Safety and Efficacy of off-label use of Ivabradine in Patients with Acute Heart Failure

Thesis

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Mohamed Ahmed Radwan Mostafa

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List of Abbreviations

Abb.	Full term
6MWD	6 -minute walk distance
6MWT	6-minute walk test
ABP	Arterial blood pressure
ACEI	Angiotensin converting enzyme inhibitor
ACS	Acute coronary syndrome
AF	Atrial fibrillation
AHF	Acute heart failure
ANP	Atrial Natriuretic Peptide
ARB	Angiotensin Receptor Blocker
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
bpm	Beat per minute
CCU	Cardiac care unit
CHD	Coronary heart disease
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
DHF	Decompensated heart failure
DM	Diabetes mellitus
ECG	Electrocardiography
EF	Ejection fraction
eGFR	Estimated Glomerular Filtration Rate
ESC	European Society of Cardiology
HF	Heart failure

List of Abbreviations (Cont...)

Abb.	Full term
HF-REF	Heart failure with reduced ejection fraction
HR	Heart rate
HRQOL	Health-Related Quality of Life
IABP	Intra Aortic Balloon Counterpulsation
ICU	Intensive care unit
INR	International Normalized Ratio
LVEDD	LV end systolic diameter (LVESD)
LVEF	Left ventricular ejection fraction
LVESD	Left ventricular end systolic diameter
MLHFQ	Minnesota Living with Heart Failure Questionnaire
MRA	Mineralocorticoid receptors antagonist
NYHA	New York Heart Association
QOL	Quality of life
RCT	Randomized controlled trial
SAN	SIANO atrial node
SBP	Systolic blood pressure
SHIFT	The Systolic Heart failure treatment with the I_f Inhibitor Ivabradine Trial

INTRODUCTION

Sympathetic hyperactivity and consequent increase in heart rate (HR) are physiological responses to low cardiac output in patients with acute heart failure. However, elevated HR may become inappropriate in these patients, increasing myocardial oxygen demand and decreasing diastolic filling time and might lead to hemodynamic deterioration, ventricular dysfunction (tachycardiomyopathy) and clinical deterioration ***(Clinical Trial, 2016)***.

Ivabradine has shown to increase survival of patients with chronic stable systolic HF. Compared to beta blockers, Ivabradine has the advantage of "pure" negative chronotropic effect, no effect on myocardial contractility and have been validated as a therapeutic option in patients with stable HF, there are no studies available on this strategy in patients with DHF ***(Clinical Trial, 2016)***.

Patients with heart failure (HF) have limited exercise tolerance, few pharmacological interventions have been proven effective in improving exercise capacity. At the presence there is conflicting evidence on the effectiveness of beta-blockers on exercise capacity. **Ivabradine** has been shown to improve prognosis in patients with ischemic heart disease, left ventricular dysfunction and heart rate $\geq$ 70 bpm. The association of **Ivabradine** and atenolol has been proven effective in increasing exercise tolerance in patients with ischemic heart disease ***(Swedberg and Komajda, 2010).***

AIM OF THE WORK

Our study aims to assess the effect and safety of Ivabradine as strategy of heart rate control, improve exercise tolerance and improve quality of life in patients with Acute heart failure.

Chapter 1
ACUTE HEART FAILURE

Definition

AHF refers to rapid onset or worsening of symptoms and/or signs of HF. It is a life-threatening medical condition requiring urgent evaluation and treatment, typically leading to urgent hospital admission. AHF may present as a first occurrence (de novo) or, more frequently, as a consequence of acute decompensation of chronic HF, and may be caused by primary cardiac dysfunction or precipitated by extrinsic factors, often in patients with chronic HF ***(Ponikowski et al., 2016)***.

Acute myocardial dysfunction (ischaemic, inflammatory or toxic), acute valve insufficiency or pericardial tamponade are among the most frequent acute primary cardiac causes of AHF. Decompensation of chronic HF can occur without known precipitant factors, but more often with one or more factors, such as infection, uncontrolled hypertension, rhythm disturbances or non-adherence with drugs/diet ***(Mentz and O'connor, 2016)***.

Pathophysiology of acute heart failure

The clinical presentation of AHF typically includes symptoms or signs related to congestion and volume overload rather than to hypoperfusion ***(Costanzo and Jessup, 2012)***.

Since congestion plays a central role for the vast majority of AHF cases, understanding of the underlying patho-physiological mechanisms related to congestion is essential for treating AHF patients ***(Gheorghiade et al., 2010)***.

More importantly, the level of congestion and the number of congested organs have prognostic relevance in HF patients ***(Gheorghiade et al., 2010)***.

Mechanisms of congestion: fluid accumulation and fluid redistribution

In presence of cardiac dysfunction, several neuro-humoral pathways, including the sympathetic nervous system, the renin-angiotensin-aldosterone system and the arginine vasopressin system, are activated to counter the negative effects of HF on oxygen delivery to the peripheral tissues.

Neuro-hormonal activation in HF leads to impaired regulation of sodium excretion through the kidneys which results in sodium and, secondary, fluid accumulation ***(Nijst et al., 2015, McKie et al., 2011)*** **(Figure 1&2).**

Significantly increased cardiac filling pressures and venous congestion are frequently observed days or weeks before the overt clinical decompensation ***(Chaudhry et al., 2007, Zile et al., 2008, Lam et al., 2009).***

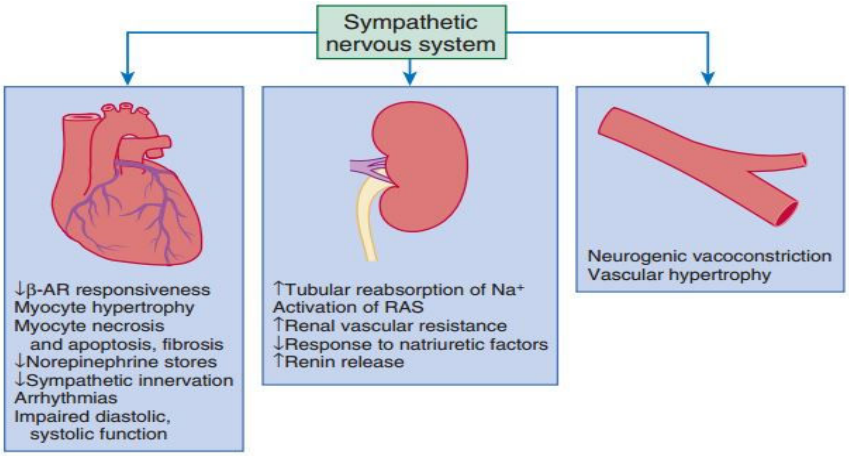

Figure (1): Activation of the sympathetic nervous system ***(McKie et al., 2011)***.

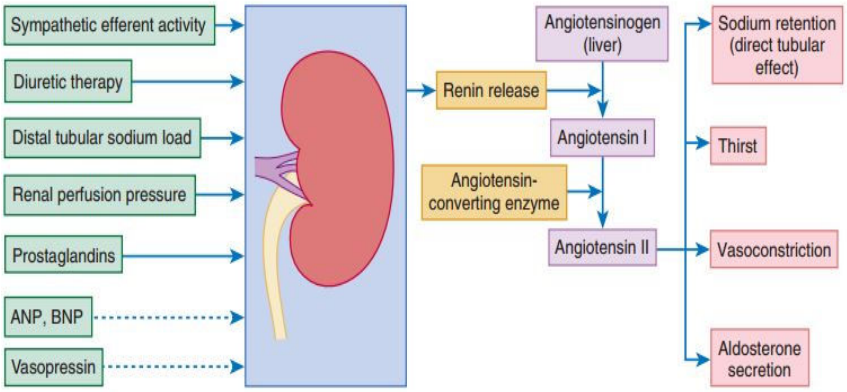

Figure (2): Activation of the renin-angiotensin system ***(McKie et al., 2011)***.

Tissue oedema occurs when the transudation from capillaries into the interstitium exceeds the maximal drainage of the lymphatic system. Transudation of plasma fluid into the interstitium results from the relation between hydrostatic and oncotic pressures in the capillaries and in the interstitium as

well as interstitial compliance. Increased transcapillary hydrostatic pressure gradient, decreased transcapillary oncotic pressure gradient and increased interstitial compliance promote oedema formation ***(Lam et al., 2009)***.

In healthy individuals, increased total body sodium is usually not accompanied by oedema formation since a large quantity of sodium may be buffered by interstitial glycosaminoglycan networks without compensatory water retention ***(Titze et al., 2004)***.

Moreover, the interstitial glycosaminoglycan networks display low compliance which prevents fluid accumulation in the interstitium ***(Guyton, 1965)***.

In HF, when sodium accumulation persists, the glycosaminoglycan networks may become dysfunctional resulting in reduced buffering capacity and increased compliance. In AHF the presence of pulmonary or peripheral oedema correlates poorly with left- and right-sided filling pressures ***(Breidthardt et al., 2012, Zile et al., 2011)***, but in patients with dysfunctional glycosaminoglycan networks even mildly elevated venous pressures might lead to pulmonary and peripheral oedemas ***(Nijst et al., 2015)***.

In addition, since a large amount of sodium is stored in the interstitial glycosaminoglycan networks and does not reach