A Pilot Study Evaluating the Effect of Ivabradine on Inflammation and Short-term Clinical Outcome of Patients with Acute Coronary Syndrome

Thesis
Submitted for the fulfillment of PhD. Degree in
Pharmaceutical sciences (Clinical Pharmacy)
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2016

Acknowledgement

I am deeply thankful to "Allah" by the grace of whom, this work was possible.

I am deeply indebted to ***Prof. Dr. Osama Ahmed Badary****, Professor of Clinical Pharmacy, Faculty of Pharmacy, Ain Shams University for his earnest support, valuable foresight, and careful guidance throughout this work.*

I would like to acknowledge with gratitude the precious supervision of ***Prof. Dr. Nagwa Ali Sabri*** *Professor of Clinical Pharmacy and Head of Clinical Pharmacy Department, Faculty of pharmacy, Ain Shams University for her generous assistance, and valuable guidance.*

I am particularly grateful and appreciating to ***Prof. Dr. Mohamed Ayman Saleh*** *Professor of Cardiology, Faculty of Medicine, Ain Shams University for his close supervision, valuable efforts, kind assistance and continuous guidance during the progress of this work and in writing the thesis.*

My appreciation to ***Dr. Sherief Mansour Soliman****, Lecturer of Cardiology, Faculty of Medicine, Ain Shams University, for his assistance in the clinical aspects in the beginning of this work.*

I also express my gratefulness to ***Prof. Dr. Inas Elattar****, professor of Biostatistics, Department of Biostatistics & Cancer Epidemiology, National Cancer Institute, Cairo University, who gave me the assistance in conducting the statistical analysis and interpretation of data.*

The patients in whom I performed the study deserve my sincere gratitude. Getting through my dissertation required more than academic support, and I would like to thank my colleagues at the department of Clinical pharmacy for their constant personal as well as professional

support. I cannot begin to express my gratitude and appreciation for their friendship.

Most importantly, none of this could have happened without ***my husband, my children, my father and mother*** *and the rest of my family members. This dissertation stands as a testament to your unconditional love and encouragement.*

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List of Abbreviations

ACE-I: angiotensin converting enzyme inhibitors

ACS: acute coronary syndromes

ACT: activated clotting time

ADP: adenosine diphosphate

aPTT: activated partial thromboplastin time

ARBs: angiotensin receptor blockers

ATP: adenosine triphosphate

AUC: area under the curve

bpm: beats per minute

CABG: coronary artery bypass graft

CAD: coronary artery disease

cAMP: cyclic adenosine monophosphate

CCBs: calcium channel blockers

CHD: coronary heart disease

CK: creatine kinase

CK-MB: creatine kinase myocardial band

CRP: C-reactive protein

CV: cardiovascular

CVD: cardiovascular disease

CYP: cytochrome P450

DAPT: dual antiplatelet therapy

DES: drug-eluting stents

eGFR: estimated glomerular filtration rate

GRACE: Global Registry of Acute Coronary Events

HCN: hyperpolarization activated-cyclic nucleotide

HDL: high density lipoprotein

HF: heart failure

HIT: heparin induced thrombocytopenia

HR: heart rate

hsCRP: high sensitivity C-reactive protein

HTN: hypertension

IV: intravenous

LDL: low density lipoprotein

LMWH: low molecular weight heparin

LVEF: left ventricular ejection fraction

LVSD: left ventricular systolic dysfunction

MI: myocardial infarction

NSTE-ACS: non-ST segment elevation acute coronary syndromes

NSTEMI: non-ST segment elevation myocardial infarction

NTG: nitroglycedrin

PCI: percutaneous coronary intervention

RCT: randomized controlled trials

SAN: sinoatrial node

SC: subcutaneous

STEMI: ST- segment elevation myocardial infarction

UA: unstable angina

UFH: unfractionated heparin

ABSTRACT

Background: 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: The current prospective, randomized, controlled, study recruited NSTE-ACS patients with HR ≥70 beats per minutes (bpm). 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 in hsCRP reduction.

Results: Forty five patients were enrolled; twenty three of them received ivabradine. The decrease (%) in HR after treatment was significantly higher in ivabradine 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.

REVIEW OF LITERATURE

Acute coronary syndromes

Definition and spectrum

Acute coronary syndromes (ACS) refers to a spectrum of clinical presentations ranging from those for ST-segment elevation myocardial infarction (STEMI) to presentations found in non–ST-segment elevation myocardial infarction (NSTEMI) or in unstable angina (UA). It is almost always associated with rupture of an atherosclerotic plaque and partial or complete thrombosis of the infarct-related artery **(Spinler and de Denus, 2014)**

Unstable angina and NSTEMI are closely related conditions, they have similar pathophysiologic origins and clinical presentations, but they differ in severity. They are grouped together under the term of non–ST-segment elevation acute coronary syndromes (NSTE-ACS).

A diagnosis of NSTEMI can be made when the ischemia is sufficiently severe to cause myocardial damage that result in the release of a biomarker of myocardial necrosis into the circulation.

In contrast, the patient is considered to have experienced UA if no such biomarker can be detected in the blood stream hours after the initial onset of ischemic chest pain.

Unstable angina exhibits 1 or more of 3 principal presentations **(Kumar and Cannon, 2009)**:

1. Rest angina (usually lasting >20 minutes)
2. New-onset (<2 months previously) severe angina
3. A crescendo pattern of occurrence (increasing in intensity, duration, frequency, or any combination of these factors).

Epidemiology

Each year in the United States, approximately 1.1 million hospitalizations are required for ACS, 150,000 of which die of a myocardial infarction (MI). About 0.81 million of the hospitalizations are for MI and the remainder are for UA. The proportion of patients with MI presenting with STEMI compared with those

presenting with NSTEMI decreased from approximately 80% in the early 1990s to between 25% and 30% currently **(Go et al., 2013)**.

This previously mentioned reduction in STEMI percentage may be secondary to the use of the more sensitive biomarker troponin (increasing the diagnosis of MI in the NSTE-ACS group), greater use of antecedent revascularization procedures, decreased reinfarction from enhanced medical therapy after an initial event, or prevention of progression of UA to MI through more effective anticoagulant and antiplatelet therapy **(Spinler and de Denus, 2014)**.

According to data from the National Registry of Myocardial Infarction, in hospital mortality has decreased by more than 20% during the last 20 years **(Go et al., 2013)**.

- **Coronary heart disease in Egypt and the Middle East:**

In 2004, the INTERHEART study (an international case-control analysis of the risk factors for a first myocardial infarction conducted in more than 15,000 patients presenting with myocardial infarction in 52 countries) showed that the median age at presentation with myocardial infarction was 51 years in the Middle East; this was 12 years lower than the median age at presentation in Western Europe **(Yusuf et al., 2004)**.

Okrainec et al. reported that a projected increase in coronary deaths in the Middle East of 171% between 1990 and 2020 was larger than corresponding values for other regions like India (127%), China (108%), sub-Saharan Africa (144%), and Latin America (144%) **(Okrainec et al., 2004)**.

The Egyptian National Hypertension Project has provided the two principal sources of information on the epidemiology of CHD in the region, in addition to data from the WHO (Figure 1) **(Almahmeed et al., 2012)**. This nationally representative survey of 6733 subjects (about half of whom were women) reported an adjusted overall prevalence of coronary heart disease of 8.3%. The prevalence of coronary heart disease (CHD) was somewhat higher in women (8.9%) relative to men (8%), but was more clearly associated with an urban versus rural location (8.8% versus 7.2%), and age >50 years versus <50 years (11.1% versus 5.1%) **(Almahmeed et al., 2012).**

According to the latest WHO data published in May 2014 CHD Deaths in Egypt reached 107,232 or 23.14% of total deaths. The Death Rate is 186.36 per 100,000 of population ranks Egypt number 23 in the world.

Urbanization, sedentary life style, high caloric - high fat diet combined with increased prevalence of hypertension, cigarette smoking, diabetes mellitus, obesity, dyslipidemia and social stress are important causes of the coming epidemic of coronary artery disease (CAD) in Egypt and other developing countries. This trend should alert the health authorities, medical and scientific community and to take active measures in order to prevent, diagnose and adequately treat these life threatening disorders **(Ibrahim MM, 2014)**.

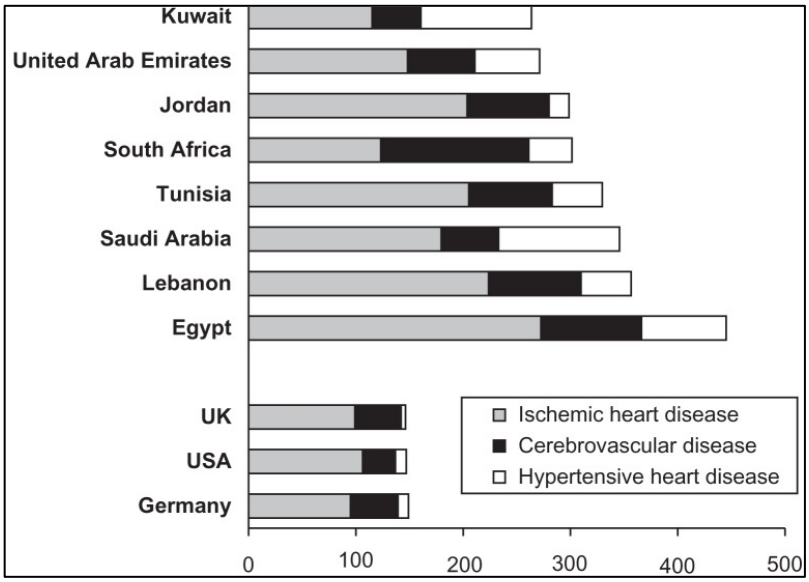

Figure 1: Death rates from cardiovascular disease in selected countries in Africa and the Middle East (Ibrahim MM, 2014)

Etiology

Endothelial dysfunction, inflammation, and the formation of fatty streaks contribute to the formation of atherosclerotic coronary artery plaques which is the underlying cause of CAD **(Schwartz et al., 2011)**.

The predominant cause of ACS in more than 90% of patients is atheromatous plaque rupture, fissuring, or erosion of an unstable atherosclerotic plaque that occludes less than 50% of the coronary lumen prior to the event, rather than a more stable 70% to 90% stenosis of the coronary artery **(Fuster et al., 2005).** Stable stenoses are characteristic of stable angina.

Pathophysiology

- **Initiation of atherosclerosis: role of the endothelium**

Atherosclerosis is the ongoing process of plaque formation that involves primarily the intima of large- and medium-sized arteries.

Several coronary risk factors influence this process; including hypercholesterolemia, hypertension, diabetes, and smoking **(Fuster et al., 1992; Libby, 2001)**. These risk factors damage the endothelium of the blood vessel and result in endothelial dysfunction.

A dysfunctional endothelium is characterized by reduced bioavailability of nitric oxide and by excessive production of endothelin 1, which impairs vascular hemostasis; increased expression of adhesion molecules (eg, selectins, vascular cell adhesion molecules, and intercellular adhesion molecules); and increased thrombogenicity of blood through the secretion of several locally active substances **(Corti et al., 2001; Kinlay et al., 2001)**.

- **Progression of atherosclerotic plaque: role of inflammation**

Once the endothelium has been damaged, the inflammatory cells, especially monocytes, migrate into the subendothelium by binding to endothelial adhesion molecules; once in the subendothelium, they undergo differentiation, becoming macrophages. Macrophages digest oxidized low-density lipoprotein (LDL) that has also penetrated the arterial wall, transforming into foam cells and causing the formation of fatty streaks **(Kinlay et al., 2001)**.

The activated macrophages release chemoattractants and cytokines (eg, monocyte chemoattractant protein 1, tumor necrosis factor α, and interleukins) that perpetuate the process by recruiting additional macrophages and vascular smooth muscle cells (which synthesize extracellular matrix components) at the site of the plaque **(Fuster et al., 1992)**.

Macrophages also elaborate matrix metalloproteinases, enzymes that digest the extracellular matrix and lead to plaque disruption **(Fuster et al., 1992)**. The ratio between smooth muscle cells and macrophages plays an important role in plaque vulnerability and the propensity for rupture **(Virmani et al., 2000)**.

Although plaque rupture may result in ACS, more often, in fact in 99% of cases, it is clinically silent. The rate of progression of atherosclerotic lesions is variable, nonlinear, and unpredictable **(Virmani et al., 2000)**.

- **Stability of plaques and tendency for rupture**

The stability of atherosclerotic plaques varies. Characteristics of so-called high-risk or vulnerable plaques include a large lipid core, thin fibrous caps, a high density of macrophages and T lymphocytes **(Moreno et al., 1994; van der Wal et al., 1994)**, a relative paucity of smooth muscle cells, locally increased expression of matrix metalloproteinases that degrade collagen **(Sukhova et al., 1999; Herman et al., 2001)**, eccentric outward remodeling and increases in plaque neovascularity and intraplaque hemorrhage **(Rauch et al., 2001)**.

Inflammation, a particularly important determinant of the "vulnerability" of plaques **(Lendon et al., 1991)**, is related to an increase in the activity of macrophages at the site of plaque; this increased activity leads to an enlargement of the lipid core and a thinning of the plaque cap, characteristics that render the plaque more vulnerable to rupture. Elevated levels of C-reactive protein (CRP) have been found to correlate positively with the number of plaque ruptures **(Tanaka et al., 2005)** and may reflect the activity of these macrophages **(Sano et al., 2003)**.

- **Plaque disruption, thrombosis, and ACS**

Angiographically, noncritical coronary lesions (<50% stenosis in the diameter of the vessel) may be associated with abrupt progression to severe or total occlusion and may eventually account for as many as two-thirds of cases of ACS **(Chen et al., 1996; Luscher et al., 1996)**.

Factors such as the lipid and tissue factor content of the plaque, the severity of the plaque rupture, the degree of inflammation at the site, the blood flow in the area, and the patient's antithrombotic and prothrombotic balance are important in controlling the degree of thrombus formation and determining whether a given plaque rupture will result in ACS **(Weiss et al., 1996)**.

After either plaque rupture or endothelial erosion, the subendothelial matrix (which is rich in tissue factor, a potent procoagulant) is exposed to the circulating blood; this exposure leads to platelet adhesion followed by platelet activation and aggregation and the subsequent formation of a thrombus.

Two types of thrombi can form: a platelet rich clot (referred to as a white clot) that forms in areas of high shear stress and only partially occludes the artery, or a fibrin-rich clot (referred to as a red clot) that is the result of an activated coagulation cascade and decreased flow in the artery (the later is usually seen in STEMI patients).