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β-Blocker Use and Risk of Mortality in Heart Failure Patients Initiating Maintenance Dialysis

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Rational & Objective: Beta-blockers are recommended for patients with heart failure (HF) but their benefit in the dialysis population is uncertain. Beta-blockers are heterogeneous, including with respect to their removal by hemodialysis. We sought to evaluate whether β-blocker use and their dialyzability characteristics were associated with early mortality among patients with chronic kidney disease with HF who transitioned to dialysis.

Study Design: Retrospective cohort study.

Setting & Participants: Adults patients with chronic kidney disease (aged ≥18 years) and HF who initiated either hemodialysis or peritoneal dialysis during January 1, 2007, to June 30, 2016, within an integrated health system were included.

Exposures: Patients were considered treated with β-blockers if they had a quantity of drug dispensed covering the dialysis transition date.

Outcomes: All-cause mortality within 6 months and 1 year or hospitalization within 6 months after transition to maintenance dialysis.

Analytical Approach: Inverse probability of treatment weights using propensity scores was used to balance covariates between treatment groups. Cox proportional hazard analysis and logistic regression were used to investigate the association between β-blocker use and study outcomes.

Results: 3,503 patients were included in the study. There were 2,115 (60.4%) patients using β-blockers at transition. Compared with nonusers, the HR for all-cause mortality within 6 months was 0.79 (95% CI, 0.65-0.94) among users of any β-blocker and 0.68 (95% CI, 0.53-0.88) among users of metoprolol at transition. There were no observed differences in all-cause or cardiovascular-related hospitalization.

Limitations: The observational nature of our study could not fully account for residual confounding.

Conclusions: Beta-blockers were associated with a lower rate of mortality among incident hemodialysis patients with HF. Similar associations were not observed for hospitalizations within the first 6 months following transition to dialysis.

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Heart failure (HF) is common in the chronic kidney disease (CKD) population, affecting up to 70% of patients transitioning to maintenance dialysis.[1,2] It is one of the most common reasons for hospitalization before this transition and a leading cause of death among patients receiving both hemodialysis (HD)[3] and peritoneal dialysis (PD).[4] Among dialysis patients with HF, the probability of survival at 24 months was reported to be only 66% compared to 83% among those without HF.[5] HF, along with coronary artery disease, arrhythmia, and cardiac arrest, accounts for ~50% of deaths in dialysis patients.[5] The benefits of β-blocker therapy are well accepted and thought to be beneficial in patients with CKD not treated by dialysis.[6,7] The 2017 American College of Cardiology/American Heart Association/The Heart Failure Society of America guidelines[8] strongly advocate for β-blocker therapy, especially in patients with reduced ejection fraction (EF; left ventricular EF ≤ 40%).[9,10]

The benefit of β-blocker therapy among the high-risk dialysis population is uncertain. Dialysis patients with cardiovascular disease are usually excluded from many important clinical trials, resulting in the lack of information for medication efficacy among this population overall. Previous observational studies have shown conflicting results on whether there are benefits with β-blocker use among dialysis patients with HF. A randomized trial of β-blockers in established dialysis patients with dilated cardiomyopathy showed a benefit with therapy but the trial was small and focused on patients who were stable on dialysis.[11] Earlier studies suggested that dialysis itself can potentially relieve HF and no additional treatment is likely needed.[12-15] Conversely, an observation from the US Renal Data System (USRDS) found better survival among β-blocker users receiving dialysis.[16] A systematic review of β-blockers considered this drug class as one of the most important methods to treat HF in kidney failure treated by dialysis.[17] These conflicting results have led to large variances in the utilization rate of β-blockers in the dialysis population, from 10% of patients in Japan to ~60% in the United States.[5,18,19] To date, there are no guidelines or consensus recommendations for the dialysis population with systolic HF.

The differing characteristics of the various β-blockers may impact their effectiveness in patients receiving dialysis. They have different pharmacologic characteristics, including their effects on α-blockade, vasodilation, β receptor selectivity, and intrinsic sympathetic activity.[20] Some β-blockers such as atenolol, metoprolol, nadolol,

and bisoprolol can be removed from the circulation during dialysis and are considered highly dialyzable, whereas others are not.[19,21,22] Among patients receiving long-term HD, initiation of treatment with poorly dialyzable β-blockers was associated with lower risk for death,[23] yet other studies have reported different findings. A retrospective cohort study suggested that higher mortality was observed among prevalent HD patients initiated on treatment with carvedilol (nondialyzable) compared with metoprolol.[24] Overall, these observations have raised awareness about the importance of selecting β-blockers more carefully among populations receiving dialysis.

In this study, we aimed to address 2 questions among patients with HF who transitioned to dialysis (HD and PD): first, whether β-blocker use is associated with improved short-term outcomes after dialysis transition; and second, whether there are differences in outcomes associated with different types of β-blockers. Accordingly, we examined a large diverse CKD population with HF who transitioned to dialysis and evaluated β-blocker use and different β-blocker types on short-term survival and hospitalizations.

Methods

Study Populations

Kaiser Permanente Southern California (KPSC) is an integrated health care delivery system serving more than 4.5 million members through 15 medical centers and more than 200 medical offices in southern California. The members share similar coverage benefits for visits and medications. Treatment of chronic conditions such as hypertension are often standardized throughout the health system.[25,26] Membership is reflective of southern California in terms of race/ethnicity and socioeconomic status.[27] All health information for this study was collected from a common electronic health record. In addition, KPSC Renal Business Group maintains a registry of patients with kidney failure receiving kidney replacement therapy, recording and following up all KPSC patients who underwent kidney transplantation or received dialysis at an outpatient dialysis center. In this study, patients in this KPSC registry were further confirmed by linkage to the USRDS. The study protocol was reviewed and approved by the KPSC Institutional Review Board and exempted from informed consent (IRB approval #10254).

A retrospective cohort was formed from adults (aged ≥18 years) who transitioned to dialysis, including those who received HD (in-center, home, or nocturnal) or PD in KPSC from January 1, 2007, to June 30, 2016. Patients who had a documented HF diagnosis and an echocardiogram result within 5 years before dialysis initiation were included.[28]

Exposure and Covariates

Information for demographic characteristics (age, sex, and race/ethnicity) and clinical history such as vital signs, laboratory results, and other medication dispensing were extracted from the electronic health record. Median heart rate and median blood pressure during the 365 days before transition were calculated. Active comorbid conditions of patients were also identified from the electronic health record using *International Classification of Diseases, Ninth or Tenth Revision* codes in the preceding 1 year. Specifically, codes used to identify HF are listed in Table S1. Echocardiogram results were extracted using a computerized natural language–processing algorithm validated in KPSC.[28] The left ventricular EF measured closest to and before the date of dialysis transition was used. The status of other medications taken at the time of transition was also identified as dispense date plus supply days covering the dialysis transition date. Modality and dialysis initiation date were obtained from the KPSC Renal Business Group registry and confirmed using the USRDS database. Primary cause of kidney failure was ascertained from USRDS records.

Information about β-blockers dispensed in quantities that would span at transition (defined as dispense date plus supply days covering the transition) was collected from outpatient pharmacy records.[19] In 1 sensitivity analysis, we further specifically compared atenolol, metoprolol, bisoprolol, carvedilol, or other β-blockers versus no β-blocker among patients with congestive HF initiating dialysis. In another sensitivity analysis, β-blockers were categorized by their dialyzability to evaluate the relationship with outcome. Atenolol, metoprolol, bisoprolol, and nadolol were categorized as highly dialyzable, whereas others including carvedilol, labetolol, and propranolol were considered poorly dialyzable.

Outcomes

The primary outcome in this study was mortality within 6 months after transition to dialysis. The risk was compared at transition to dialysis between those taking β-blockers and those who were not. Mortality was identified from the KPSC mortality database, which combines information from 7 data sources including California State Death Master Files, Social Security Administration Death Master Files, and KPSC hospital and emergency room records. Patients were followed up from dialysis initiation date to first disenrollment, death, or 6 months, whichever came first. Mortality rates were reported as events per 1,000 patient-years. Mortality within 1 year after transition to dialysis was also evaluated and compared.

Risks for all-cause hospitalization and hospitalization with primary cause of HF or myocardial infarction (MI) were evaluated and compared between patients taking and not taking β-blockers.

Inverse Probability of Treatment Weighting With Propensity Score

To reduce the effects of bias from treatment selection and mimic a randomized controlled trial, a propensity score was created using logistic regression for each patient to

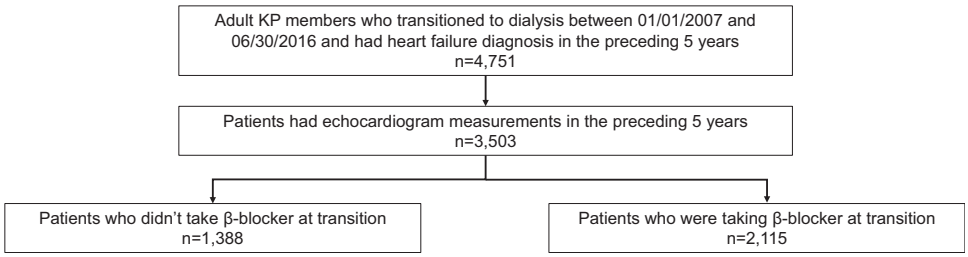

Figure 1. Cohort assembly of dialysis patients. Abbreviation: KP, Kaiser Permanente.

estimate the probability of taking a β-blocker at transition based on patient profiles. Risk factors found to be significantly related to β-blocker use or from previous clinical knowledge were included in the model to produce a propensity score. These factors included age, sex, race/ethnicity, primary cause of kidney failure, EF values, median heart rate, average systolic blood pressure in the 1 year before dialysis, active comorbid conditions (atrial fibrillation, liver disease, and coronary artery disease), and concomitant use of other medications, including angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, α-blockers, clopidogrel, calcium channel blockers, diuretics, hydralazine, nitrates, and statins. To avoid bias from extremely large or low weights, stabilized weights were calculated using original propensity score multiplied by the marginal distribution of treatment and control in the overall population separately.[29,30] Then the stabilized weight with propensity score was applied to the study population to create a pseudo cohort with balanced covariates between the 2 groups.

Statistical Methods

Patients' demographic and clinical characteristics were compared between patients taking and not taking β-blockers at dialysis transition. The standardized mean difference (SMD) was applied to compare covariates at baseline before and after inverse probability of treatment weighting (IPTW).[31,32] Cohen's guideline was applied in the study to evaluate the magnitude of difference: small, SMD = 0.1; medium, SMD = 0.5; and large, SMD = 0.8. The *t* test and χ^2 test were used to indicate statistical difference for continuous and categorical variables, respectively, between patients taking high- and low-dialyzable β-blockers.

To evaluate the effect of β-blockers on risk for mortality after transition, Cox proportional hazard regression was performed in the weighted sample using intent-to-treat or time-varying analysis. A sensitivity analysis among HD patients with HF was performed to test whether specific β-blockers and the varying dialyzability of β-blockers affect short-term mortality. The effect of β-blockers on mortality by EF values was examined by testing for interaction and also by performing a stratified analysis.

To examine the effect of β-blockers on hospitalizations within 6 months of transition, logistic regression was performed and odds ratios were obtained for all-cause hospitalization, hospitalization for a primary cause of HF or acute MI, and combined end point of all-cause mortality and hospitalization due to HF and MI.

All statistical analyses were performed using the SAS Enterprise Guide (version 7.1; SAS Institute).

Results

Among all adult members of KPSC who transitioned to dialysis in the study period, 4,751 (49.0%) had a diagnosis of HF in the preceding 5 years. The final cohort was composed of 3,503 patients with HF diagnosis and documented EF measured in the same period (Fig 1).

Mean age of the cohort was 68 ± 12 (standard deviation) years with 42.0% women. Twenty percent of patients with HF had reduced EF (EF ≤ 40%; Table 1). Using outpatient pharmacy dispensing records, we identified 2,115 (60.4%) patients with HF who were taking β-blockers at dialysis transition. Among 1,388 patients who were not taking β-blockers at transition, 81.3% had a history of taking β-blockers. Median duration of β-blocker exposure was 12 months. The median time when discontinued was 6 months before initiating dialysis. Compared with those who were not using β-blockers, patients using β-blockers were older and had more comorbid conditions such as diabetes (69.6% vs 65.9%) and coronary heart disease (68.2% vs 60.5%). Patients using β-blockers also had higher concomitant use of other common cardiac medications, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, hydralazine, and nitrates (Table 1). Among patients who were taking β-blockers, 906 (42.8%) were using metoprolol (894 using metoprolol tartrate), 650 (30.7%) were using carvedilol, and 444 (21.0%) were using atenolol. Only 48 (3.1%) were using bisoprolol or other β-blocker subtypes. Patients who were using highly dialyzable β-blockers had higher blood pressures and had a greater proportion with a median heart rate < 60 beats/min in the 365 days before dialysis (Table S2).

Propensity scores were calculated and compared between patients who were using versus not using β-blockers at transition (Fig S1). After IPTW with stabilized

Table 1. Characteristics of Dialysis Patients With HF Who Were or Were Not Taking β-Blockers at Transition to Dialysis

	Unweighted		After IPTW	
	Nonuser at Transition (n = 1,388)	β-Blocker User at Transition (n = 2,115)	Nonuser at Transition (n = 1,400)	β-Blocker User at Transition (n = 2,106)
Age at transition, y	67.3 ± 12.5	68.5 ± 11.1	68.2 ± 12.1	68.1 ± 11.4
Female sex	603 (43.4%)	870 (41.1%)	598 (42.7%)	891 (42.3%)
Race/ethnicity				
White	425 (30.6%)	680 (32.2%)	446 (31.9%)	664 (31.5%)
Asian	123 (8.9%)	215 (10.2%)	130 (9.3%)	200 (9.5%)
Black	354 (25.5%)	448 (21.2%)	322 (23.0%)	485 (23.0%)
Hispanic	458 (33.0%)	726 (34.3%)	474 (33.9%)	714 (33.9%)
Other/unknown	28 (2.0%)	46 (2.1%)	28 (1.9%)	44 (2.1%)
Primary cause of kidney failure				
Diabetes	914 (65.9%)	1,471 (69.6%)	949 (67.8%)	1,434 (68.1%)
Primary glomerulonephritis	33 (2.4%)	43 (2.0%)	33 (2.4%)	46 (2.2%)
Secondary glomerulonephritis/vasculitis	19 (1.4%)	10 (0.5%)	11 (0.8%)	16 (0.8%)
Interstitial nephritis/pyelonephritis	13 (0.9%)	18 (0.9%)	12 (0.8%)	18 (0.9%)
Hypertension/large vessel disease	264 (19.0%)	411 (19.4%)	280 (20%)	411 (19.5%)
Cystic/hereditary/congenital disease	8 (0.6%)	6 (0.3%)	5 (0.3%)	7 (0.4%)
Neoplasms/tumors	26 (1.9%)	25 (1.2%)	21 (1.5%)	33 (1.6%)
Miscellaneous conditions	80 (5.8%)	94 (4.4%)	65 (4.6%)	101 (4.8%)
Unknown	31 (2.2%)	37 (1.7%)	25 (1.8%)	39 (1.8%)
Ejection fraction ≤ 40%	268 (19.3%)	419 (19.8%)	271 (19.3%)	410 (19.5%)
Mean SBP ≥ 140 mm Hg[a]	710 (51.2%)	1,064 (50.3%)	718 (51.3%)	1,070 (50.8%)
Median pulse rate < 60 beats/min[a]	124 (8.9%)	235 (11.1%)	141 (10.1%)	216 (10.2%)
Charlson Comorbidity Index score ≥ 9	727 (52.4%)	1,162 (54.9%)	775 (55.2%)	1,143 (54.2%)
Pre-existing comorbid conditions				
Atrial fibrillation	258 (18.6%)	432 (20.4%)	279 (20.0%)	417 (19.8%)
Peripheral arterial disease	77 (5.5%)	105 (5.0%)	83 (5.9%)	101 (4.8%)
Coronary heart disease	840 (60.5%)	1,443 (68.2%)	914 (65.2%)	1,374 (65.2%)
Liver disease	112 (8.1%)	174 (8.2%)	116 (8.3%)	174 (8.3%)
CVA	64 (4.6%)	94 (4.4%)	64 (4.6%)	94 (4.4%)
Other medications used at transition				
ACEi	138 (9.9%)	376 (17.8%)	222 (15.8%)	315 (14.9%)
ARB	107 (7.7%)	267 (12.6%)	151 (10.8%)	226 (10.7%)
Aldosterone antagonist	41 (3.0%)	86 (4.1%)	51 (3.6%)	77 (3.7%)
Diuretics	542 (39%)	1,198 (56.6%)	710 (50.7%)	1,056 (50.1%)
Hydralazine	244 (17.6%)	541 (25.6%)	322 (23.0%)	479 (22.7%)
Nitrates	155 (11.2%)	408 (19.3%)	228 (16.2%)	342 (16.2%)
α-Blocker	150 (10.8%)	326 (15.4%)	192 (13.7%)	289 (13.7%)
Clopidogrel	87 (6.2%)	134 (6.3%)	87 (6.2%)	134 (6.3%)
Calcium channel blocker	469 (33.5%)	695 (33.0%)	471 (33.6%)	696 (33.0%)
Statin	387 (27.9%)	945 (44.7%)	542 (38.6%)	811 (38.4%)

Age given as mean ± standard deviation; values for categorical variables given as count (percentage).
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angotensin receptor blocker; CVA, cerebrovascular accident; HF, heart failure; SBP, systolic blood pressure.
[a]In 365 days before transition.

propensity score was applied, baseline characteristics in the pseudo sample were examined (Table 1). SMDs of all potential confounders between β-blocker–treated and –nontreated persons were less than 0.1, indicating good balance (Fig 2).

Mortality Within 6 Months and 1 Year

There were 455 deaths reported within 6 months and 726 within 1 year after dialysis initiation. The crude mortality rate among patients with HF but not taking β-blockers was higher than for those who were taking β-blockers at transition (26.1/1,000 person-years vs 21.8/1,000 person-years). As shown in Table 2, compared with those not taking β-blockers, the hazard ratio (HR) for mortality within 6 months was 0.79 (95% CI, 0.65-0.94) among those taking β-blockers while transitioning to dialysis. The lower mortality HRs for those taking β-blockers were similar within different race/ethnicity groups (Table S3).

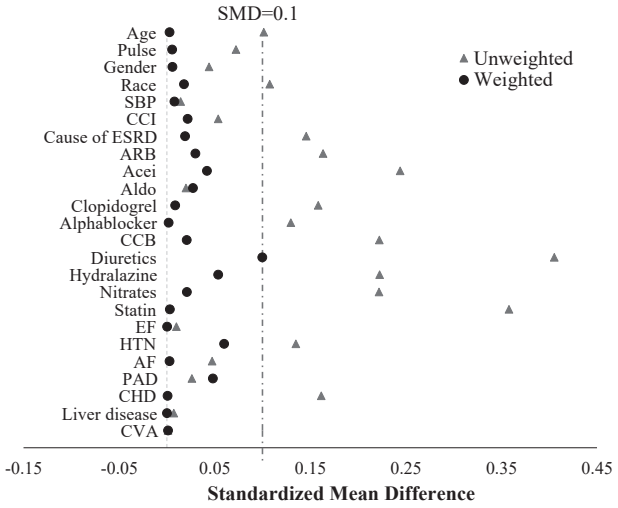

Figure 2. Standardized mean difference (SMD) of patients' characteristics comparison before and after inverse probability of treatment weighting with propensity score. Abbreviations: Acei, angiotenin-converting enzyme inhibitor; AF, atrial fibrillation; Aldo, aldosterone antagonist; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CCI, Charlson Comorbidity Index; CHD, coronary heart disease; CVA, cerebrovascular accident; EF, ejection fraction; ESRD, end-stage renal disease; HTN, hypertension; PAD, peripheral arterial disease; SBP, systolic blood pressure.

The 1 year-mortality HR was 0.78 (95% CI, 0.68-0.91) for those taking β-blockers compared with those not taking β-blockers (Table 2). To account for the updated β-blocker status within 1 year after onset of maintenance dialysis, a time-varying analysis was performed that demonstrated that β-blocker use had a 1-year mortality HR of 0.80 (95% CI, 0.68-0.93; Table S4).

We further compared the effect of the most commonly used β-blockers among patients receiving HD. Among patients who transitioned to HD, the HR for mortality within 6 months was 0.79 (95% CI, 0.65-0.95) if they were using β-blockers. We observed that the mortality HR within 6 months was 0.68 (95% CI, 0.53-0.88) for metoprolol versus no β-blockers, whereas the HR with other β-blockers did not reach significance (Table 3). When categorized by dialyzability, mortality HR within 6 months was 0.72 (95% CI, 0.58-0.90) for patients using highly dialyzable β-blockers and 0.86 (95% CI, 0.68-1.10) for patients using poorly dialyzable β-blockers compared with patients not using β-blockers at transition (Table S5). To account for possible effects from additional vasodilatory characteristics of β-blockers, we repeated the analysis after excluding carvedilol and nebivolol and obtained similar results (Table S5).

We also examined whether the effects of β-blockers may be different among patients with reduced (≤40%) or preserved (>40%) EF. Crude mortality rates were 36.1/1,000 person-years among patients with reduced EF and 20.6/1,000 person-years among those with preserved EF. No significant interaction between EF and β-blockers on risk for short-term mortality was found ($P = 0.4$). Compared with those not using β-blockers, the HR for mortality within 6 months for β-blocker users at transition with preserved EF was 0.75 (95% CI, 0.61-0.93), whereas for patients with reduced EF, this HR was 0.88 (95% CI, 0.62-1.24; Table S6).

Table 3. HRs of Mortality Within 6 Months by β-Blocker Type Among Incident Hemodialysis Patients With Propensity Score Weighted

	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
Not taking β-blockers (n = 1,300)	1.00 (reference)	1.00 (reference)
Atenolol (n = 411)	0.69 (0.50-0.95)	0.82 (0.59-1.13)
Metoprolol (n = 824)	0.67 (0.53-0.86)	0.68 (0.53-0.88)
Bisoprolol (n = 46)	1.18 (0.58-2.39)	0.70 (0.34-1.42)
Carvedilol (n = 600)	1.01 (0.79-1.28)	0.87 (0.68-1.12)
Other (n = 60)	0.61 (0.28-1.34)	0.81 (0.37-1.79)

N = 3,241.
Abbreviation: HR, hazard ratio.
[a]Adjusted for age, sex, race/ethnicity, ejection fraction values, primary cause of kidney failure, median pulse and average systolic blood pressure in 365 days pretransition, atrial fibrillation, coronary heart disease, and taking calcium channel blocker, diuretics, angiotensin receptor blocker, angiotensin-converting enzyme inhibitor, α-blocker, clopidogrel, nitrates, hydralazine, and statin.

Hospitalization

A total of 1,964 (56.1%) patients were hospitalized in the 6 months following dialysis transition (Table S7). The average number of all-cause hospitalizations per patient was 1.0 (interquartile range, 0-2) and the highest frequency of hospitalizations within 6 months was 17. Compared with those not taking β-blockers, there was no statistically significant difference in risk for hospitalization among patients taking β-blockers (odds ratio, 0.92 [95%

Table 2. HRs of Mortality Within 6 Months or Within 1 Year Among Propensity Score–Weighted Incident Dialysis Patients or HD Patients Only

	Mortality Within 6 mo		Mortality Within 1 y	
	All Dialysis Patients (n = 3,503)	HD Patients (n = 3,241)	All Dialysis Patients (n = 3,503)	HD Patients (n = 3,241)
Not taking β-blockers	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Taking β-blockers	0.79 (0.65-0.94)	0.79 (0.65-0.95)	0.78 (0.68-0.91)	0.79 (0.68-0.91)

Values shown are HR (95% confidence interval).
Abbreviations: HD, hemodialysis; HR, hazard ratio.

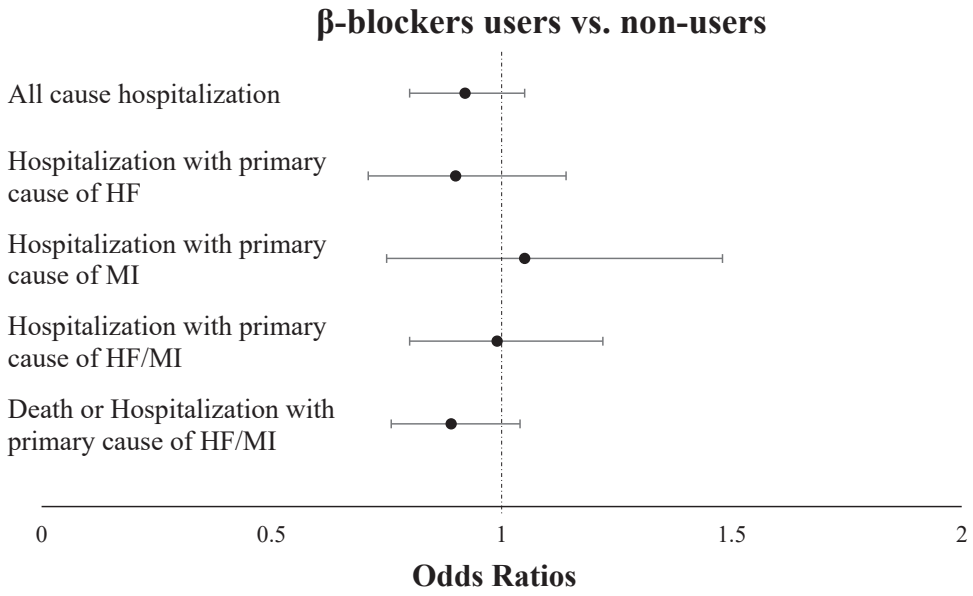

Figure 3. Risk for severe occurrence (hospitalization or death) comparison. Abbreviations: HF, heart failure; MI, myocardial infarction.

CI, 0.80-1.05]). To account for the possibility of death before hospitalization due to HF/MI, these 2 events were combined as 1 outcome. As shown in Figure 3, no significant difference was observed in the combined risk for mortality and hospitalization due to HF/MI based on β-blocker use.

Discussion

In this study of a large diverse population of patients with CKD with HF who transitioned to dialysis, we observed 21% lower 6-month mortality risk among patients with HF who were using β-blockers at transition to dialysis compared with those not using β-blockers. Our findings suggest a potential benefit of the use of β-blockers among patients with HF who transition to dialysis.

Kidney failure affects more than 726,000 persons in the United States and rates continue to increase. In 2016 alone, 124,675 patients with CKD initiated kidney replacement therapy, with 87% receiving HD and 10% starting PD.[33] The adjusted 5-year mortality rate for dialysis patients is worse than for patients with malignancy.[34] Cardiovascular disease (cerebrovascular disease, coronary artery disease, arrhythmia, and HF) is the major cause of death in the adult dialysis population.

Given the high morbidity and mortality in both the HF and dialysis populations, studies on comparative management strategies to improve outcomes would have tremendous impact. Our study findings on potential β-blocker benefit are similar to what has been shown in randomized clinical trials and observational studies.[35-37] Conversely, a cohort study from Ontario, Canada, observed no beneficial effect of β-blockers in the dialysis population.[38] However, this Canadian study included only older patients (aged ≥66 years) who newly started β-blocker therapy after dialysis and had survived for at least 90 days after dialysis transition. This potentially introduced survival bias in that patients who had survived the first 3 months may not be representative of the overall dialysis population, including the highly vulnerable new-start dialysis population. In another similar study performed among a propensity-score–matched cohort of HD patients 35 years and older, those initiating β-blocker therapy after HF diagnosis had 20% lower risk for all-cause mortality within 5 years.[39] Taken together, these 2 studies suggest that β-blocker use and potential benefits may vary by age.

We observed that metoprolol (a highly dialyzable β-blocker) had a lower HR for mortality. Our findings are consistent with a previous study that showed metoprolol initiation was associated with lower 1-year mortality compared with carvedilol (a poorly dialyzable β-blocker) among HD patients.[24] Conversely, Weir et al[23] reported that highly dialyzable β-blockers were associated with higher risk for death in dialysis patients compared with poorly dialyzable β-blockers. However, they included bisoprolol, which has been recently found to be dialyzable with a clearance rate of 44 mL/min, in the poorly dialyzable group.[22] Overall, it remains to be determined whether highly dialyzable β-blockers alone affect clinical outcomes in maintenance dialysis patients.

Differences in the pathophysiology of cardiovascular disease among dialysis patients may account for the differences in our findings compared with the general population. We observed that in patients with HF treated by

dialysis who have preserved EF, there appeared to be a stronger association between β-blocker use and survival. This finding is in contrast to what has been reported in patients with HF with preserved EF not receiving dialysis in which β-blockers have not demonstrated significant benefit. This type of equipose is consistent with other studies in which interventions that benefited the general population such as statins[40,41] and implantable cardioverter-defibrillators[42,43] did not show benefit in the dialysis population. Another potential explanation is that the risk for mortality among patients with HF with reduced EF and those transitioning to dialysis is extremely high (36.1/1,000 person-years in reduced EF vs 20.6/1,000 person-years in preserved EF). The lack of benefit from β-blockers in those with reduced EF may be because they have high mortality regardless of any intervention. In addition, mortality in this population may be mitigated by other competing causes of death, such as infections and nonrhythmic cardiac death.

No guidelines or consensus recommendations exist for medical therapy in dialysis patients with systolic HF. Past observations on β-blocker use in dialysis patients have been indeterminate and thus the benefits must be weighed against potential harm. Some studies have shown that β-blockers have unfavorable metabolic side effects such as increased risk for diabetes,[44] stroke,[45] or hyperkalemia.[46] Conversely, some have argued that β-blockers are underprescribed given the high prevalence of HF (31%-41%), ischemic heart disease (33%-39%), and arrhythmia (7%-31%) in the dialysis poulation.[18,47] In addition, the heterogeneity of the β-blockers makes it more difficult for clinicians to prescribe them with confidence.[48] The different β-blocker classes vary in pharmacodynamics, pharmacokinetics, side effects, and dialyzability. Therefore, clinicians often rely on their anecdotal experiences to determine type of β-blocker therapy, including the consideration of dialyzability.[19]

There are several potential limitations that may confound the interpretation of our study findings. Although we applied IPTW with propensity scoring to control for confounding by indication, the observational nature of our study could not fully account for residual confounding such as prevalent user bias and confounding by contraindication including β-blocker intolerance. In our sensitivity analysis, we compared highly and poorly dialyzable β-blocker classes separately. Due to differences in patients prescribed these 2 categories of β-blockers, further adjustments were performed to remove possible remaining differences among the IPTW weighted population. No statistically significant associations were found between poorly dialyzable β-blockers and mortality rates. Therefore, it remains uncertain if the lack of benefit from poorly dialyzable β-blockers was due to unmeasured confounders, other pharmacodynamic differences, or inadequate power given limited sample size.

In addition, we observed no differences in hospitalizations between β-blocker users and nonusers, which is surprising given the difference in mortality. This may suggest that the benefit of β-blockers could be due to the reduction in arrhythmia or sudden cardiac death. Sudden cardiac death is the single greatest cause of death in the dialysis population, and these patients may not neccearily be hospitalized immediately before.[49,50] Despite these potential limitations, our study provides insights into the potential effects of β-blockers in the high-risk dialysis population with HF. Using clinical information from a real-world clinical environment and a large diverse population, we were able to evaluate the effects of β-blockers among a more generalizable population. Second, we had echocardiogram information and thus EF values that we adjusted for. We found no effect modification from reduced versus preserved EF on β-blocker use and mortality. Finally, important clinical characteristics and laboratory data (blood pressure, heart rate, other comorbid conditions, and medication use at transition) were collected and used in the propensity score modeling, which provided a better comparison between β-blocker users and nonusers.

Among a large diverse CKD population that transitioned to HD or PD, we observed that patients with CKD with HF using β-blockers compared with no β-blockers had lower mortality within the first year after transition to dialysis.

Supplementary Material

Supplementary File (PDF)

Figure S1: Distribution of estimated propensity score between patients taking β-blockers vs nonusers.

Table S1: *ICD9/10* codes used for HF identification.

Table S2: Comparison of patients taking poorly vs highly dialyzable β-blockers.

Table S3: Effects of β-blockers on the risk of mortality within 6 months after dialysis initiation by race/ethnicity among patients with HF.

Table S4: Time-varying analysis for effects of β-blockers on the risk of mortality within 1 year after dialysis initiation among patients with HF.

Table S5: Analysis for effects of β-blockers with different dialyzability on the risk of mortality within 6 months after hemodialysis initiation among patients with HF.

Table S6: Effects of β-blockers on short-term mortality after dialysis initiation among patients with HF with reduced and preserved ejection fraction.

Table S7: Frequency of hospitalizations in 6 months after initiating dialysis among patients with HF.

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