JOURNAL OF DRUG ASSESSMENT, 2018
VOL. 7, NO. 1, 8–13
https://doi.org/10.1080/21556660.2018.1423988
Article 0007/1423988

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ORIGINAL ARTICLE

Clinical tolerability of generic versus brand beta blockers in heart failure with reduced left ventricular ejection fraction: a retrospective cohort from heart failure clinic

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ABSTRACT

Background: Beta-blockers have been shown to decrease mortality and morbidity in heart failure with reduced ejection fraction (HFrEF) patients. However, the side effects are also dose-related, leading to the underdosing. Cost constraint may be one of the limitations of appropriate beta-blocker use; this can be improved with generic drugs. However, the effects in real life practice have not been investigated.

Methods and results: This study aimed to compare the efficacy and safety of generic and brand beta-blockers in HFrEF patients. We performed a retrospective cohort analysis in HFrEF patients who received either generic or brand beta-blocker in Chiang Mai Heart Failure Clinic. The primary endpoint was the proportion of patients who received at least 50% target dose of beta-blocker between generic and brand beta-blockers. Adverse events were secondary endpoints. 217 patients (119 and 98 patients received generic and brand beta-blocker, respectively) were enrolled. There were no differences between groups regarding age, gender, etiology of heart failure, New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF), rate of receiving angiotensin converting enzyme inhibitor (ACEI), angiotensin recepter blocker (ARB), or spironolactone. Patients receiving brand beta-blockers had lower resting heart rate at baseline (74.9 and 84.2 bpm, $p = .001$). Rate of achieved 50% target dose and target daily dose did not differ between groups (40.4 versus 44.5% and 48.0 versus 55.0%, $p > .05$, respectively). Rate of side effects was not different between groups (32.3 versus 29.5%, $p > .05$) and the most common side effect was hypotension.

Conclusion: This study demonstrated that beta-blocker tolerability was comparable between brand and generic formulations. Generic or brand beta-blockers should be prescribed to HFrEF patients who have no contraindications.

ARTICLE HISTORY
Received 6 December 2017
Accepted 23 December 2017

KEYWORDS
Beta-blocker; tolerability; heart failure; generic drug; brand drug

Introduction

Heart Failure (HF) is a major health problem with increasing prevalence globally and regionally, including Thailand. HF is associated with high mortality, high morbidity, and cost of care [1–7]. Neurohormonal activation in systems such as the renin-angiotensin-aldosterone system (RAAS) and sympathetic systems has been shown to be associated with adverse outcomes in HF [8–10]. Treatments with neurohormonal blockage have shown to reduce mortality and morbidity in heart failure with reduced left ventricular ejection fraction (HFrEF) [11–30]. Beta-blockers are well established as beneficial for morbidity and mortality reduction in HFrEF. Their use has been studied in chronic symptomatic HF as well as left ventricular systolic dysfunction associated with acute myocardial infarction (AMI) [22]. However, there are heterogeneous effects among beta blockers in HFrEF. Some beta-blockers, including carvedilol, bisoprolol and metoprolol succinate, have shown beneficial effects [21–24], while bucinodol does not show benefits in HFrEF [31]. In addition, a head to head study which compared the effects of carvedilol and metoprolol tartate in chronic HFrEF showed the benefits of carvedilol over metoprolol tartrate [26]. Therefore, several guidelines for the management of heart failure have recommended only clinically proven beta-blockers [4,32]. Dose titration to target recommendation dose is also essential for a higher magnitude of benefits from beta-blockers. Although beta-blockers have been recommended by guidelines, several cohorts have shown the limited use of these drugs [33–37]. The factors limiting beta-blocker use include physician's attitude, tolerability, adverse effects and cost constraints.

HF management is costly due to high cost of medications, device therapy and cost of patient care. Due to multiple comorbidities such as coronary artery disease, hypertension, and diabetes, the cost of total medications used is high [2], resulting in a burden for the health care system and households. Nevertheless, unlike some other guideline-recommended

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medications for HF beta-blockers have lost their patent protection and are available at relatively low cost. Generic drugs can provide better access to medications for HF patients. However, there are some concerns over the manufacturing process leading to concerns of safety and tolerability of these generic drugs [38,39]. However, no previous report has directly compared tolerability between generic and brand beta-blockers in HFrEF patients. Only one study compared pharmaceutical quality between brand and generic beta-blockers, and it reported that at least 48% generic beta-blockers were worse than brand beta-blockers [40]. Therefore, we aimed to study the safety and tolerability of generic beta-blockers in HFrEF patients in real life practice. The primary objective was to compare the proportion of patients receiving at least 50% of the target dose of beta-blockers. The secondary objective was to compare the proportion of patients with adverse events and the reasons for not achieving the target dose between generic and brand beta-blockers.

Materials and methods

This is a retrospective cohort study from Chiang Mai University HF clinic. The HF clinic, established in 2004, aimed to provide a multidisciplinary management program for high risk HF patients. The HF patients with high risk factors, such as a history of frequent hospitalization, having multiple co-morbidities or poor compliance were invited to participate in the HF management program. Their information, including symptoms, physical examination and laboratory data, was prospectively collected and recorded. Examination and analysis procedures complied with the rules of the Declaration of Helsinki, and the study was approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand.

For this study, data from patients who met inclusion criteria for our study were retrieved from the medical records. Inclusion criteria for this study consisted of HF patents with left ventricular ejection fraction of less than 0.4 who received at least 1 dose of generic or brand beta-blockers (carvedilol or bisoprolol). Patients with absolute contraindication for beta-blockers were excluded from the analysis.

The data, including symptoms, signs, dose titration, maximum dose, adverse effects and management of adverse effects, were recorded at 3 points including the starting day (day with the first dose of beta-blockers), 4 ± 2 weeks, and 24 ± 4 weeks after starting point.

The target dose of beta-blockers was determined according to standard recommendation guidelines as follows: carvedilol 50 mg/day and bisoprolol 10 mg/day at 6 months after starting beta-blockers.

Brand beta-blockers in this study were Dilatrend (Roche, Switzerland) and Concor (MERCK, Germany). Generic carvedilol was Caraten (Berlin Pharm, Thailand) and generic bisoprolol were Hypercor (Sriprasit Pharma, Thailand) and Bisloc (Unison, Thailand).

Sample size calculation

Sample size was calculated on the basis of the proportion of patients who received at least 50% of the target dose of brand beta-blockers, which was around 80% [21–23,26,41]. The estimated proportion of patients who received at least 50% of the target dose of generic beta-blockers was around 40% [42]. This study aimed to compare the proportion of two independent samples at type I error =0.05, type II error =0.10. The calculated sample size for each group =30, and with an estimated occurrence of incomplete data of around 50%, a total sample size of at least 90 patients was needed.

Statistical analysis

Continuous variables are presented as mean ± SD or median (IQR) where appropriate. Categorical variables are presented as numbers and percentages. Comparisons between groups of continuous variable were performed using the Student t-test or Mann-Whitney U test as appropriate. Comparisons of categorical variables were performed using the Chi-square or Fisher exact tests as appropriate. A $p < .05$ (2-tailed) was considered significant. Statistical analyses were performed using SPSS 18 (IBM, New York, United States).

Results

From medical records of 500 patients in the HF clinic, 217 patients met the inclusion criteria and were enrolled in this analysis. Ninety-eight patients received brand beta-blockers and 119 patients received generic beta-blockers.

At baseline, there were no differences in age (59.4 ± 14.3 *vs* 57.5 ± 14.9 years old, $p = .45$), gender (male 53.1 *vs* 61.3%, $p = .27$), New York Heart Association (NYHA) functional class (FC) (2.9 ± 0.8 *vs* 2.6 ± 0.8, $p = .14$, in brand and generic beta-blockers, respectively). Patients were in NYHA FC II 34 *vs* 43%, FC III 43.6 *vs* 42.4%, $p = .14$, in brand and generic beta-blockers, respectively. There were no differences in concomitant diseases including atrial fibrillation (AF) 26.0 *vs* 27.7%, $p = .49$, chronic obstructive pulmonary disease (COPD) 10.5 *vs* 7.6%, $p = .45$, diabetes 37.4 *vs* 28.6%, $p = .38$, chronic kidney disease (CKD) 48.4 *vs* 36.1%, $p = 01$, in brand and generic beta-blockers, respectively. The proportion of left ventricular systolic dysfunction from ischemia was not significantly different between groups (22.7 *vs* 31.1%, $p = .06$ in brand and generic beta-blockers, respectively). There was no significant difference in LVEF (27.0 ± 10.3 *vs* 25.4 ± 7.9%, $p = .49$% in brand and generic beta-blockers, respectively). The proportions of patients receiving recommended treatment for HFrEF were not different between groups: angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) (79.1 *vs* 76.1%, $p = .64$), spironolactone (65.7 *vs* 73.5%, $p = .31$), digoxin (14.9 *vs* 25.66%, $p = .09$) and device therapy including automatic implantable cardioverter-defibrillator (AICD) and cardiac resynchronization therapy (CRT) (7.3 *vs* 13.4%, $p = .28$) in brand and generic beta-blockers, respectively. There were no differences in systolic blood pressure and diastolic blood pressure: 115.9 ± 21.3 *vs* 111.9 ± 16.8 mmHg, $p = .11$ and 67.4 ± 13.9 *vs* 67.4 ± 14.2, $p = 1.00$ in brand and generic beta-blockers, respectively. However, patients in the brand beta-blocker group had a

lower mean heart rate than the generic beta-blocker group (74.8 ± 16.7 *vs* 84.2 ± 16.2 bpm, $p < .01$) (Table 1).

At 6 months, both beta-blocker groups were similar in percent of heart rate reduction (5.6 ± 2.0 *vs* 7.4 ± 2.6 bpm, $p = .61$, in brand and generic beta-blockers, respectively)

Both beta-blockers had a similar proportion of patients achieving at least 50% of the target dose (40.4 *vs* 44.5%, $p = .25$ in brand and generic beta-blocker groups, respectively). The daily dose achievement as a percentage of target dose was not different between the brand and generic beta-blocker groups (48 *vs* 55% of target dose, $p = .27$) (Figure 1).

There were also similar proportions in achievement of at least 50% of maximum dose (34.7 ± 19.7 *vs* 44.3 ± 24.1%, $p = .27$) and percent mean daily dose achievement (42.0 ± 49.7 *vs* 56.7 ± 49.9%, $p = .09$) between brand and generic bisoprolol. There were also similar proportions in achievement of at least 50% of maximum dose (56.5 ± 34.4 *vs* 45.3 ± 30.4%, $p = .14$) and percent of maximum target daily dose (68.0 ± 47.6 *vs* 52.4 ± 50.3%, $p = .18$) between brand and generic carvedilol. The titrations of beta-blocker dose during 6 months of treatment were not different between brand and generic beta-blockers, including increased dose (46.9 *vs* 66.8%), stable dose (39.8 *vs* 26.3%) and decreased dose (13.3 *vs* 6.8%), $p = .39$ (Figure 2).

The reasons of not achieving target beta-blocker dose include target heart rate achievement, postural hypotension, reactive airway disease, acute decompensated HF, bradycardia, and unspecified reasons (51.1 *vs* 43.4%, 27.8 *vs* 16.8%, 2.22 *vs* 5.3%, 3.3 *vs* 2.65%, 10.0 *vs* 23.8% in brand and generic beta-blockers, respectively).

Five patients (2.3%) in each group discontinued beta-blocker usage at 6 months. Three patients in the brand beta-blocker group discontinued due to Acute Decompensated Heart Failure (ADHF), bradycardia, and an unknown cause while 2 patients in the generic beta-blocker group discontinued due to reactive airway and bradycardia. Two patients in the brand beta-blocker group and 6 patients in the generic beta-blocker group were lost to follow up.

The percentage of patients who reported side effects was not significantly different between brand and generic beta-blockers (32.3 *vs* 29.5%, $p = .75$). Acute decompensated HF, bradycardia, hypotension, dizziness and reactive airway disease were present in 4.1 *vs* 3.4%, 3.1 *vs* 3.4%, 10.2 *vs* 10.9%, 1.0 *vs* 1.7% and 0.8 *vs* 0%, in brand and generic beta-blockers, respectively (Table 2).

Table 1. Proportion of patient receiving beta-biockers.

Character	Brand beta-blocker ($n = 98$)	Generic beta-blocker ($n = 119$)	p value
Age (year)	59 ± 14.3	57.5 ± 14.9	.45
Male (%)	46.9	38.7	.27
NYHAFC			.14
II (%)	34.0		
III (%)	43.6	42.4	
IV (%)		11.9	
SBP (mmHg)	115.9 ± 21.3	111.9 + 16.8	.11
HR (bpm)	74.9 ± 16.7	84.2 ± 16.2	.00
AF (%)	26.0	27.7	.49
LVEF (%)	27.0 ± 10. 3	25.4 ± 7.9	.49
Ischemic cause (%)	22.7	31.1	.06
COPD (%)	10.5	7.6	.45
Diabete (%)	37.4	28.6	.38
CKD (%)	48.4	36.1	.07
ACEi/ARB usaged (%)	79.1	76.1	.64
Aldactone usage (%)	65.7	73. 5	.31
Digoxin usage (%)	14.9	25.7	.09
Device usage (%)	7.3	13. 4	.28

Abbreviations. NYHA FC: New York Heart Association Functional Class, SBP: Systolic Blood Pressure, HR: Heart Rate, AF: Atrial Fibrillation, LVEF: Left Ventricular Ejection Fraction, COPD: Chronic Obstructive Pulmonary Diseases, CKD: Chronic Kidney Disease, ACEI: Angiotensin Converting Enzyme Inhibitor, ARB: Angiotensin Receptor Blocker.

Discussion

This study showed similar tolerability of brand and generic beta-blockers both in terms of proportion achieving 50% of the maximum target daily dose and percent of the maximum

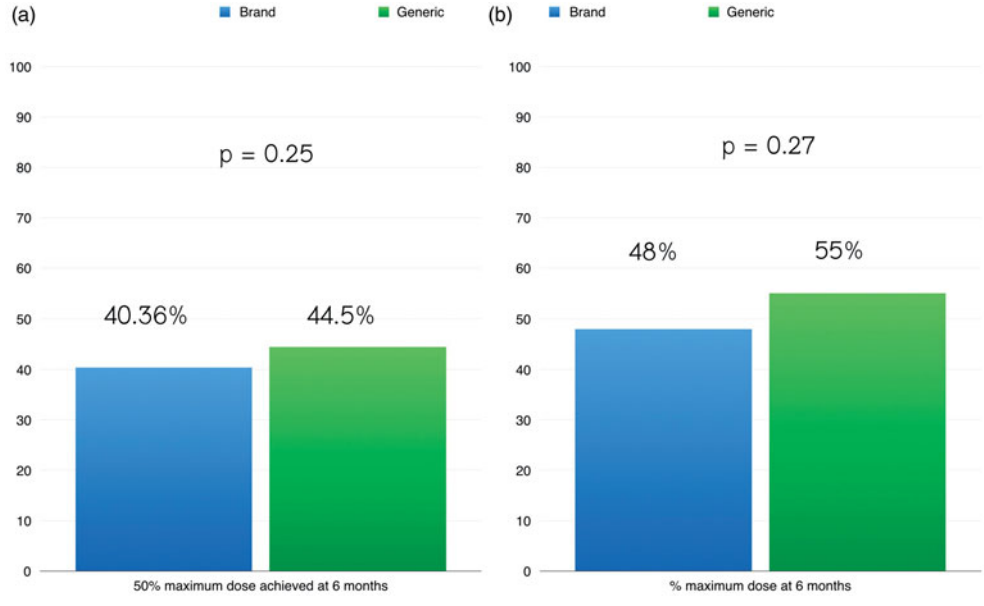

Figure 1. Percentage of maximum target dose.

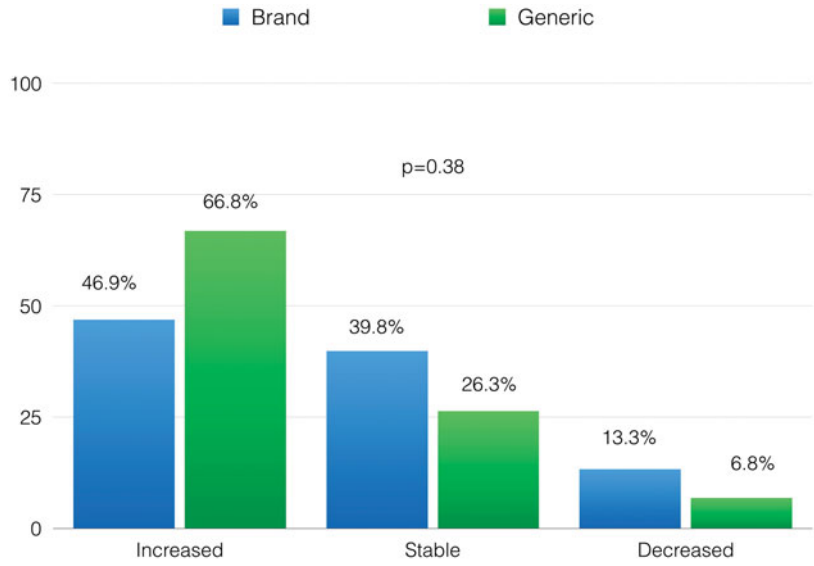

Figure 2. The titrations of beta-blocker dose during 6 months of treatment.

Table 2. Side effects.

Side effect	Brand beta-blocker ($n = 20$)	Generic beta-blocker ($n = 23$)
Heart Failure (%)	4.1	3.4
Dizziness (%)	1.0	1.7
Bradycardia (%)	3.1	3.4
Hypotension (%)	10.2	10.9
Reactive airway (%)	0.8	0

daily dose. The proportion of patients achieving at least 50% of the maximum target daily dose achieved in this study was lower than previously reported in clinical trials [21–24,26] and community surveys [33–36,41,43].

There are possible reasons for the disparity, including patient body size, disease severity, comorbidities and heart rate response to beta-blockers. The patients in our study had more disease severity, in terms of a higher proportion of patients in NYHA FC III and IV and lower LVEF than previous reported. Target heart rate response was achieved in more than half of our patients which may preclude the physician from dose up-titration. Previous studies also showed that causes of drug discontinuation or not achieving the target daily dose were hypotension, bradycardia, worsening heart failure symptoms and reactive airway diseases [44–46]. However, our study ensured that both brand and generic beta-blockers were well tolerated, and most HFrEF patients can tolerate low to moderate doses of beta-blockers.

Generic medications have been used in clinical practice to improve patient access to treatment and cost effectiveness. Previous studies in China demonstrated that generic, low cost or free of charge anti-hypertension drugs had enhanced medication adherence in hypertensive patients leading to prevention of cardiovascular outcomes, reduced total medical costs and more cost effectiveness [47,48]. However, the efficacy and safety of generic medications are important to achieve the benefits of treatment.

Heart failure is a major health economic burden due to high cost of medications, device use and hospitalization. Generic neurohormonal blockage can improve patient access to treatment, improve outcomes and reduce cost of care. This study demonstrated that generic beta-blockers were not different from brand beta-blockers in tolerability and safety. Although this study did not investigate clinical outcomes, beta-blocker dose and heart rate have been shown to be associated with clinical outcomes. Therefore, brand or generic carvedilol and bisoprolol in our study could be prescribed to HFrEF patients who do not have contraindications.

Limitations

Since this was a retrospective study, there were some limitations such as uncontrolled factors and incomplete data recorded. The adverse effects were not adjudicated and dose titration was at the discretion of the cardiologists. The study data showed only on beta-blocker tolerability and side effects but did not compare the clinical efficacy of brand and generic beta-blockers. Further investigation should be performed to define similarities in their clinical efficacy.

Conclusions

The proportion of patients achieving 50% of the target dose and maximum target dose was comparable between generic and brand beta-blockers. Clinical tolerability was also not different. This data ensures that evidence-based beta-blockers could be prescribed to HFrEF patients who have no contraindication regardless of if they are brand or generic formulations.

Transparency

Declaration of funding

There is no funding to report for this study.

Declaration of financial/other relationships

The authors have no financial or other relationships to disclose. JDA peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Acknowledgements

This study was supported by the Faculty of Medicine Fund for Medical Research, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand.

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