International Journal of Cardiology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Evaluating the effectiveness of different beta-adrenoceptor blockers in heart failure patients

Tien-Yu Lin [a,1], Chung-Yu Chen [a,b,*,1], Yaw-Bin Huang [a,b,*,1]

[a] School of Pharmacy, Master Program in Clinical Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan
[b] Department of Pharmacy, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

ARTICLE INFO

Article history:
Received 4 August 2016
Received in revised form 13 November 2016
Accepted 17 December 2016
Available online xxxx

Keywords:
Heart failure
beta-Blockers
Effectiveness

ABSTRACT

Background: According to guidelines and pivotal trials, β-blockers are associated with better survival in patients with heart failure (HF). However, the superiority of any β-blockers is still unclear.
Methods: This retrospective cohort study was conducted using the National Health Insurance Research Database in Taiwan to evaluate the effectiveness of β-blockers and compare the clinical outcomes of different β-blockers in patients with HF. We enrolled patients diagnosed with HF between 2005 and 2012. We then stratified the β-blockers according to the starting dose: lower in group 1 and higher in group 2. A time-dependent Cox proportional hazards regression model was applied to evaluate the effectiveness of the β-blockers.
Results: A total of 14,875 patients with HF were identified during the study period. After propensity-score matching, 5688 patients were included in both the β-blocker user and nonuser groups. We found that group 2 carvedilol and group 2 bisoprolol significantly reduced the risk of death and hospitalization for HF, whereas metoprolol did not. Compared with group 2 carvedilol, survival was not significantly different for group 2 bisoprolol (adjusted hazard ratio = 1.18, 95% confidence interval = 0.88–1.58).
Conclusion: From results, carvedilol and bisoprolol were associated with better outcomes, with no difference between these two β-blockers in patients with HF in Taiwan.

1. Introduction

Heart failure (HF) is an abnormality of cardiac function or structure that impairs the ability of the heart to deliver oxygen to the rest of the body [1]. Although survival has improved over time, the death rate within 5 years of a diagnosis of HF remains at approximately 50% [2]. A randomized controlled trial showed that carvedilol, bisoprolol, and metoprolol improved survival and reduced the risk of hospitalization for cardiac events in patients with HF [3–5]. However, this was a head-to-head comparison of different β-blockers, and the formulation and dosage were controversial in this study [6].

Most current observational studies compared carvedilol with metoprolol. Two studies found that carvedilol was superior to metoprolol tartrate with respect to survival, whereas another study showed no difference between the two medications [6–8]. A Danish study demonstrated no difference between carvedilol and metoprolol succinate [9]. However, a few studies comparing bisoprolol with the other two β-blockers, and the findings do not support differences between these medications [10,11]. Nevertheless, both studies were limited in sample size. In a Danish database study, compared with other β-blockers, carvedilol significantly lowered all-cause mortality and the risk of hospitalization [12]. Another study demonstrated that all three β-blockers improved survival even in chronic hemodialysis patients with HF, and no differences were found between any two of the three β-blockers [13].

In summary, although many current studies evaluated the difference between carvedilol and metoprolol, the results were inconclusive. However, carvedilol and bisoprolol, which are the most commonly approved β-blockers in Taiwan, were rarely discussed, and the results are inconsistent. Therefore, we conducted a retrospective study to evaluate the effectiveness of β-blockers and investigate differences among three β-blockers in patients with HF based on real-world information from a health insurance database.

2. Methods

2.1. Data source

On March 1, 1995, Taiwan launched a single-payer National Health Insurance program. As of 2014, 99.9% of Taiwan's population was enrolled. In this study, we used the Longitudinal Health Insurance Database 2005, which contains all original claim data from 1,000,000 beneficiaries enrolled in the year 2005, randomly sampled from the year

* Corresponding authors at: No. 100, Shih-Chuan 1st Rd., Sanmin District, Kaohsiung City 80708, Taiwan, ROC).
E-mail addresses: jk2975525@hotmail.com (C.-Y. Chen), yabihu@kmu.edu.tw (Y.-B. Huang).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

http://dx.doi.org/10.1016/j.ijcard.2016.12.098
0167-5273/

2005 Registry for Beneficiaries (ID) of the National Health Insurance Research Database (NHIRD) [14]. This study was approved by the institutional review board of Kaohsiung Medical University Hospital on March 14, 2016 [KMUHIRB-EXEMPT (II)-20160014]. Current NHIRD and hospital regulations and guidelines did not mandate informed consent in this retrospective cohort study. All procedures performed were in accordance with the ethical standards of the institutional research committee and with the directives of the Declaration of Helsinki.

2.2. Study population

We identified adults (age ≥ 20 years) with newly diagnosed HF (ICD-9 codes 401.91, 402.11, 404.01, 404.03, 404.11, 404.91, 404.93, and 428) between January 1, 2005, and December 31, 2012. The diagnosis of HF had to meet the criteria of more than three outpatient visit claims with an HF diagnosis within 365 days, or one claim for hospitalization with an HF diagnosis. The date of diagnosis was defined as the index date. We excluded patients who ever stayed in a hospital for longer than 180 days, did not take any HF-related drugs (β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aliskiren, diuretics, milrinone, hydralazine, isosorbide dinitrate, and isosorbide mononitrate) within 1 year of the index date, or died within 30 days of an HF diagnosis.

2.3. Study group and baseline characteristics

Users and nonusers of β-blockers were defined as patients who took any β-blockers for >90 days, and for <90 days, respectively, after the index date. We used 1:1 propensity-score matching to balance the baseline characteristics between β-blocker users and nonusers. Baseline characteristics including age, sex, comorbidities, and co-medications were used to generate predicted probability using logistic regression. Comorbidities were identified if two outpatient diagnoses or one inpatient diagnosis was made within 1 year before the index date. Co-medication was identified if the patient had taken the medication for longer than 30 days (Supplementary eTable 7). The β-blocker users group was further subdivided according to the average daily dose in each 90-day interval, as time-dependent covariates. Therefore, our study population was stratified into the following groups: nonusers (carvedilol <3.125 mg/day, bisoprolol <0.625 mg/day, or metoprolol <25 mg/day), group 1 carvedilol (≥3.125 and <6.25 mg/day), group 2 carvedilol (≥6.25 mg/day), group 1 bisoprolol (≥0.625 and <1.25 mg/day), group 2 bisoprolol (≥1.25 mg/day), group 1 metoprolol (≥25 and <50 mg/day), group 2 metoprolol (≥50 mg/day), and combine (the ratio of the exposure days to any two β-blockers between 0.5 and 2).

2.4. Outcomes

The primary and secondary end points were death from any cause, and hospitalization due to HF exacerbation, respectively. Death was defined as a status record at discharge of "died during hospitalization" or "discharged due to terminal stage" plus disenrollment within 3 days of discharge, or "discharged against medical advice" plus disenrollment within 3 days of discharge [15]. In addition, we defined hospitalization for HF exacerbation as hospitalization with a primary or secondary diagnosis of HF, and after radiography in hospital.

2.5. Statistical analysis

The distributions of baseline data were compared between β-blocker users and nonusers. All data are displayed as a frequency (percentage) or mean and standard deviation. Categorical and continuous variables were examined using the χ^2 test and *t*-test, respectively. Because patients might switch to a different β-blocker, stop their medication, or not take their medication for an interval, traditional methods may be inappropriate to evaluate the relationship between exposure and risk of outcome. To calculate the precise drug exposure, a time-dependent Cox proportional hazards regression model was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) to evaluate the effect of β-blockers on survival outcome and hospitalization for HF exacerbation, with β-blocker groups as time-dependent covariates. The model was adjusted for age, sex, comorbidities, and co-medication. Age, comorbidities, and co-medications were treated as time-dependent covariates. All analyses were performed using SAS statistical software (version 9.4; SAS Institute, Inc., Cary, NC, USA), and a *p*-value <0.05 was considered statistically significant.

2.6. Sensitivity analysis

We performed sensitivity analyses to strengthen our results. First, we excluded patients who used β-blockers within 3 months before the diagnosis of HF in model 1 because the disease severity might differ between prevalent and incident users [16]. Second, because the baseline characteristics might be imbalanced between β-blocker users and nonusers after assignment to one of the β-blocker groups, we included only patients who used one kind of β-blocker (and did not switch to another β-blocker) and had a medication possession ratio of ≥50% in model 2. For comparing users and nonusers, we used 1:2 propensity-score matching to match each β-blocker user to nonusers. For comparing different β-blockers, 1:1 matching was applied to balance the baseline characteristics between β-blockers. Third, evidence-based β-blockers (EBBBs), including carvedilol, bisoprolol, and metoprolol, are associated with better outcomes in patients with HF. In addition, EBBBs and non-EBBBs, divided into selective and nonselective β-blockers, were also commonly used in the population evaluated in our study. However, evidence is lacking regarding their benefits [17]. Therefore, we included patients using any type of β-blocker, to evaluate the effectiveness of EBBBs and non-EBBBs in model 3.

3. Results

3.1. Baseline characteristics

A total of 6502 β-blocker users and 8373 nonusers were included between 2005 and 2012. A flow chart of patient selection is illustrated in Fig. 1. In the full cohort, numerous baseline characteristics were significantly different between the two groups. After 1:1 propensity-score matching, there were 5688 patients in both the β-blocker user and nonuser groups. All demographic information was balanced, with a mean age of 68.2 years, and a similar distribution with respect to sex (Table 1).

3.2. Outcomes in β-blocker users and nonusers

After adjusting for covariates, β-blocker users had a significantly reduced risk of both death from any cause [adjusted HR (aHR) = 0.72, 95% CI = 0.64–0.81, $p < 0.001$] and hospitalization for HF (aHR = 0.74, 95% CI = 0.65–0.85, $p < 0.001$), as shown in Table 2. Stratifying by different β-blockers revealed that death from any cause was significantly decreased in group 2 carvedilol (aHR = 0.56, 95% CI = 0.44–0.71, $p < 0.001$) and group 2 bisoprolol (aHR = 0.67, 95% CI = 0.56–0.80, $p < 0.001$). Additionally, both of these groups also had a significantly lower risk of hospitalization for HF (group 2 carvedilol: aHR = 0.53, 95% CI = 0.39–0.71, $p < 0.001$; group 2 bisoprolol: aHR = 0.50, 95% CI = 0.40–0.63, $p < 0.001$).

3.3. Effectiveness of different β-blockers in the user group

As shown in Table 3, there was no survival benefit in group 2 bisoprolol (aHR = 1.18, 95% CI = 0.88–1.58, $p = 0.269$), or difference in the risk of hospitalization for HF (aHR = 0.94, 95% CI = 0.65–1.34, $p = 0.717$) compared with group 2 carvedilol.

3.4. Sensitivity analysis

A total of 4543 β-blocker users initially fulfilled the new user criteria. After matching, 4425 patients were included in both the user and nonuser groups. Similar to the main results, group 2 carvedilol and group 2 bisoprolol had a significantly reduced risk of death and hospitalization for HF (Supplementary eTable 1). Furthermore, no difference was found between group 2 carvedilol and group 2 bisoprolol (Supplementary eTable 2). In model 2, there were 612 carvedilol users, 1072 bisoprolol users, and 44 metoprolol users. After 1:2 propensity-score matching, there were 1800 (600 users and 1200 nonusers) and 3177 (1059 users and 2118 nonusers) patients in the carvedilol and bisoprolol matched cohort, respectively. Owing to an insufficient sample size of metoprolol users, subsequent analysis included only the carvedilol and bisoprolol users. Consistent with initial analyses, both carvedilol and bisoprolol were associated with a lower risk of death and hospitalization for HF (Supplementary eTables 3 and eTable 4). Additionally, there were no differences in these risks between the two β-blockers (Supplementary eTable 5). Finally, in model 3, there were 8236 β-blocker users and 6639 nonusers included in the sensitivity analysis. A total of 5356 users and 5356 nonusers were included in subsequent analysis after matching. EBBBs showed similar results in the main analysis (Supplementary eTable 6). However, non-EBBBs showed a borderline significant difference in both outcomes (death from any cause: aHR = 0.84, 95% CI = 0.72–0.99, $p = 0.039$; hospitalization for HF: aHR = 0.81, 95% CI = 0.66–1.00, $p = 0.045$).

Please cite this article as: T.-Y. Lin, et al., Evaluating the effectiveness of different beta-adrenoceptor blockers in heart failure patients, Int J Cardiol (2016), http://dx.doi.org/10.1016/j.ijcard.2016.12.098