the Cardiology Intensive Care Unit, Department of Cardiology, Ain Shams University Hospitals, Cairo, Egypt. The study protocol was revised and approved by the Institutional Human Research Committee as it conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 2002. Patients signed informed consent forms authorizing the participation in the study.

The included patients were above 18 years, presenting with typical ischemic chest pain occurring at rest or with minimal effort (>10 min) with at least one of the following: (a) ECG changes revealing new ischemia (ST depression of at least 1 mm or transient ST elevation or ST elevation of <1mm or T wave inversion >3mm in at least 2 contiguous leads; or (b) Elevated cardiac enzymes (e.g., CK-MB) or biomarkers (troponin I or T) above the upper limit of normal. Patients were in sinus rhythm with a resting HR of ≥ 70 beats per minute on a resting standard 12-lead ECG. The included patients were admitted to the unit within 12 hours of symptom onset.

Patients were excluded if there was a history of myocardial infarction, coronary revascularization, stroke, or transient ischemic attack within the preceding 3 months. Patients with implanted pacemaker or implantable cardioverter defibrillator, sick sinus syndrome, sinoatrial block, congenital long QT, 2nd degree and complete atrioventricular block were not enrolled in the study. Also those requiring or likely to require macrolide antibiotics,

cyclosporin, gestodene, antiretroviral drugs or azole antifungals were not eligible. We excluded patients with untreated endocrine diseases and those with systemic or cardiac inflammatory processes with the exception of atherosclerosis. Patients with severe renal or liver diseases were not included.

A total of 45 consecutive NSTE-ACS patients were recruited from September 2013 to October 2014. Each was randomly assigned to either the ivabradine(23 patients) or the control (22 patients) group. All patients received the conventional cardiovascular treatment including: β-blockers, nitrates, statins, antiplatelet drugs, and antithrombin therapy according to the European Society of Cardiology (ESC) Guidelines for the management of ACS. [19] All patients received atorvastatin 40 mg daily for the 30 days. The treating clinicians were given recommendations for starting a suitable β-blocker dose while patients were hospitalized and for keeping the dose constant until the end of the study.Bisoprolol2.5, 5, 10 (Concor®/ Concor®cor, Merck Serono, Darmstadt, Germany) was the β-blocker used in this study. Angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) were given to all patients. Arterial blood pressure was adjusted depending on ACE-I or ARB.

Patients in the ivabradine group received ivabradine (Procoralan®, Les Laboratoires Servier Industrie - France) 5mg twice daily [20] starting from day two after admission and during 30 days plus the previously mentioned medications required for the management of ACS. Patients were advised to take the ivabradine tablet once in the morning and once in the evening during meals. [20] Patients who received 5 mg twice daily for a week after inclusion with a resting HR of $\geq$ 70 beats per minute had their dose increased to 7.5 mg twice daily till the end of 30 days.

After obtaining the informed consent, baseline evaluation included demographics and history taking was performed. Information comprising age, weight, height, smoking state was reported. Concurrent diseases including hypertension, diabetes, dyslipidemias, coronary artery disease (CAD), previous stroke, myocardial infarction, peripheral vascular disease were documented for each patient. Data including left ventricular ejection fraction (LVEF), number of diseased coronary arteries (DCA) and if PCI was performed, were collected from patients' files. All medications received by the patients were recorded.

Thorough clinical examination was done for every patient with assessment of HR, blood pressure, and standard 12-lead ECG and echocardiogram. The GRACE score was calculated on admission and discharge to estimate the in-hospital and 6-months outcomes.

Blood samples were withdrawn from patients for evaluation of hsCRP by ELISA technique kit known as Hs C-Reactive Protein Enzyme Immunoassay (hsCRP ELISA), DRG International Inc., USA. Evaluation of serumhs CRP was doneonce within 24-48hours of symptom onset. Fasting total cholesterol, LDL and HDL cholesterol were estimated by enzymatic colorimetric assays, Human Gesellschaftfür Biomedica und Diagnosticamb H, Germany. The fasting blood lipids were assessed within 24 hours of symptom onset. Blood samples were stored at -20 till analysis. Complete blood count, liver and renal function tests were performed as part of the routine admission care.

All patients were followed up for 30 days. Follow-up visits were scheduled to see each patient once per week and on day 30. Each follow up visit included assessment of ischemic events, of recent medical history since the last follow-up appointment, recording the occurrence of major adverse cardiovascular events (MACE: death, nonfatal myocardial infarction, unstable angina, urgent revascularization, stroke, hospitalization for HF, arrhythmias, or cardiac arrest), documentation of concomitant medications and records of adverse drug effects.

Medical examination including determination of HR and a standard 12-lead ECG was carried out. Evaluation of compliance with study medication by pill count was obtained at all study visits. The 30-day visit included as well laboratory reassessment of hsCRP, fasting blood lipids, creatinine, and ALT.

Statistical methods:

Data management and analysis were performed using Statistical Package for Social Sciences (SPSS) vs. 22. Numerical data were summarized using means and standard deviations or medians and 25 – 75% interquartile ranges. Categorical data were summarized as percentages. Data were explored for normality using Kolmogrov-Smirnov test and Shapiro-Wilk test. Exploration of data revealed that the collected values were not normally distributed. Comparisons between the groups were done by Mann-Whitney test. Chi-square or Fisher's exact tests was used to compare between the groups with respect to categorical data. To measure the strength of association between the measurements, Spearman's correlation coefficients (r) were calculated. All p-values are two-sided. P-values < 0.05 were considered significant. The change after treatment as percentage (%change) is calculated as follows:

% change = (baseline value – end value)/baseline*100

RESULTS: Median age of the study cohort was 56 years and the range was 37-80 years; 29 (64.4%) were males. Patients of both ivabradine and control groups were similar in their calculated GRACE risk score. Baseline characteristics and clinical measurements of the study patients are represented in **Table 1**. No statistical significant difference was observed between the control and the ivabradine groups at baseline except in the platelets count, 276 (217 - 317) vs. 223 (185 - 274), *p*=0.040. However the platelets counts for all patients were within the normal range (normal: 150 - 450x 10^3/cc).

TABLE 1: BASELINE CHARACTERISTICS AND MEASUREMENTS OF THE STUDY GROUPS

Variable	Group		*p*-value
	Control (n=22)	Ivabradine (n=23)	
Age, years	60.5 (52.8 - 65.3)	54 (50 - 58)	0.060
BMI, Kg/m^2	31.1 (27.8 - 34.6)	30 (28 - 35)	0.649
Male	12 (54.5)	17 (73.9)	0.175
Current smokers	7 (31.8)	9 (39.1)	0.608
GRACE score at admission	137.5 (126 -146.5)	136 (117 - 154)	0.937
GRACE score at discharge	106 (97 - 116)	103 (92 - 120)	0.541
Elevated troponin levels	16 (72.7)	17 (73.9)	0.928
Number of DCA			
1 artery	5 (23.8)	5 (23.8)	1.000
2 arteries	7 (33.3)	7 (33.3)	
3 arteries	9 (42.9)	9 (42.9)	
PCI	13 (59.1)	9 (39.1)	0.181
LVEF, %	55 (45 - 65.5)	52(35.6 - 63)	0.203
HR on admission, bpm	80 (70 - 90)	82 (75 – 100)	0.105
Hemoglobin, gm/dL	13.5 (12.6 - 14)	14 (12.7 - 14.7)	0.140
Leucocyte count x 10^3/cc	9.3 (6.6 - 11.9)	8.7 (7.3 - 11.4)	0.547
Platelet count x 10^3/cc	276 (217 - 317)	223 (185 - 274)	0.040*

Data are expressed as median and range (25th and 75th percentiles) for continuous variables, and number of patients (%) for categorical variables.* *p*-value< 0.05: significant. BMI: body mass index; bpm: beats per minute; DCA: diseased coronary arteries; GRACE: Global Registry of Acute Cardiac Events; HR: heart rate; LVEF: left ventricular ejection fraction; n: number of patients; PCI: percutaneous coronary interventions; % change: the percent of change occurred by treatment.

Regarding medical history of the study patients, the two groups were statistically similar in the concomitant diseases, no difference in hypertension, diabetes, dyslipidemias or previous myocardial infarction, **Table 2**.

Also - not illustrated - one patient in each group had previous stroke, and one also in each group had peripheral vascular disease. The two groups were not different also in the percentage of patients who were receiving antiplatelets, β-blockers or ACE-I before admission, refer to **Table 2**.

TABLE 2: MEDICAL HISTORY AND MEDICATIONS OF PATIENTS ACCORDING TO TREATMENT GROUP

Variable	Group		*p*-value
	Control (n=22)	Ivabradine (n=23)	
Medical history			
Hypertension	13 (59.1)	13 (56.5)	0.862
Hypercholesterolemia	4 (18.2)	10 (43.5)	0.067
Diabetes Mellitus	12 (54.5)	16 (69.5)	0.299
Previous MI	4 (18.2)	10 (43.5)	0.067
Medications on admission			
Antiplatelets	16 (72.7)	17 (73.9)	0.928
β-blockers	10 (45.5)	6 (26.1)	0.175
ACE-inhibitors	7 (31.8)	9 (39.1)	0.608

Data are expressed as number of patients (%) for categorical variables. *p*-value >0.05: non-significant. ACE-I: Angiotensin converting enzyme inhibitors; MI: myocardial infarction; n: number of patients.

The 45 patients were compliant to the prescribed medications during the study, medians and 25-75% interquartile range of the β-blocker dose at discharge was 5 (2.5-5) in the ivabradine group and 2.5 (2.5-5) in the control group, p = 0.374. The β-blocker dose was increased in only one patient of the ivabradine group and it was mandatory to be increased in 4 patients in the control group during the study due to their elevated heart rate.

With regard to ACE-I/ARB prescribed on discharge, two patients in the ivabradine group and one in the control group received ARB. The rest of the patients, 11 (47.8%) of the ivabradine group received enalapril as an ACE-I and 11 (52.4%) of the control group received the same ACE-I, enalapril. Four patients (17.4%) in the ivabradine group and 4 (18.2%) in the control group were prescribed ramipril. Six patients (26.1%) and 5 patients (23.8%) were administered captopril in the ivabradine and the control groups respectively. Any change during the study was to adjust for arterial blood pressure.

On admission, HR did not differ between the two groups, p = 0.105, however by treatment, the percent decrease in HR was significantly larger in the ivabradine group, p = 0.040, this is illustrated in **Table 3**.

Table 4 shows the biochemistry of patients according to the treatment groups. Initially, no significant difference was encountered between the study groups except in ALT, and all our patients' ALT initial levels were not abnormally elevated, also at the end of the study, patients of both groups didn't differ significantly in their ALT levels. The two groups were similar with regard to the changes in biochemical parameters after the treatment period. The difference between control and ivabradine groups in hsCRP-% did not reach a statistical significance, P = 0.057.

TABLE 3: CHANGE IN HR AFTER TREATMENT

Variable	Group		*p*-value
	Control (n=22)	Ivabradine (n=23)	
HR on admission, bpm	80 (70 - 90)	82 (75 – 100)	0.105
HR at 30 days, bpm	70 (61 - 77.5)	65 (60 - 73)	0.294
HR-% change#	4.7 (0 - 22.5)	23.8 (7.3 – 31)	0.040*

Data are expressed as median and range (25th and 75th percentiles) for continuous variables,* *p*-value < 0.05: significant. HR: heart rate; n: number of patients; % change: the percent of change occurred by treatment; #: n=21 for the control.

TABLE 4: BIOCHEMICAL MEASUREMENTS OF THE TWO STUDY GROUPS

Variable		Group		*p*-value
		Control (n=22)	Ivabradine (n=23)	
Total cholesterol, mg/dL	at baseline	162 (149 - 181)	175 (146 - 235)	0.334
	at day 30	140 (120 - 177)	146 (116 - 177)	0.769
	% change#	11.1 (5.2 - 24.3)	15.2 (9.4 - 24.3)	0.431
LDL cholesterol, mg/dL	at baseline	94.5 (66 - 118)	115 (80 - 138)	0.134
	at day 30	67 (50 - 103.5)	88 (59 - 114)	0.318
	% change#	14.8 (2.6 - 44.4)	20.7 (9 - 29.4)	0.613
HDL cholesterol, mg/dL	at baseline	38 (36 - 40)	38 (37 - 40)	0.854
	at day 30	40 (38 - 42)	39 (38 - 40)	0.128
	% change#	-2.6 (-5.5 - 0)	-5.1 (-8.1 - 0)	0.152
Creatinine, mg/dL	at baseline	0.84 (0.7 - 1.1)	1 (0.9 - 1.3)	0.124
	at day 30	0.8 (0.6 - 0.95)	0.9 (0.8 - 1.1)	0.264
	% change#	9 (0 - 26)	11.1 (0 - 25)	0.962
ALT, U/L	at baseline	20 (14 - 31.5)	32 (17 - 46)	0.018*
	at day 30	19 (14 - 34)	23 (13 - 41)	0.458
	% change#	-10 (-52 - 9.8)	22.7 (-29 - 51)	0.084
hsCRP, mg/L	at baseline	29 (16.5 - 40)	39 (21 - 85)	0.095
	at day 30	9 (5.5 - 20.5)	11 (4 - 18)	0.605
	% change#	61.3 (24 - 76.4)	80 (38 - 90.6)	0.057

Data are expressed as median and range (25th and 75th percentiles) for continuous variables, and number of patients (%) for categorical variables. #: n=21 for the control. * *p*-value< 0.05: significant.ALT: alanine transaminase; HDL: high density lipoprotein; hsCRP: high sensitivity C-reactive protein; LDL: low density lipoprotein; % change: the percent of change occurred by treatment.

Of importance, when Spearman's correlation coefficient (r) was calculated, a positive correlation was found between HR-% change and hsCRP-% change, r = 0.445, *p*=0.003 and this is for the total number of our patients.

A total of 9 patients (40%) developed MACE in the control group (1 death and 8 other ischemic events) compared to four patients (17%) in the ivabradine group; this difference did not reach significance, p = 0.082.

What noteworthy is the difference between the HR means of all patients who developed MACE and those who did not. This difference was statistically significant both on admission, p = 0.012 and at the end of the study period, p = 0.046, as illustrated in **Table 5**.

Only one patient in the ivabradine group complained from blurred vision which subsided when the dose was decreased from 7.5 mg bid to 5 mg bid, no visual disturbances were observed in the control group. None of our 45 patients suffered from serious adverse drug outcomes, nor had any one stopped the treatment during the study period.

Table 5: Difference between HR of patients with and without MACE

Variable	MACE		*p*-value
	No (n=32)	Yes (n=13)	
HR on admission, bpm mean ± SD	79.6 ± 13.4	93.1 ± 16.9	0.012*
HR at day 30, bpm mean ± SD	66.3 ± 9.3	73.2 ± 9.0	0.046*

bpm: beats per minute; HR: heart rate; SD: standard deviation. * *p*-value< 0.05: significant.

DISCUSSION: Experimental and clinical data suggest that increased HR may contribute to endothelial dysfunction by up-regulation of inflammatory cytokines.[3]

The main aim of this study was to examine whether HR lowering by ivabradine decreased inflammation (hsCRP levels) when added to the standard guideline based treatment of NSTE-ACS patients. Ivabradine significantly decreased HR in ACS patients when compared to control. A positive correlation was found between the decrease in HR and the decrease in hsCRP levels after 30 days of treatment.

It is now evident from large clinical trialsin CAD that Ivabradine alone or when combined with β-blockers is efficacious in reducing resting HR.[8-10, 21] The reduction is dose dependent and the maximal effect is achieved after 2-4 weeks of therapy. [22] At the end of our study, the percent decrease from baseline HR was significantly higher in the ivabradine group when compared to control.

The positive correlation appeared between the decrease in HR and hsCRP levels after the treatment periodin the current study is in harmony with studies reporting a positive association between resting HR and markers of inflammation.[14-16]

After the reduction in HR, we expected a significant reduction in hsCRP levels with ivabradine, only a trend toward a larger reduction in hsCRP levels was seen in the ivabradine group when compared to control. The lack of statistical significance may be attributed to the small number of patients in this study. However this trend together with the association between HR and hsCRP reduction encourages the suggestion that pure HR lowering in CAD may render atherosclerosis and accordingly leads to lessening of cardiovascular morbidity and mortality.

The aforementioned findings gain support from experimental trials suggesting a role of ivabradine in the reduction of atherosclerosis in ACS patients. In apolipoprotein E deficient mice, cholesterol-induced atherosclerosis was inhibited by HR reduction with ivabradine. [23] Ivabradine also significantly reducedvascular oxidative stress, oxidase activity of nicotinamide adenine dinucleotide phosphate, superoxide production, and lipid peroxidation. Ivabradine also prevented atherogenesis when given concurrently with a high-cholesterol diet, it was effective as well in reducing plaques size in animals after 4 weeks of administration of a highcholesteroldiet [24] Higher HR might lead to endothelial dysfunction increased oxidative stress, and enhanced plaque formation through mechanical burden on the vessel wall, this can be reversed or prevented by ivabradine. [25]

Schirmer et al. showed that ivabradine modulates both systemic and local inflammatory cytokine expression, in an experimental model of hind limb ischemia.[26]

Till now, the only published clinical study examining the effect of ivabradine on inflammation is a placebo controlled pilot study by Dominguez et al.[13], recruiting merely 27 NSTE-ACS patients. They administered ivabradine to 12 of those patients in a dose of 5mg twice daily for 1 month. The authors stated that a significant larger reduction in hsCRP levels was obtained in the ivabradine group compared to placebo; hsCRP was measured serially, initially on admission, at 24h, and at 48h from the attack then finally after one month. They calculated the decrease in hsCRP from the "in hospital" levels to the "30-day" level, yet it is worth noting that the 24 h and the 48 h median CRP levels were statistically different between the two groups of their study which may confound the results. The authors didn't offer an explanation for this initial difference between the study groups before assuming their final conclusion.

In our study, we recruited 45 patients, hsCRP levels were measured once between 24 and 48 hours after the onset of symptoms, this is the known peak time of hsCRP. [27] We compared the percent change from this peak to the 30-day level between ivabradine and control groups. The decrease was greater in the ivabradine group, but the difference between the two groups did not reach a significance, $p = 0.057$.

Ivabradine use was found to be safe in large randomized trials within the approved doses (up to 7.5 mg bid). The main adverse effects of ivabradine administration are visual symptoms and bradycardia. In the BEAUTIFUL study the incidence of symptomatic sinus bradycardia was 3%. The rate of visual symptoms (phosphenes, blurred vision, and visual disturbances) was also very low and led to discontinuation in only 0.5% of patients receiving ivabradine *vs* 0.2% of patients receiving placebo. [21]Blurred visionwas encountered by one of the ivabradine group patients, who stopped to complain from this side effect when the dose was decreased to 5mg bid. In addition, we did not notice any adverse effects on kidney or liver functions represented by creatinine and ALT levels respectively.

Fox et al presented the SIGNIFY trial [28] in September 2014. SIGNIFY was a placebo-controlled trial that randomized >19 000 patients with stable CAD. Not only adding ivabradine to standard therapy in SIGNIFY had no overall effect on cardiovascular events, but also was associated with significantly worse outcomes in patients with angina of Canadian Cardiovascular Society class ≥ 2, one of the approved indications for the drug in Europe. The results were surprising and were not expected. It was proposed that too much HR reduction may have been the problem. Mean HR at 3 months was reduced to 60.7±9.0 bpm with ivabradine.

In our study the HR was reduced to only a mean of 66 ± 9.0 (median and percentiles= 65 (60 - 73)) bpm at one month of treatment which was maintained over the study period. We did not have a statistically significant difference in MACE occurrence between the two study groups, although of concern, the difference between means of HR of patients with 30-day MACE and those without Mace was observed to be significant before and after the treatment period. Studies such as BEAUTIFUL and CASS demonstrated a positive association between increased resting HR and cardiovascular adverse outcomes.[21, 29] Nevertheless larger randomized controlled studies are required to better demonstrate the effect of ivabradineon clinical outcome in ACS patients.

CONCLUSION: Hence we conclude that addition of ivabradine effectively reduced HR in NSTE-ACS patients. The administration of ivabradine seems to be safe within the used dose. The positive correlation between HR and hsCRP reduction warrants the performance of large randomized clinical trial for further assessment of HR lowering effects on inflammation and cardiovascular outcome in ACS patients.

ACKNOWLEDGEMENT: We are thankful for the facilities provided for us at Cardiology Intensive Care Unit, Department of Cardiology, Ain Shams University Hospitals, Cairo, Egypt, to perform our study. We deeply acknowledge nurses

of the unit. Special thanks to Dr. Inas Elattar, Professor of Biostatistics, Department of Biostatistics & Cancer Epidemiology, National Cancer Institute, Cairo University, Egypt for aiding in statistical work.

REFERENCES:

1. Dipiro JT, Talbert RT, Yee GC, Matzke GR, Wells BG and Posey LM: Pharmacotherapy: The Pathophysiologic Approach, McGraw-hill, New York, Edition 9, 2014:491-475.
2. Custodis F, Reil JC, Laufs U and Böhm M: Heart rate: a global target for cardiovascular disease and therapy along the cardiovascular disease continuum. Journal of cardiology 2013; 62(3):183-187.
3. Custodis F, Schirmer SH, Baumhäkel M, Heusch G, Bhm M and Laufs U: Vascular pathophysiology in response to increased heart rate. Journal of the American College of Cardiology 2010; 56:1973–1983.
4. O Hartaigh B, Bosch JA, Carroll D, Hemming K, Pilz S, Loerbroks A, Kleber ME, Grammer TB, Fischer JE, Boehm BO, März W and Thomas GN: Evidence of a synergistic association between heart rate, inflammation, and cardiovascular mortality in patients undergoing coronary angiography. European heart journal 2013; 34(12):932-941.
5. Nanchen D, Stott DJ, Gussekloo J, Mooijaart SP, Westendorp RG, Jukema JW, Macfarlane PW, Cornuz J, Rodondi N, Buckley BM, Ford I, Sattar N and de Craen AJ; PROSPER Group: Resting heart rate and incident heart failure and cardiovascular mortality in older adults: role of inflammation and endothelial dysfunction: the PROSPER study. European journal of heart failure 2013; 15(5):581-588.
6. Perski A, Hamsten A, Lindvall K and Theorell T: Heart rate correlates with severity of coronary atherosclerosis in young postinfarction patients. American Heart Journal 1988; 116:1369-1373.
7. Cheng JJ, Wung BS, Chao YJ and Wang DL: Cyclic strain enhances adhesion of monocytes to endothelial cells by increasing intercellular adhesion molecule-1 expression. Hypertension 1996; 28:386–391.
8. Tardif JC, Ponikowski P and Kahan T; Associate Investigators: Effects of ivabradine in patients with stable angina receiving beta-blockers according to baseline heart rate: an analysis of the ASSOCIATE study. International Journal of Cardiology 2013; 168(2):789–794.
9. Scicchitano P, Cortese F, Ricci G, Carbonara S, Moncelli M, Iacoviello M, Cecere A, Gesualdo M, Zito A, Caldarola P, Scrutinio D, Lagioia R, Riccioni G and Ciccone MM: Ivabradine, coronary artery disease, and heart failure: beyond rhythm control. Drug Design, Development and Therapy2014; 8:689-700.
10. Menown IB, Davies S, Gupta S, Kalra PR, Lang CC, Morley C and Padmanabhan S: Resting heart rate and outcomes in patients with cardiovascular disease: where do we currently stand?. Cardiovascular Therapeutics 2013; 31(4):215-223.
11. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F and Zeiher A: ESC Committee for Practice. "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". European heart journal 2012; 33 (14): 1787–1847.
12. "FDA approves Corlanor to treat heart failure". www.fda.gov. Retrieved 2015-04-16.
13. Dominguez-Rodriguez A, Consuegra-Sanchez L, Blanco-Palacios G, Abreu-Gonzalez P, Sanchez-Grande A, Bosa-Ojeda F and Kaski JC: Anti-inflammatory effects of ivabradine in patients with acute coronary syndrome: a pilot study. International Journal of Cardiology 2012; 28:158(1):160-162.
14. Rogowski O, Shapira I, Shirom A, Melamed S, Toker S and Berliner S: Heart rate and microinflammation in men: a relevant atherothrombotic link. Heart. 2007; 93:940–944.
15. Sajadieh A, Nielsen OW, Rasmussen V, Hein HO, Abedini S and Hansen JF: Increased heart rate and reduced heart-rate variability are associated with subclinical inflammation in middle-aged and elderly subjects with no apparent heart disease. European heart journal 2004; 25:363–370.
16. Whelton SP, Narla V, Blaha MJ, Nasir K, Blumenthal RS, Jenny NS, Al-Mallah MH, Michos ED: Association between resting heart rate and inflammatory biomarkers (high-sensitivity C-reactive protein, interleukin-6, and fibrinogen) (from the Multi-Ethnic Study of Atherosclerosis). American Journal of Cardiology 2014; 113(4):644-649.
17. Yousuf O, Mohanty BD, Martin SS, Joshi PH, Blaha MJ, Nasir K, Blumenthal RS, and Budoff MJ: High-sensitivityC-reactive protein and cardiovascular disease: a resolute belief or an elusive link?. Journal of the American College of Cardiology 2013; 62(5):397-408.
18. Koenig W: High-sensitivity C-reactive protein and atherosclerotic disease: from improved risk prediction to risk-guided therapy. International Journal of Cardiology 2013; 168(6):5126-5134.
19. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W, Zahger D; ESC Committee for Practice Guidelines: ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). European heart journal 2011; 32(23):2999-3054.
20. Summary of product characteristics http://www.ema.europa.eu/docs/en_GB/document_library/EPAR-Product_Information/human/000597/WC500043590.pdf. (1 August 2013).
21. Fox K1, Komajda M, Ford I, Robertson M, Böhm M, Borer JS, Steg PG, Tavazzi L, Tendera M, Ferrari R and Swedberg K: Effect of ivabradine in patients with left-ventricular systolic dysfunction: a pooled analysis of individual patient data from the BEAUTIFUL and SHIFT trials. European Heart Journal 2013; 34: 2263–2270.
22. Parakh N and Bhargava B: Rate control with ivabradine: angina pectoris and beyond. American Journal of Cardiovascular Drugs 2011; 11(1):1-12.
23. Custodis F, Baumhäkel M, Schlimmer N, List F, Gensh C, Böhm M and Laufs U: Heart rate reduction by ivabradine

reduces oxidative stress, improves endothelial function, and prevents atherosclerosis in apolipoprotein E-deficient mice. Circulation 2008; 117:2377–87.

24. Baumhäkel M, Custodis F, Schlimmer N, Laufs U and Böhm M: Heart rate reduction with ivabradine improves erectile dysfunction in parallel to decrease in atherosclerotic plaque load in ApoE-knockout mice. Atherosclerosis 2010; 212:55–62.
25. Drouin A, Gendron ME, Thorin E, Gillis MA, Mahlberg-Gaudin F and Tardif JC: Chronic heart rate reduction by ivabradine prevents endothelial dysfunction in dyslipidemia mice. British Journal of Pharmacology 2008; 154:749–57.
26. Schirmer SH1, Degen A, Baumhäkel M, Custodis F, Schuh L, Kohlhaas M, Friedrich E, Bahlmann F, Kappl R, Maack C, Böhm M and Laufs U: Heart-rate reduction by If-channel inhibition with ivabradine restores collateral artery growth in hypercholesterolemic atherosclerosis. European heart journal 2012; 33(10):1223-1231.
27. Bodí V and Sanchis J: C - reactive protein in Acute Coronary Syndrome. Looking Back in Order to Move Forward. RevEspCardiol 2006; 59:418-420.
28. Fox K, Ford I, Steg PG, Tardif JC, Tendera M and Ferrari R; SIGNIFY Investigators: Ivabradine in stable coronary artery disease without clinical heart failure. New England Journal of Medicine 2014; 18; 371(12):1091-1099.
29. Diaz A, Bourassa MG, Guertin MC and Tardif JC: Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. European heart journal 2005; 26:967–974.

How to cite this article:
Adel M, Mansour S, Sabri NA, Badary OA and Saleh MA: A Clinical Study Evaluating the Effect of Ivabradine on Inflammation in Patients with Non St-Segment Elevation Acute Coronary Syndromes. Int J Pharm Sci Res 2016; 7(4): 1441-49.doi: 10.13040/IJPSR.0975-8232.7(4).1441-49.