Clinical Kidney Journal, 2021, vol. 14, no. 3, 983–990

doi: 10.1093/ckj/sfaa248
Advance Access Publication Date: 4 January 2021
Original Article

ORIGINAL ARTICLE

Comparative effectiveness of bisoprolol and carvedilol among patients receiving maintenance hemodialysis

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ABSTRACT

Background. Despite widespread use, there is no trial evidence to inform β-blocker's (BB) relative safety and efficacy among patients undergoing hemodialysis (HD). We herein compare health outcomes associated with carvedilol or bisoprolol use, the most commonly prescribed BBs in these patients.

Methods. We created a cohort study of 9305 HD patients who initiated bisoprolol and 11 171 HD patients who initiated carvedilol treatment between 2004 and 2011. We compared the risk of all-cause mortality and major adverse cardiovascular events (MACEs) between carvedilol and bisoprolol users during a 2-year follow-up.

Results. Bisoprolol initiators were younger, had shorter dialysis vintage, were women, had common comorbidities of hypertension and hyperlipidemia and were receiving statins and antiplatelets, but they had less heart failure and digoxin prescriptions than carvedilol initiators. During our observations, 1555 deaths and 5167 MACEs were recorded. In the multivariable-adjusted Cox model, bisoprolol initiation was associated with a lower all-cause mortality {hazard ratio [HR] 0.66 [95% confidence interval (CI) 0.60–0.73]} compared with carvedilol initiation. After accounting for the competing risk of death, bisoprolol use (versus carvedilol) was associated with a lower risk of MACEs [HR 0.85 (95% CI 0.80–0.91)] and attributed to a lower risk of heart failure [HR 0.83 (95% CI 0.77–0.91)] and ischemic stroke [HR 0.84 (95% CI 0.72–0.97)], but not

Received: 2.8.2020; Editorial decision: 26.10.2020

to differences in the risk of acute myocardial infarction [HR 1.03 (95% CI 0.93–1.15)]. Results were confirmed in propensity score matching analyses, stratified analyses and analyses that considered prescribed dosages or censored patients discontinuing or switching BBs.

Conclusions. Relative to carvedilol, bisoprolol initiation by HD patients was associated with a lower 2-year risk of death and MACEs, mainly attributed to lower heart failure and ischemic stroke risk.

Keywords: acute coronary syndrome, bisoprolol, cardiovascular event, carvedilol, heart failure, hemodialysis, mortality, stroke

INTRODUCTION

Persons with end-stage kidney disease (ESKD) undergoing dialysis are at high risk of developing and dying from cardiovascular (CV) disease [1], for which they often receive CV prevention medications. β-blockers (BBs) are the most commonly used CV medications in hemodialysis (HD) patients, despite scarce interventional evidence on their benefit in them [2–4]. To the best of our knowledge, only two small trials have evaluated BB safety and efficacy in HD patients. First, carvedilol compared with placebo was associated with improved survival among 114 HD patients with dilated cardiomyopathy [5]. Second, atenolol had a lower risk of CV events than lisinopril in 200 HD patients with hypertension and left ventricular hypertrophy [6].

The BB class is heterogeneous with respect to pharmacodynamics and pharmacokinetics. Network meta-analyses of BB trials in patients with heart failure suggest that there are no obvious differences when comparing the different BBs for the risk of death, sudden cardiac death, death due to pump failure or drug discontinuation [7]. However, this may not be the case in patients undergoing HD, given both the unique risk profile of these patients [8, 9] and the possibility that BBs hemodialytic clearance may influence their effectiveness [10, 11]. A large retrospective US cohort study showed that new carvedilol users had an increased risk of 1-year all-cause and CV mortality compared with new metoprolol users [12]. The relative effectiveness of other BBs is unknown and knowledge of these potential differences may support clinicians in their day-to-day decisions [13].

In many health systems [11, 14–16], bisoprolol and carvedilol are the two most commonly used BBs. Bisoprolol may offer advantages over carvedilol because of its β_1 selectivity [9] and moderate dialyzability with less intradialytic hypotension potential [10, 12]. The objective of this study was to evaluate the risk for all-cause mortality and CV events associated with bisoprolol compared with carvedilol in HD patients.

MATERIALS AND METHODS

Study design and data sources

All HD subjects were registered in the Taiwan National Health Insurance Research Database (NHIRD) [17]. The inclusion in the dialysis register requires a medical examination by two nephrologists that investigate underlying disease, laboratory data, renal ultrasonography and indications for dialysis treatment. Diagnosis of HD was confirmed by International Classification of Diseases, Ninth Revision code 585, consecutive HD procedure codes and inclusion in the Catastrophic Illness Patient Database. For this study we enrolled all adult (>18 years) patients who underwent chronic maintenance HD for >90 days with BB use ($n = 58\,476$) between 1 January 2004 and 31 December 2011. We selected those who initiated bisoprolol or carvedilol therapy after HD initiation (identified as the first prescription post-dialysis with an absence of any other BB prescription in the previous 90 days). The date of bisoprolol or carvedilol prescription was set as the index date (Supplementary data, Figure S1). Furthermore, to assess the dose effect, we analyzed the risk of outcomes according to the dose groups as per heart failure guidelines [18, 19] during the 90-day exposure period. The study subjects were assigned to one of the following groups: high-dose bisoprolol (≥10 mg/day), low-dose bisoprolol (≥1.25–<10 mg/day), high-dose carvedilol (≥50 mg/day) and low-dose carvedilol (≥6.25–<50 mg/day).

Study covariates

Comorbidities were defined by the presence of at least one hospital discharge or three consistent diagnoses in medical records during the 180-day time window before the index date. Comorbidities included diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease and tachyarrhythmias (Supplementary data, Table S1). Concurrent medications, including renin–angiotensin–aldosterone system inhibitors, calcium channel blockers, warfarin, statins, digoxin and antiplatelets (aspirin or clopidogrel), were identified by Anatomical Therapeutic Chemical codes (Supplementary data, Table S2).

Study outcomes and follow-up

The main study outcomes were all-cause mortality and major adverse CV events (MACEs). A MACE was defined as a hospital admission with a primary diagnosis of acute myocardial infarction, heart failure or ischemic stroke. All outcome definitions are detailed in Supplementary data, Table S1. Information on deaths was collected from the Catastrophic Illness Database. Patients were followed up until death, deregistration, dialysis modality change, renal transplantation, events or until 2 years from the index date, whichever occurred first. Our main analysis followed an intention-to-treat (ITT) design, whereby we assumed that the patient remained on therapy until the event or end of follow-up.

Statistical analysis

Data are presented as the mean [standard deviation (SD)] for normally distributed continuous variables and proportions for categorical variables. Kaplan–Meier curves were generated showing cumulative probabilities of study outcomes over the 2-year observation time and differences were tested using a log-rank test in the full cohort. After ensuring the fulfillment of proportional hazards assumptions by the Schoenfeld residuals trend test, we applied univariate and multivariable Cox proportional hazards regression for the study of all-cause mortality

associated with bisoprolol or carvedilol use. Covariates included in the multivariable adjustments were age, sex, dialysis vintage, comorbidities and use of concomitant medications. Because dialysis patients are at high risk of death, we applied competing risk analyses to estimate the associated risks of nonfatal events (MACEs and single vascular events) using cause-specific hazard regression. Our main analysis followed an ITT design whereby we assumed that the patient remained on therapy until the event or the end of follow-up.

To address confounding by indication resulting from nonrandom treatment allocation, 1:1 propensity score (PS) matching [20, 21] was performed to balance confounders (age, sex, dialysis vintage, comorbidities and concomitant medications) between bisoprolol and carvedilol users. We created PS-matched pairs with the Mahalanobis metric method [22, 23] without replacement by the nearest number matching with a caliper of 0.0001. Baseline characteristics were then compared before and after PS matching using a standardized mean difference. A standardized mean difference <0.1 was considered to indicate an adequate balance in variables between groups. A Cox regression model and cause-specific hazard regression were applied for all-cause mortality and MACEs, respectively.

In order to evaluate the robustness of our findings, we performed various sensitivity analyses, including subgroup analyses stratifying by baseline coronary artery disease or heart failure comorbidity, modification of our definition of new user as the first identified prescription post-dialysis with an absence of any other BB prescription in the previous 120 and 180 days, censoring patients at the time of BB treatment discontinuation or switching to another BB during follow-up (as-treated analyses), excluding subjects who switched BBs during follow-up and, to assess the impact of residual confounding [24, 25], by applying the E-value methodology [26]. The E-value identifies the minimum strength of the association that unmeasured confounders would need to have with both treatment and outcome, conditional on the measured covariates, to explain the observed association fully. This estimates what the relative risk would have to be for any unmeasured confounder to overcome the observed association of BB with death or MACEs [26]. All analyses were performed using Stata version 14 (StataCorp, College Station, TX, USA). A two-tailed P-value <0.05 was considered significant.

RESULTS

Patient characteristics

During 2004–11, a total of 58 476 patients initiated dialysis treatment in Taiwan. After excluding prevalent BB users ($n = 18\,240$), there were 36 603 patients who initiated BB after incident dialysis treatment. From this pool we then identified patients initiating bisoprolol ($n = 9305$) or carvedilol ($n = 11\,171$) (Figure 1).

The characteristics of the included patients are listed in Table 1. Before PS matching, patients receiving bisoprolol were younger, had shorter dialysis vintage, were more often women, had a higher proportion of hypertension and hyperlipidemia and more commonly used statins and antiplatelets than patients receiving carvedilol. Conversely, carvedilol users had a higher proportion of heart failure and more often used digoxin compared with bisoprolol users. PS matching resulted in 4107 matched pairs with well-balanced baseline characteristics (all standardized differences <0.1). The mean patient age was 55.4 ± 12.3 years, 51.6% were men, 39.9% had diabetes and 78.6% had hypertension (Table 1).

Primary analysis

In the full cohort ($n = 20\,476$), the mean follow-up time was 1.79 years in the bisoprolol group and 1.39 years in the carvedilol group. During this period, 1555 deaths and 5167 MACEs were recorded (Supplementary data, Table S3). Kaplan–Meier curves graphically showed a lower incidence of all-cause mortality and MACEs among patients taking bisoprolol compared with carvedilol users (Figure 2). After multivariable adjustment, patients initiating bisoprolol had a lower mortality risk {adjusted hazard ratio [HR] 0.66 [95% confidence interval (CI) 0.60–0.73]} compared with patients using carvedilol (Table 2). Using cause-specific hazards analysis, users of bisoprolol were at a lower risk of MACEs [HR 0.85 (95% CI 0.80–0.91)], mainly attributed to a lower risk of heart failure [HR 0.83 (95% CI 0.77–0.91)] and ischemic stroke [HR 0.84 (95% CI 0.72–0.97)] (Table 2). No suggestion for heterogeneity was observed in the stratified analysis (Supplementary data, Table S4). Compared with patients who took low-dose carvedilol, those who were prescribed low- or high-dose bisoprolol had a lower risk of all-cause mortality, MACEs and heart failure, but did not differ in their risk of myocardial infarction (Table 3).

Secondary analysis: PS-matched cohort

We identified 4107 pairs of new users of carvedilol and bisoprolol with comparable characteristics as identified through PS matching (Table 1). Compared with carvedilol initiators, bisoprolol initiators had a lower risk of all-cause mortality, MACEs, heart failure and ischemic stroke (Table 2).

Sensitivity analyses

Redefining a new user in our study with larger predispensation windows (120 and 180 days) yielded similar results as the main analysis (Supplementary data, Tables S5 and S6). Censoring at the time of bisoprolol or carvedilol discontinuation/switch (Supplementary data, Table S7), as well as excluding these patients (Supplementary data, Table S8), yielded similar results to our primary analysis.

E-values suggested that unmeasured confounding of considerable strength would be needed to fully explain the observed associations in the unmatched cohort with the multivariable-adjusted model (Supplementary data, Table S9); for example, E-values of bisoprolol compared with carvedilol indicated that the observed HR of 0.66 for all-cause mortality could only be explained by unmeasured confounders that were associated with both initiation of bisoprolol and risk of death by a risk ratio >2.40 over that of the confounders that were measured in this study (upper confidence bound 2.08). The adjusted HRs of most covariates in our multivariable model lie below this value. For example, the adjusted HR was 1.58 for diabetes mellitus and 1.42 for CV disease.

DISCUSSION

In persons with ESKD undergoing dialysis, both interventional [5, 27] and observational studies [3, 14, 28] agree that BBs, compared with nonuse, offer cardioprotection and improved survival. However, BB classes possess different pharmacologic and pharmacokinetic properties, vasodilatory capabilities and beta-adrenergic receptor selectivity [9, 11, 12] that may alter risk–benefit profiles. As emphasized by recent HD guidelines, comparative effectiveness studies on CV medications are needed to inform treatment decisions [13]. Nevertheless,

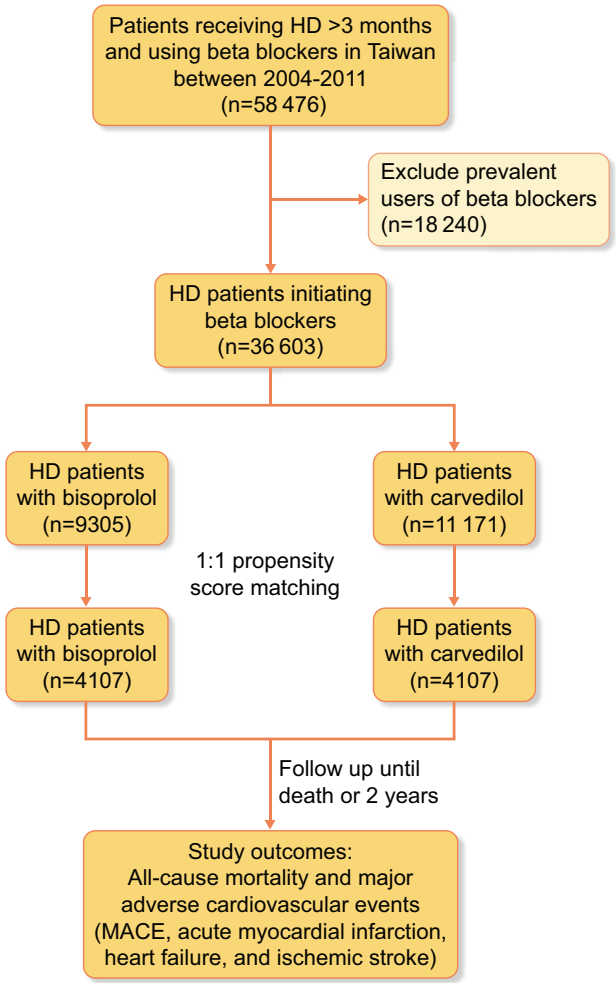

FIGURE 1: Study design and patient selection flow chart.

recruiting patients for such trials has proved challenging, resulting in the premature termination of the BB to LOwer CV Dialysis Events (BLOCADE) trial [29] and accentuating the need to rely on observational studies from routine clinical practice.

Bisoprolol and carvedilol are two of the most commonly used BBs for HD patients in many countries [11, 14–16], but we are not aware of previous studies comparing their relative efficacy. In this nationwide study, we observed that relative to carvedilol, bisoprolol initiation was associated with a 20% lower risk of all-cause mortality and a 13% lower risk of MACEs. Supporting this observation, we also found that both low-dose bisoprolol (≥1.25–<10 mg/day) or high-dose bisoprolol (≥10 mg/day) were associated with a lower risk of all-cause mortality, MACEs and heart failure compared with low-dose carvedilol (≥6.25–<50 mg/day). However, we did not find a dose-dependent protective effect for bisoprolol. Because bisoprolol exerts a strong β_1 selectivity effect that is estimated as 10-fold higher than that of propranolol [9, 30], it is possible that even at regular or low doses, bisoprolol may provide a benefit. Further supporting our observations, cardioselective BBs (atenolol and metoprolol) were found to reduce both all-cause and CV mortality compared with nonselective BBs (carvedilol and labetalol) in a cohort of 4398 incident US hemodialysis and peritoneal dialysis patients [31]. Another carefully designed pharmacoepidemiological analysis from the USA noted that carvedilol initiation had slightly increased rates of all-cause, CV mortality and intradialytic hypotension than metoprolol initiation [12]. Unfortunately, the infrequent use of metoprolol in our study prevented us from confirming or refuting that study.

This is an observational study, and despite our careful design to avoid biases, residual confounding and confounding by indication may explain the observed differences between BBs. Nonetheless, there are differences in bisoprolol and carvedilol pharmacokinetics that provide a rationale in support of bisoprolol's observed superiority. Both drugs lower cardiac contractility and heart rate, but carvedilol has, in addition, α-blocking effects that confer increased vasodilation [32]. It has been proposed that carvedilol's α blockade may increase the risk of intradialytic

Table 1. Baseline characteristics of HD patients initiating bisoprolol or carvedilol before and after PS matching

	Full cohort			1:1 PS matched cohort		
Baseline characteristics	Bisoprolol ($n = 9305$)	Carvedilol ($n = 11\,171$)	Standardized differences	Bisoprolol ($n = 4107$)	Carvedilol ($n = 4107$)	Standardized differences
Age (years), mean ± SD	56.3 ± 13.0	57.1 ± 13.1	0.06	55.4 ± 12.3	55.3 ± 12.3	0.003
Men, *n* (%)	4716 (50.7)	5853 (52.4)	0.034	2121 (51.6)	2124 (51.7)	0.001
Dialysis vintage (years), mean ± SD	4.72 ± 2.65	4.89 ± 2.72	0.061	5 ± 2.69	5.26 ± 2.76	0.096
Comorbidities, *n* (%)						
Diabetes mellitus	4581 (49.2)	5536 (49.6)	0.007	1640 (39.9)	1638 (39.9)	0.001
Hypertension	7313 (78.6)	8476 (75.9)	0.065	3228 (78.6)	3226 (78.5)	0.001
Hyperlipidemia	2063 (22.2)	2270 (20.3)	0.045	442 (10.8)	444 (10.8)	0.002
Coronary artery disease[a]	3374 (36.3)	4122 (36.9)	0.013	955 (23.3)	952 (23.2)	0.002
Myocardial infarction	830 (8.9)	949 (8.5)	0.015	131 (3.2)	129 (3.1)	0.003
Heart failure	2391 (25.7)	3348 (30.0)	0.095	731 (17.8)	729 (17.8)	0.001
Peripheral vascular disease	615 (6.6)	718 (6.4)	0.007	54 (1.3)	51 (1.2)	0.007
Cerebrovascular disease	1059 (11.4)	1265 (11.3)	0.002	113 (2.8)	108 (2.6)	0.008
Tachyarrhythmias[b]	418 (4.5)	448 (4.0)	0.024	155 (3.8)	116 (2.8)	0.053
Concomitant drugs, *n* (%)						
RAAS inhibitors	1157 (12.4)	1296 (11.6)	0.026	205 (5.0)	203 (4.9)	0.002
Calcium channel blockers	588 (6.3)	683 (6.1)	0.008	39 (0.9)	39 (0.9)	0
Warfarin	134 (1.4)	149 (1.3)	0.009	32 (0.8)	28 (0.7)	0.011
Statins	1988 (21.4)	2082 (18.6)	0.068	405 (9.9)	404 (9.8)	0.001
Digoxin	190 (2.0)	290 (2.6)	0.037	56 (1.4)	62 (1.5)	0.012
Antiplatelets (aspirin, clopidogrel)	2530 (27.2)	2860 (25.6)	0.036	496 (12.1)	492 (12.0)	0.003
PS probability, mean ± SD	0.46 ± 0.04	0.45 ± 0.04	0.162	0.45 ± 0.03	0.45 ± 0.03	0

[a]Coronary artery disease includes myocardial infarction, history of percutaneous coronary interventions and history of coronary artery bypass surgery.
[b]Tachyarrhythmias included paroxysmal supraventricular tachycardia, atrial flutter and atrial fibrillation.
RAAS: renin–angiotensin–aldosterone system.

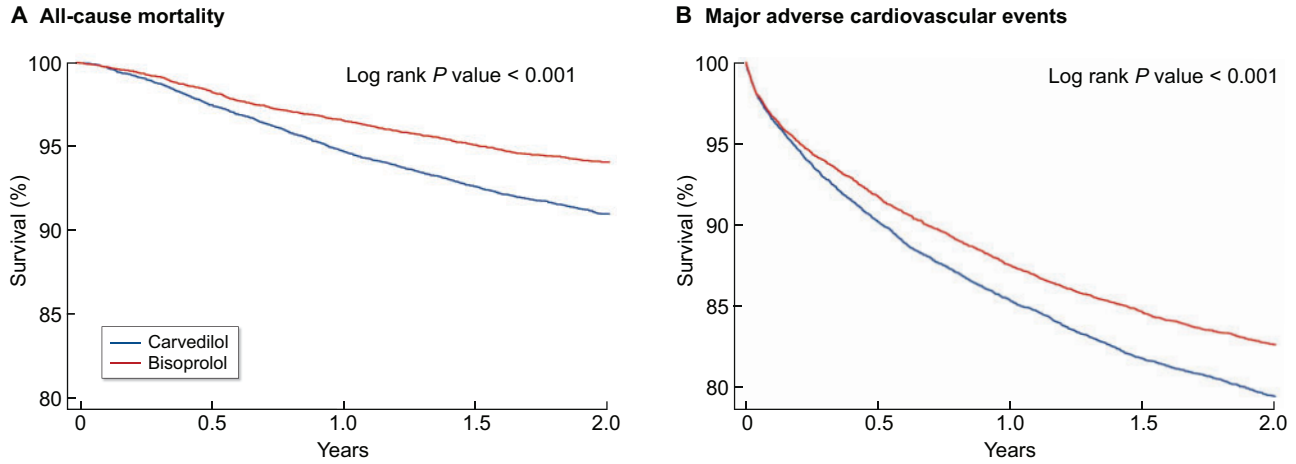

FIGURE 2: Kaplan–Meier curves for the incidence of (**A**) all-cause death and (**B**) MACEs according to the initiation of bisoprolol or carvedilol in patients undergoing HD (full cohort).

hemodynamic instability during HD because it inhibits the compensatory effect of sympathetic nervous system–mediated peripheral vasoconstriction [12]. Unfortunately, we lack records of intradialytic blood pressure in our study to test this hypothesis. On the other hand, the removal of BBs by HD may also affect intradialytic blood pressure. While carvedilol is poorly dialyzed, bisoprolol is moderately dialyzed [10]. Thus the blood pressure–lowering effects of carvedilol may persist throughout the dialysis course, whereas the blood pressure–lowering effects of bisoprolol may be reduced as circulating drug concentrations decrease during HD therapy [33–36]. Although carvedilol has antioxidant properties and a good metabolic profile compared with other BBs [37, 38], the hypotensive side effects of carvedilol exacerbated by marked fluctuations in extracellular fluid volume in HD may counteract the CV protection benefit. In a secondary analysis of BLOCADE, treatment with carvedilol did not modify surrogate cardiac biomarkers, but instead increased both brain natriuretic peptide and N-terminal pro-B-type natriuretic peptide natriuretic peptide levels [39].

Strengths and limitations

This study has several strengths, including large sample sizes, comprehensive follow-up and outcome applicable to real-world

Table 2. Outcomes associated with the initiation of bisoprolol versus carvedilol in patients undergoing HD (ITT analysis)

Main outcomes	Full cohort, no. of events/no. of subjects	HR (95% CI) Full cohort, crude ($n = 20\,476$)	HR (95% CI) Full cohort, adjusted[b] ($n = 20\,476$)	HR (95% CI) 1:1 PS-matched cohort ($n = 8214$)
All-cause mortality				
Bisoprolol	550/9305	0.65 (0.58–0.72)	0.66 (0.60–0.73)	0.80 (0.67–0.96)
Carvedilol	1005/11 171	1 (Reference)	1 (Reference)	1 (Reference)
MACE[a]				
Bisoprolol	2184/9305	0.83 (0.78–0.89)	0.85 (0.80–0.91)	0.87 (0.77–0.98)
Carvedilol	2983/11 171	1 (Reference)	1 (Reference)	1 (Reference)
Single MACE				
Acute myocardial infarction				
Bisoprolol	789/9305	1.01 (0.91–1.13)	1.03 (0.93–1.15)	1.03 (0.85–1.26)
Carvedilol	941/11 171	1 (Reference)	1 (Reference)	1 (Reference)
Heart failure				
Bisoprolol	1560/9305	0.80 (0.73–0.86)	0.83 (0.77–0.91)	0.81 (0.71–0.94)
Carvedilol	2182/11 171	1 (Reference)	1 (Reference)	1 (Reference)
Ischemic stroke				
Bisoprolol	366/9305	0.82 (0.71–0.95)	0.84 (0.72–0.97)	0.70 (0.54–0.91)
Carvedilol	509/11 171	1 (Reference)	1 (Reference)	1 (Reference)

[a]MACE events included myocardial infarction, heart failure hospitalization and ischemic stroke. Major CV outcomes and single CV outcomes were analyzed by a cause-specific hazard model as a competing risk model.
[b]The multivariable-adjusted model was obtained from Cox regression models adjusted for age, sex, dialysis vintage, comorbidities and concomitant medications.

Table 3. Outcomes associated with carvedilol or bisoprolol use by prescribed dose categories (ITT analysis)

Outcomes	No. of events/no. of subjects	HR (95% CI) Crude	HR (95% CI) Multivariable adjusted model[b]
All-cause mortality			
High-dose bisoprolol	193/2870	0.73 (0.63–0.86)	0.81 (0.69–0.94)
Low-dose bisoprolol	357/6435	0.60 (0.53–0.68)	0.61 (0.54–0.69)
High-dose carvedilol	27/358	0.83 (0.57–1.22)	1.32 (0.90–1.94)
Low-dose carvedilol	978/10 813	1 (Reference)	1 (Reference)
MACE[a]			
High-dose bisoprolol	558/2870	0.75 (0.68–0.83)	0.88 (0.79–0.97)
Low-dose bisoprolol	1626/6435	0.85 (0.79–0.92)	0.84 (0.78–0.91)
High-dose carvedilol	54/358	0.58 (0.43–0.79)	0.87 (0.64–1.17)
Low-dose carvedilol	2929/10 813	1 (Reference)	1 (Reference)
Acute myocardial infarction			
High-dose bisoprolol	200/2870	0.92 (0.78–1.08)	1.07 (0.90–1.26)
Low-dose bisoprolol	589/6435	1.04 (0.92–1.17)	1.02 (0.91–1.15)
High-dose carvedilol	16/358	0.65 (0.39–1.06)	1.01 (0.62–1.66)
Low-dose carvedilol	925/10 813	1 (Reference)	1 (Reference)
Heart failure			
High-dose bisoprolol	379/2870	0.70 (0.62–0.80)	0.84 (0.74–0.96)
Low-dose bisoprolol	1181/6 435	0.82 (0.75–0.90)	0.83 (0.75–0.90)
High-dose carvedilol	36/358	0.50 (0.34–0.75)	0.78 (0.52–1.16)
Low-dose carvedilol	2146/10 813	1 (Reference)	1 (Reference)
Ischemic stroke			
High-dose bisoprolol	102/2870	0.80 (0.64–1.01)	0.88 (0.70–1.10)
Low-dose bisoprolol	264/6435	0.82 (0.69–0.97)	0.82 (0.70–0.97)
High-dose carvedilol	11/358	0.71 (0.38–1.33)	0.99 (0.53–1.85)
Low-dose carvedilol	498/10 813	1 (Reference)	1 (Reference)

BB dosage definition: high-dose bisoprolol, ≥10 mg/day; low-dose bisoprolol, ≥1.25–<10 mg/day; high-dose carvedilol, ≥50 mg/day; low-dose carvedilol, ≥6.25–<50 mg/day). Low-dose carvedilol users are the reference group.
[a]Major CV events included myocardial infarction, heart failure hospitalization and ischemic stroke. Major CV outcome was analyzed by a cause-specific hazard model as a competing risk model.
[b]Multivariable adjusted model was obtained from Cox regression models adjusted for age, sex, dialysis vintage, comorbidities and concomitant medications.

practice. However, this study also has limitations. Despite careful control for potential confounders, observational studies can never eliminate the influence of indication bias, coding errors or misdiagnoses in administrative records. This being said, the diagnostic accuracy of NHIRD claims was previously found be high for our study outcomes [17, 40, 41]. Some confounders were not available in our study and must be acknowledged, including body mass index, heart rate, blood pressure, echocardiography parameters, lifestyle and actual drug utility time. Because of this, the bisoprolol or carvedilol effect on HD patients with heart failure with preserved ejection fraction could not be evaluated. Our efforts to quantify this risk of residual confounding (falsification outcomes and E value estimations) suggest, however, that this bias risk is moderately low. In addition, although we tried to evaluate the dose–effect between bisoprolol and carvedilol, we still need to acknowledge that BB prescription does not guarantee that the patient complies with the treatment. Finally, our study pertains to Taiwan healthcare in a population of Asian ethnicity. Extrapolation to other practices and populations should be done with caution.

CONCLUSION

Our study showed that relative to carvedilol, bisoprolol initiation in patients undergoing HD was associated with a lower risk of death and MACEs. While our findings may inform clinical decisions regarding the choice of BBs in this high-risk population. In the absence of trial evidence, this study may inform the choice of BB therapy in this high-CV-risk population with a void of evidence.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

ACKNOWLEDGEMENTS

This study is based in part on data from the NHIRD provided by the Bureau of National Health Insurance, Department of Health and managed by the National Health Research Institutes. The interpretation and conclusions contained herein do not represent the views of the Bureau of National Health Insurance, Department of Health or National Health Research Institutes.

FUNDING

This work was supported by grants from the Swedish Research Council (grant 2019-01059), the Swedish Heart and Lung Foundation, Kaohsiung Medical University (KMU-Q108024) and Kaohsiung Medical University Hospital (KMUH108-8M11, KMUH107-7R16, KMUH106-6T03, KMUH 106-6R17, KMUH104-4R11 and KMUH103-3R10).

AUTHORS' CONTRIBUTIONS

P.H.W. and Y.T.L. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. P.H.W., Y.T.L. and J.J.C. were involved in the study concept and design. P.H.W, Y.T.L. and J.S.L. were responsible for the acquisition, analysis and interpretation of data. P.H.W. and Y.T.L. drafted the manuscript. Y.C.T., M.C.K., Y.W.C. and S.J.H. were responsible for critical revision of the manuscript for important intellectual content. Y.T.L and J.S.L. were responsible for the statistical analysis. P.H.W. and Y.W.C. obtained funding. J.S.L., M.C.K. and Y.W.C. were responsible for administrative, technical or material support. Y.W.C., S.J.H. and J.J.C were responsible for supervision.

CONFLICT OF INTEREST STATEMENT

None declared.

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