



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم



MONA MAGHRABY



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شبكة المعلومات الجامعية التوثيق الإلكتروني والميكروفيلم



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**Therapeutic Equivalence of Generic Product Versus Reference Product of Ivabradine
in patients with Chronic Heart Failure: A Comparative Study**

**A thesis Submitted for the partial fulfillment of the Master's Degree in
Pharmaceutical Sciences (Clinical Pharmacy)**

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List of Abbreviations

ACC/AHA	American College of Cardiology/American Heart Association
ACEI	Angiotensin Converting Enzyme Inhibitor
AHF	Acute Heart Failure
ALT	Alanine Transaminase Enzyme
ARBs	Angiotensin Receptor Blockers
AST	Aspartate Transaminase Enzyme
AV node	Atrioventricular Node
BEAUTIFUL	Morbidity-mortality evaluation of the If-inhibitors ivabradine in patients with CAD and left ventricular dysfunction
BUN	Blood Urea Nitrogen
CAD	Coronary artery disease
cAMP	Cyclic adenosine monophosphate
CARVIVA	Carvedilol, ivabradine or their combination on exercise capacity in patients with HF
cGMP	Cyclic guanosine monophosphate
CHF	Chronic Heart Failure
CO	Cardiac Output
COMET	Carvedilol or Metoprolol European Trial
CVD	Cardiovascular disease
DCM	Dilated cardiomyopathy
DIG	Digitalis intervention Group
ESC	European society of cardiology
FDA	Food and Drug Administration
HCN	Hyperpolarization activated cyclic nucleotide-gated
HF	Heart Failure
HFpEF	Heart Failure with preservative Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
HTN	Hypertension
IHF	Ischemic heart failure
LVEF	Left Ventricular Ejection Fraction

MI	Myocardial infarction
NIHF	Non-ischemic heart failure
NYHA FC	New York Heart Association Functional Classification
RAAS	Renin- angiotensin -aldosterone system
RHR	Resting heart rate
SAN	Sino-atrial node
SHIFT	Systolic HF treatment with the If inhibitor ivabradine trial
SNS	Sympathetic nervous system
Sr.cr	Serum Creatinine

Abstract

Background:

Generic substitution of brand ivabradine prescriptions can reduce drug expenditures and improve adherence. However, the distrust of generic medicines by practitioners and patients due to doubts regarding their quality and fear of counterfeiting compromise the acceptance of this practice.

Aim of the Work:

The current study was designed to compare the therapeutic equivalence of brand product versus generic product of ivabradine in adult patients with chronic heart failure with reduced ejection fraction ($\leq 40\%$) (HFrEF).

Patients and Methods:

The study was carried out on 32 Egyptian patients with HFrEF who were randomized to one of the two groups: Group A received branded ivabradine (Procrolan ©) for 12 weeks followed by another 12 weeks of receiving generic (Bradipect ©), while Group B received the same intervention with opposite order without washout period. All patients received their guideline directed medical therapy throughout the study period. The following parameters were evaluated at the end of the 12th week and 24th week of either receiving branded or generic ivabradine: Primary outcomes were resting heart rate (HR), New York Heart Association NYHA FC, Quality of life (QoL) using Minnesota Living with Heart Failure (MLWHF) and EF. Secondary outcomes were number of hospitalizations for worsening HFrEF and adverse effects. Washout period was not allowed for ethical reasons.

Results:

At the 12th week, the reduction in HR was comparable in the two groups (90.13 ± 7.11 to 69 ± 11.41 vs 96.13 ± 17.58 to 67.31 ± 8.68 bpm in group A and group B, respectively). Also, the increase in EF was comparable in the two groups (27.44 ± 4.59 to 33.38 ± 5.62 vs 32 ± 5.96 to 39.31 ± 8.95 in group A and group B, respectively). The improvement in NYHA FC was comparable in both groups (87.5% in group A vs 93.8% in group B). The mean value of the QOL improved from 31.63 ± 15.8 to 19.6 ± 14.7 vs 35.68 ± 17.63 to 22.9 ± 15.1 for the group A and group B, respectively. Similarly, at end of 24th week, no significant changes were observed from data observed at 12th week regarding HR, EF, QoL and NYHA FC. Only

minor side effects, mainly phosphenes, and a comparable number of hospitalizations were observed in both groups.

Conclusion:

The study revealed no statistically significant differences in the therapeutic effect and safety between generic and branded ivabradine. Study results supports the assumption that practitioners can safely switch to generic ivabradine for economic reasons.

Key words:

Heart Failure, Ivabradine, Bradipect ©, Procoralan ©, Therapeutic Equivalence, Crossover study

1. Introduction

European Society of Cardiology (ESC) defined heart failure (HF) as a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/ or elevated intracardiac pressures at rest or during stress (Ponikowski et al., 2016).

1.1 Types of Heart Failure

The main terminology used to describe HF is historical and is based on measurement of the left ventricular ejection fraction (LVEF). HF comprises a wide range of patients, from those with normal LVEF [typically considered as $\geq 50\%$; HF with preserved EF (HFpEF)] to those with reduced LVEF [typically considered as $\leq 40\%$; HF with reduced EF (HFrEF)] (Ponikowski et al., 2016). Differentiation of patients with HF based on LVEF is important due to different underlying etiologies, demographics, co-morbidities and response to therapies (Butler J et al., 2012).

1.1.1. Heart Failure with Preserved EF (HFpEF) (diastolic dysfunction)

Definition of HFpEF based on American College of Cardiology/American Heart Association (ACC/AHA) and ESC is LVEF $\geq 50\%$ (Yancy et al., 2013; Ponikowski et al., 2016; Yancy et al., 2017). It has been suggested that the incidence of HFpEF is increasing and that a greater portion of patients hospitalized with HF have HFpEF (Steinberg et al., 2012).

HFpEF is sub classified into a) HFpEF, borderline with LVEF 41% to 49%. These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patients with HFpEF. b) HFpEF, improved with LVEF $>40\%$. It has been recognized that a subset of patients with HFpEF previously had HFrEF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF (Yancy et al., 2013).