A Comparative Study of Carvedilol Versus Metoprolol Initiation and 1-Year Mortality Among Individuals Receiving Maintenance Hemodialysis

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Background: Carvedilol and metoprolol are the β-blockers most commonly prescribed to US hemodialysis patients, accounting for ~80% of β-blocker prescriptions. Despite well-established pharmacologic and pharmacokinetic differences between the 2 medications, little is known about their relative safety and efficacy in the hemodialysis population.

Study Design: A retrospective cohort study using a new-user design.

Setting & Participants: Medicare-enrolled hemodialysis patients treated at a large US dialysis organization who initiated carvedilol or metoprolol therapy from January 1, 2007, through December 30, 2012.

Predictor: Carvedilol versus metoprolol initiation.

Outcomes: All-cause mortality, cardiovascular mortality, and intradialytic hypotension (systolic blood pressure decrease ≥ 20 mm Hg during hemodialysis plus intradialytic saline solution administration) during a 1-year follow-up period.

Measurements: Survival models were used to estimate HRs and 95% CIs in mortality analyses. Poisson regression was used to estimate incidence rate ratios (IRRs) and 95% CIs in intradialytic hypotension analyses. Inverse probability of treatment weighting was used to adjust for several demographic, clinical, laboratory, and dialysis treatment covariates in all analyses.

Results: 27,064 individuals receiving maintenance hemodialysis were included: 9,558 (35.3%) carvedilol initiators and 17,506 (64.7%) metoprolol initiators. Carvedilol (vs metoprolol) initiation was associated with greater all-cause (adjusted HR, 1.08; 95% CI, 1.02-1.16) and cardiovascular mortality (adjusted HR, 1.18; 95% CI, 1.08-1.29). In subgroup analyses, similar associations were observed among patients with hypertension, atrial fibrillation, heart failure, and a recent myocardial infarction, the main cardiovascular indications for β-blocker therapy. During follow-up, carvedilol (vs metoprolol) initiators had a higher rate of intradialytic hypotension (adjusted IRR, 1.10; 95% CI, 1.09-1.11).

Limitations: Residual confounding may exist.

Conclusions: Relative to metoprolol initiation, carvedilol initiation was associated with higher 1-year all-cause and cardiovascular mortality. One potential mechanism for these findings may be the increased occurrence of intradialytic hypotension after carvedilol (vs metoprolol) initiation.

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Individuals receiving maintenance hemodialysis have cardiovascular mortality rates that exceed those of the general population by 5- to 7-fold.[1] Cardioprotective medications such as β-blockers, among others, are often prescribed to reduce cardiovascular risk. However, clinical trials establishing the cardioprotective nature and safety of β-blockers largely excluded individuals with end-stage renal disease (ESRD).[2,3] Approximately 65% of the US hemodialysis population is treated with a β-blocker.[4] Despite widespread use, surprisingly little is known about the relative safety and efficacy of different β-blockers in hemodialysis patients, a population with special drug dosing considerations.

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Within the β-blocker class, individual medications possess different pharmacologic and pharmacokinetic properties. Pharmacologically, β-blockers differ with respect to their β-adrenergic receptor selectivity and vasodilatory capabilities. Kinetically, physiochemical factors, such as molecular size, hydrophilicity, plasma protein binding, and volume of distribution, influence the extent of β-blocker clearance by the hemodialysis procedure (ie, dialyzability). These key differences may plausibly alter the hemodynamic and antiarrhythmic risk-benefit profiles of individual β-blockers in the setting of ESRD.

Observational data suggest that the potential survival benefit conferred by β-blockers may differ across agents. In a Canadian cohort, Weir et al[5] found that the risk of all-cause death was significantly higher among hemodialysis patients treated with high-dialyzability β-blockers (acebutolol, atenolol, and metoprolol tartrate) as compared to patients treated with low-dialyzability β-blockers (bisoprolol and propranolol). However, carvedilol and metoprolol succinate, 2 commonly prescribed β-blockers in the United States,[4] were not considered due to Canadian provincial prescription formulary restrictions. Carvedilol is

a nonselective β-blocker with α-blocking effects and is minimally cleared by hemodialysis. Metoprolol (tartrate and succinate) is a cardioselective β-blocker and is extensively cleared by hemodialysis. The marked pharmacologic and pharmacokinetic heterogeneity between carvedilol and metoprolol may differentially influence clinical outcomes and safety among individuals receiving maintenance hemodialysis and warrants further study.

Although a head-to-head randomized clinical trial would be the ideal approach to investigate the comparative safety and efficacy of carvedilol and metoprolol in the dialysis population, a recent feasibility study suggests that recruitment for such a trial may be challenging.[6] Well-designed pharmacoepidemiologic studies are thus needed to inform clinical decision making. We undertook this study to investigate the association between carvedilol versus metoprolol initiation and 1-year mortality in a cohort of prevalent hemodialysis patients treated at a large US dialysis organization.

Methods

This study was approved by the University of North Carolina at Chapel Hill Institutional Review Board (#15-2651). A waiver of consent was granted due to the study's large size, data anonymity, and retrospective nature.

Data Source

Study data were extracted from the clinical database of a large US dialysis organization and the US Renal Data System (USRDS). Data were linked at the patient level. The dialysis organization operates more than 1,500 outpatient dialysis clinics throughout the nation. Its database captures detailed demographic, clinical, laboratory, and dialysis treatment data. Laboratory data were measured on a biweekly or monthly basis. Hemodialysis treatment parameters were recorded on a treatment-to-treatment basis. The USRDS is a national ESRD surveillance system that includes the Medical Evidence and ESRD Death Notification forms, the Medicare Enrollment database (a repository of Medicare beneficiary enrollment and entitlement data), and Medicare standard analytic files (final action administrative claims data including Medicare parts A, B, and D).

Study Design and Population

We conducted a retrospective cohort study using an active comparator new-user design,[7] the observational analogue to a head-to-head randomized controlled trial, to investigate the association between carvedilol versus metoprolol initiation and 1-year all-cause and cardiovascular mortality (separately) among individuals receiving maintenance hemodialysis. Using a new-user study design to evaluate the comparative safety and/or effectiveness of medications in retrospective investigations helps mitigate biases common to observational studies of prescription drugs, such as selection and immortal time biases.

Figure 1 displays the study design. First, using Medicare Part D claims, we identified dialysis patients treated at the large dialysis organization who initiated oral β-blocker therapy from January 1, 2007, to December 30, 2012, following a 180-day baseline period free of any documented oral β-blocker use (ie, a β-blocker washout period). We then applied the following exclusion criteria: (1) age younger than 18 years at the start of the baseline period; (2) dialysis vintage of 90 days or less at the start of the baseline period (to ensure that all potential study patients were eligible for Medicare coverage regardless of their age); (3) lack of continuous Medicare parts A, B, and D coverage during the entire baseline period; (4) receipt of home hemodialysis or peritoneal dialysis during the baseline period; (5) receipt of fewer than 6 center-based hemodialysis treatments in the last 30 days of the baseline period; (6) receipt of hospice care during the baseline period; (7) missing demographic or laboratory data; and (8) initiation of treatment with an oral β-blocker other

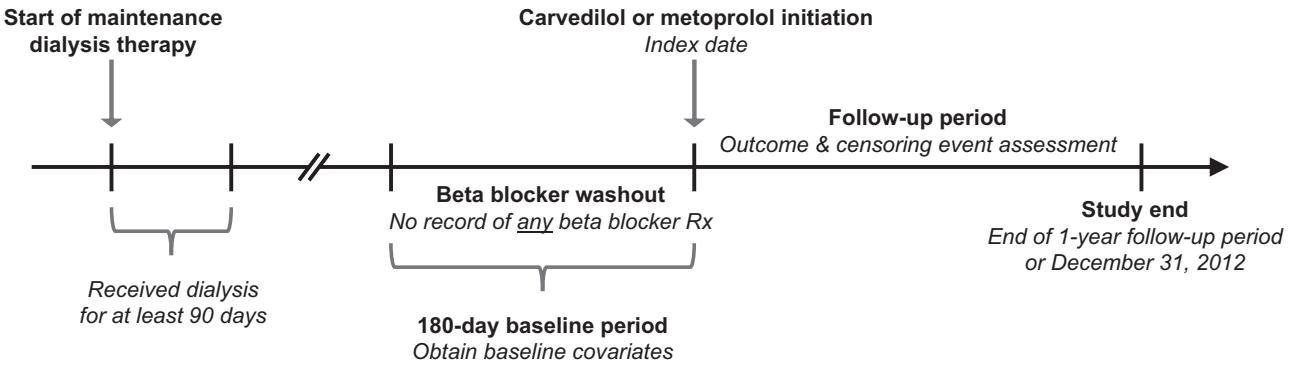

Figure 1. Study design. Carvedilol and metoprolol initiators were defined as hemodialysis patients who had no record of a β-blocker prescription in the previous 180 days (β-blocker washout period). Among these patients, the index date was defined as the date of carvedilol or metoprolol initiation. Baseline covariates were identified in the 180-day period before the index date. Study follow-up began immediately after the index date. To ensure that all potential study patients were eligible for Medicare coverage regardless of their age, individuals needed to have dialysis vintage longer than 90 days at the start of the baseline period. Abbreviation: Rx, prescription.

than carvedilol or metoprolol. The study cohort consisted of prevalent center-based hemodialysis patients who were carvedilol or metoprolol new-users.

Study Exposure, Outcomes, and Censoring Events

Exposures of interest were carvedilol and metoprolol initiation. The index date was designated as the date of the first carvedilol or metoprolol prescription after the washout period. Primary study outcomes were 1-year all-cause and cardiovascular mortality (assessed separately). Secondary outcomes were all-cause and cardiovascular hospitalizations (assessed separately) during the 1-year follow-up period. Mortality and hospitalization outcomes were defined using established USRDS definitions (Table S1).[8] Censoring events included kidney transplantation; dialysis modality change; recovery of kidney function; loss of Medicare Part A, B, or D coverage; being lost to follow-up; reaching 1-year of follow-up post–index date; or study end (December 31, 2012).

Baseline Covariate Determination

Baseline covariates included potential confounders and variables known to be strong risk factors for death in the hemodialysis population.[9] Similar to previous pharmacoepidemiologic analyses using USRDS data,[10-13] covariates were identified in the 180 days before the index date and included patient demographics, comorbid conditions, laboratory data, dialysis treatment parameters, and prescription medication use (Table S2). Use of a 180-day baseline period enabled us to maximize cohort generalizability and facilitated capture of patient characteristics that: (1) occurred close to study medication initiation that may have influenced β-blocker prescribing decisions,[14] and (2) are highly predictive of the study outcomes.[15]

Statistical Analysis

All analyses were performed using SAS, version 9.4 (SAS Institute Inc). Baseline characteristics were described across carvedilol and metoprolol initiators as count and percent for categorical variables and mean ± standard deviation for continuous variables. Baseline covariate distributions were compared using standardized differences. A standardized difference > 0.1 represents meaningful imbalance between treatment groups.[16]

In primary analyses, we used an intent-to-treat approach to evaluate the association between carvedilol (vs metoprolol) initiation and 1-year all-cause and cardiovascular mortality. Individuals were followed forward in historical time from the index date to the first occurrence of a study outcome or censoring event. Cox proportional hazards models were used to assess the study β-blocker–all-cause mortality association. Fine and Gray proportional subdistribution hazards models,[17] that treated non-cardiovascular death as a competing risk, were used to assess the study β-blocker–cardiovascular mortality association. Both models estimate hazard ratios (HRs) and their 95% confidence intervals (CIs). Robust variance estimation was used in all analyses.[18] Inverse probability of treatment (IPT) weighting was used to control for confounding. We used multivariable logistic regression to calculate the predicted probability (ie, propensity score) of receiving carvedilol (vs metoprolol) as a function of baseline covariates. Propensity scores were used to generate IPT weights.[19,20] We estimated adjusted HRs by applying IPT weights in regression models.

We conducted several sensitivity analyses to assess the robustness of our primary results. First, because the effect of metoprolol (vs carvedilol) on all-cause mortality may differ by metoprolol formulation,[21] we repeated primary analyses and separately compared: (1) carvedilol versus metoprolol tartrate (the immediate-release formulation), and (2) carvedilol versus metoprolol succinate (the controlled/extended-release formulation). Second, we repeated primary analyses using an on-treatment (ie, per-protocol) approach. In these analyses, index β-blocker treatment discontinuation and switching to a nonindex β-blocker during follow-up were considered as additional censoring events. Third, to further minimize the influence of potential confounding by indication (ie, indication bias), we evaluated the association between carvedilol (vs metoprolol) initiation and 1-year mortality among individuals who did not experience a cardiovascular hospitalization during the last 30 days of the baseline period. Fourth, we tested the specificity of our findings by examining the association between carvedilol (vs metoprolol) initiation and hospitalized bowel obstruction, a tracer (ie, negative control) outcome that we did not expect to be influenced by the use of either of the study medications.

In secondary analyses, we evaluated the study β-blocker–mortality associations within clinically relevant subgroups. We assessed the association between carvedilol (vs metoprolol) initiation and 1-year mortality among individuals with hypertension, atrial fibrillation, heart failure, and a recent myocardial infraction, the main cardiovascular indications for β-blocker therapy. In additional analyses, we assessed the associations between carvedilol (vs metoprolol) initiation and the occurrence of hospitalizations during the 1-year follow-up by estimating incidence rate ratios (IRRs) and their 95% CIs using Poisson regression.

We also conducted post hoc analyses to evaluate potential mechanistic explanations for our study findings. We assessed the association between carvedilol (vs metoprolol) initiation and the occurrence of intradialytic hypotension during the 1-year follow-up period by estimating IRRs and their 95% CIs using Poisson regression. Episodes of intradialytic hypotension were identified using 2 different definitions: (1) a systolic blood pressure decrease ≥ 20 mm Hg during hemodialysis plus intradialytic saline solution administration (a guideline-based definition),[22-24] and (2) an intradialytic nadir systolic blood pressure < 90 mm Hg (a definition shown to associate with mortality).[25] We also evaluated study β-blocker–mortality associations among patients with and without a recent history of frequent intradialytic hypotension. Patients were classified as having a recent history

of frequent intradialytic hypotension if they experienced an episode of intradialytic hypotension (defined both ways, separately) in at least 30% of outpatient hemodialysis treatments during the last 30 days of the baseline period.[25]

Results

Study Cohort Characteristics

Figure 2 displays a flow diagram of study cohort selection. A total of 27,064 individuals receiving maintenance hemodialysis were included in the study: 9,558 (35.3%) carvedilol initiators and 17,506 (64.7%) metoprolol initiators. Overall, study patients had an average age of 59.6 ± 14.7 years, 46.7% were women, 42.9% were black, 19.5% were Hispanic, and the most common ESRD cause was diabetes (49.0%). Cardiovascular comorbid conditions were common; 13.9% of the cohort had atrial fibrillation, 29.9% had coronary atherosclerosis, 72.7% had hypertension, 34.6% had heart failure, 6.6% had a recent myocardial infarction, and 21.7% had peripheral arterial disease.

The propensity score distribution of carvedilol and metoprolol initiators exhibited substantial overlap (Fig S1), indicating that the study groups were highly comparable. Patient baseline characteristics stratified by study β-blocker are presented in Table 1. Before IPT weighting, baseline covariates were generally well balanced between treatment groups (standardized differences ≤ 0.1), with a few exceptions (year of index carvedilol or metoprolol initiation, heart failure, and an ESRD cause of diabetes). After IPT weighting, all baseline covariates were well balanced between treatment groups.

Primary Analyses

Under the intent-to-treat paradigm, the study cohort was followed up for a total of 20,863 person-years (7,219 person-years for carvedilol initiators and 13,644 person-years for metoprolol initiators). Average durations of follow-up were 276 days for carvedilol initiators and 285 days for metoprolol initiators. During follow-up, 4,296 all-cause deaths (1,625 in the carvedilol group and 2,671 in the metoprolol group) and 1,943 cardiovascular deaths (782 in the carvedilol group and 1,161 in the metoprolol group) occurred. Figure 3 displays the associations between carvedilol (vs metoprolol) initiation and 1-year all-cause and cardiovascular mortality. Compared with individuals initiating metoprolol treatment, individuals initiating carvedilol treatment had a higher rate of all-cause mortality (225.1 vs 195.8 events/1,000 person-years; adjusted HR, 1.08 [95% CI, 1.02-1.16]) and cardiovascular mortality (108.3

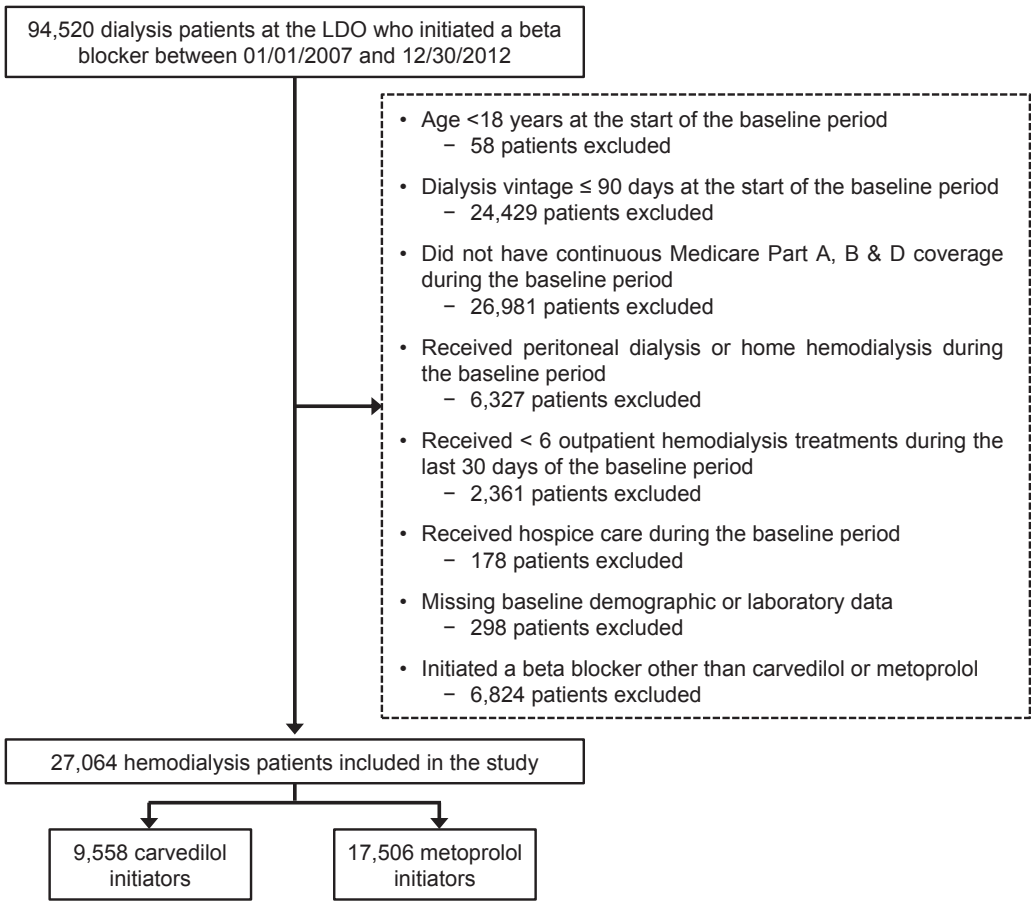

Figure 2. Flow diagram depicts the assembly of the study cohort. Abbreviation: LDO, large dialysis organization.

Table 1. Baseline Characteristics of Study Patients Initiating Carvedilol and Metoprolol

Characteristic	Unweighted			Weighted		
	Carvedilol (n = 9,558)	Metoprolol (n = 17,506)	Std Diff[a]	Carvedilol (n = 9,533)	Metoprolol (n = 17,521)	Std Diff[a]
Age, y	59.8 ±14.4	59.5 ±14.9	0.026	59.8 ± 14.4	59.5 ± 14.9	0.026
Female sex	4,314 (45.1%)	8,316 (47.5%)	0.048	4,444 (46.6%)	8,183 (46.7%)	0.002
Race						
White	4,848 (50.7%)	9,054 (51.7%)	0.020	4,881 (51.2%)	8,991 (51.3%)	0.002
Black	4,186 (43.8%)	7,419 (42.4%)	0.029	4,103 (43.0%)	7,524 (42.9%)	0.002
Other	524 (5.5%)	1,033 (5.9%)	0.018	549 (5.8%)	1,006 (5.7%)	0.001
Hispanic ethnicity	1,925 (20.1%)	3,351 (19.1%)	0.025	1,874 (19.7%)	3,428 (19.6%)	0.002
Low-income subsidy	7,259 (75.9%)	13,524 (77.3%)	0.031	7,328 (76.9%)	13,463 (76.8%)	0.001
Year index β-blocker was prescribed						
2007	1,339 (14.0%)	3,364 (19.2%)	0.140	1,631 (17.1%)	3,034 (17.3%)	0.005
2008	1,385 (14.5%)	3,011 (17.2%)	0.074	1,534 (16.1%)	2,833 (16.2%)	0.002
2009	1,440 (15.1%)	2,561 (14.6%)	0.012	1,406 (14.8%)	2,588 (14.8%)	0.000
2010	1,524 (15.9%)	2,696 (15.4%)	0.015	1,497 (15.7%)	2,736 (15.6%)	0.002
2011	1,804 (18.9%)	2,852 (16.3%)	0.068	1,665 (17.5%)	3,029 (17.3%)	0.005
2012	2,066 (21.6%)	3,022 (17.3%)	0.110	1,801 (18.9%)	3,302 (18.8%)	0.001
Cause of ESRD						
Diabetes	5,027 (52.6%)	8,227 (47.0%)	0.112	4,703 (49.3%)	8,606 (49.1%)	0.004
Hypertension	2,563 (26.8%)	5,051 (28.9%)	0.045	2,686 (28.2%)	4,927 (28.1%)	0.001
Glomerular disease	909 (9.5%)	1,936 (11.1%)	0.051	982 (10.3%)	1,828 (10.4%)	0.004
Other	1,059 (11.1%)	2,292 (13.1%)	0.062	1,163 (12.2%)	2,160 (12.3%)	0.004
Body mass index						
<18.5 kg/m^2	474 (5.0%)	844 (4.8%)	0.006	464 (4.9%)	854 (4.9%)	0.000
18.5-24.9 kg/m^2	3,555 (37.2%)	6,285 (35.9%)	0.027	3,475 (36.5%)	6,371 (36.4%)	0.002
25.0-29.9 kg/m^2	2,761 (28.9%)	4,978 (28.4%)	0.010	2,719 (28.5%)	5,005 (28.6%)	0.001
≥30.0 kg/m^2	2,768 (29.0%)	5,399 (30.8%)	0.041	2,875 (30.2%)	5,292 (30.2%)	0.001
History of prior kidney transplantation	502 (5.3%)	1,204 (6.9%)	0.068	594 (6.2%)	1,103 (6.3%)	0.003
Dialysis vintage						
0.7-0.9 y	595 (6.2%)	935 (5.3%)	0.038	536 (5.6%)	988 (5.6%)	0.001
1.0-1.9 y	2,118 (22.2%)	3,705 (21.2%)	0.024	2,053 (21.5%)	3,778 (21.6%)	0.001
2.0-2.9 y	1,668 (17.5%)	2,778 (15.9%)	0.042	1,556 (16.3%)	2,875 (16.4%)	0.002
≥3.0 y	5,177 (54.2%)	10,088 (57.6%)	0.070	5,388 (56.5%)	9,881 (56.4%)	0.003
CV admission during the last 30 d of baseline	1,801 (18.8%)	2,815 (16.1%)	0.073	1,618 (17.0%)	2,989 (17.1%)	0.002
Atrial fibrillation	1,236 (12.9%)	2,525 (14.4%)	0.043	1,300 (13.6%)	2,426 (13.8%)	0.006
Other arrhythmia	930 (9.7%)	1,630 (9.3%)	0.014	906 (9.5%)	1,657 (9.5%)	0.002
Angina	210 (2.2%)	302 (1.7%)	0.034	182 (1.9%)	334 (1.9%)	0.000
Cancer	312 (3.3%)	661 (3.8%)	0.028	335 (3.5%)	627 (3.6%)	0.003
Conduction disorder	367 (3.8%)	496 (2.8%)	0.056	304 (3.2%)	559 (3.2%)	0.000
COPD/asthma	1,704 (17.8%)	2,795 (16.0%)	0.050	1,601 (16.8%)	2,922 (16.7%)	0.003
Coronary atherosclerosis	3,126 (32.7%)	4,960 (28.3%)	0.095	2,867 (30.1%)	5,251 (30.0%)	0.002
Diabetes	5,473 (57.3%)	9,286 (53.0%)	0.085	5,236 (54.9%)	9,586 (54.7%)	0.004
GI bleed	471 (4.9%)	932 (5.3%)	0.018	503 (5.3%)	911 (5.2%)	0.004
Heart failure	4,107 (43.0%)	5,251 (30.0%)	0.272	3,332 (34.9%)	6,087 (34.7%)	0.004
Hypertension	7,021 (73.5%)	12,652 (72.3%)	0.027	6,960 (73.0%)	12,763 (72.8%)	0.004
Liver disease	421 (4.4%)	783 (4.5%)	0.003	434 (4.6%)	784 (4.5%)	0.004
Myocardial infarction	642 (6.7%)	1,151 (6.6%)	0.006	644 (6.8%)	1,171 (6.7%)	0.003
Peripheral artery disease	2,149 (22.5%)	3,729 (21.3%)	0.029	2,095 (22.0%)	3,820 (21.8%)	0.004
Stroke	975 (10.2%)	1,876 (10.7%)	0.017	1,030 (10.8%)	1,861 (10.6%)	0.006
Valvular disease	904 (9.5%)	1,337 (7.6%)	0.065	795 (8.3%)	1,457 (8.3%)	0.001

(Continued)

Table 1 (Cont'd). Baseline Characteristics of Study Patients Initiating Carvedilol and Metoprolol

Characteristic	Unweighted			Weighted		
	Carvedilol (n = 9,558)	Metoprolol (n = 17,506)	Std Diff[a]	Carvedilol (n = 9,533)	Metoprolol (n = 17,521)	Std Diff[a]
History of treatment nonadherence[b]	594 (6.2%)	1,021 (5.8%)	0.016	581 (6.1%)	1,051 (6.0%)	0.004
Vascular access						
Fistula	5,645 (59.1%)	10,054 (57.4%)	0.033	5,516 (57.9%)	10,150 (57.9%)	0.001
Graft	2,428 (25.4%)	4,451 (25.4%)	0.001	2,448 (25.7%)	4,470 (25.5%)	0.004
Catheter	1,485 (15.5%)	3,001 (17.1%)	0.043	1,570 (16.5%)	2,902 (16.6%)	0.003
Interdialytic weight gain ≥ 3 kg	2,377 (24.9%)	4,196 (24.0%)	0.021	2,310 (24.2%)	4,253 (24.3%)	0.001
Delivered dialysis treatment time < 240 min	7,657 (80.1%)	13,940 (79.6%)	0.012	7,628 (80.0%)	13,989 (79.8%)	0.004
Predialysis systolic BP						
<130 mm Hg	1,384 (14.5%)	2,159 (12.3%)	0.063	1,241 (13.0%)	2,289 (13.1%)	0.001
130-149 mm Hg	2,696 (28.2%)	4,744 (27.1%)	0.025	2,621 (27.5%)	4,808 (27.4%)	0.001
150-169 mm Hg	3,175 (33.2%)	6,084 (34.8%)	0.032	3,253 (34.1%)	5,997 (34.2%)	0.002
≥170 mm Hg	2,303 (24.1%)	4,519 (25.8%)	0.040	2,419 (25.4%)	4,427 (25.3%)	0.002
Recent history of frequent IDH[c]	1,349 (14.1%)	2,363 (13.5%)	0.018	1,321 (13.9%)	2,415 (13.8%)	0.002
Albumin						
≤3.0 g/dL	468 (4.9%)	883 (5.0%)	0.007	483 (5.1%)	877 (5.0%)	0.003
3.1-4.0 g/dL	6,221 (65.1%)	11,057 (63.2%)	0.040	6,092 (63.9%)	11,191 (63.9%)	0.001
>4.0 g/dL	2,869 (30.0%)	5,566 (31.8%)	0.038	2,959 (31.0%)	5,453 (31.1%)	0.002
Calcium						
<8.5 mg/dL	1,338 (14.0%)	2,497 (14.3%)	0.008	1,352 (14.2%)	2,488 (14.2%)	0.001
8.5-10.2 mg/dL	7,756 (81.1%)	14,159 (80.9%)	0.007	7,714 (80.9%)	14,180 (80.9%)	0.000
>10.2 mg/dL	464 (4.9%)	850 (4.9%)	0.000	467 (4.9%)	853 (4.9%)	0.002
Phosphorus						
<3.5 mg/dL	1,088 (11.4%)	1,907 (10.9%)	0.016	1,050 (11.0%)	1,936 (11.0%)	0.001
3.5-5.5 mg/dL	5,224 (54.7%)	9,431 (53.9%)	0.016	5,175 (54.3%)	9,495 (54.2%)	0.002
>5.5 mg/dL	3,246 (34.0%)	6,168 (35.2%)	0.027	3,309 (34.7%)	6,091 (34.8%)	0.001
Potassium						
<4.0 mEq/L	1,064 (11.1%)	1,918 (11.0%)	0.006	1,047 (11.0%)	1,931 (11.0%)	0.001
4.0-6.0 mEq/L	8,152 (85.3%)	14,915 (85.2%)	0.003	8,127 (85.2%)	14,934 (85.2%)	0.000
>6.0 mEq/L	342 (3.6%)	673 (3.8%)	0.014	360 (3.8%)	656 (3.7%)	0.002
Hemoglobin						
<9.5 g/dL	663 (6.9%)	1,166 (6.7%)	0.011	650 (6.8%)	1,185 (6.8%)	0.002
9.5-12.0 mg/dL	6,164 (64.5%)	10,709 (61.2%)	0.069	5,972 (62.6%)	10,942 (62.4%)	0.004
>12.0 mg/dL	2,731 (28.6%)	5,631 (32.2%)	0.078	2,912 (30.5%)	5,394 (30.8%)	0.005
Equilibrated Kt/V < 1.2	2,235 (23.4%)	3,850 (22.0%)	0.033	2,145 (22.5%)	3,944 (22.5%)	0.000
No. of medications in last 30 d of baseline	5.5 ± 3.8	5.5 ± 3.9	0.014	5.5 ± 3.9	5.5 ± 3.9	0.014
α-Blocker	63 (0.7%)	168 (1.0%)	0.034	83 (0.9%)	151 (0.9%)	0.001
ACE inhibitor	2,232 (23.4%)	4,040 (23.1%)	0.006	2,224 (23.3%)	4,070 (23.2%)	0.002
Angiotensin receptor blocker	1,212 (12.7%)	1,848 (10.6%)	0.066	1,103 (11.6%)	2,004 (11.4%)	0.004
Calcium channel blocker	3,060 (32.0%)	5,959 (34.0%)	0.043	3,195 (33.5%)	5,853 (33.4%)	0.002
Central α-agonist	1,272 (13.3%)	2,486 (14.2%)	0.026	1,339 (14.0%)	2,446 (14.0%)	0.003
Diuretic	1,239 (13.0%)	1,845 (10.5%)	0.075	1,095 (11.5%)	2,010 (11.5%)	0.000
Vasodilator	997 (10.4%)	1,916 (10.9%)	0.017	1,030 (10.8%)	1,893 (10.8%)	0.000
Statin	2,578 (27.0%)	4,509 (25.8%)	0.028	2,512 (26.4%)	4,606 (26.3%)	0.001
Other cholesterol medication[d]	394 (4.1%)	717 (4.1%)	0.001	394 (4.1%)	720 (4.1%)	0.001
Digoxin	258 (2.7%)	332 (1.9%)	0.054	205 (2.2%)	382 (2.2%)	0.002
Long-acting nitrate	845 (8.8%)	1,216 (6.9%)	0.070	733 (7.7%)	1,344 (7.7%)	0.001
Antiplatelet medication	1,280 (13.4%)	2,065 (11.8%)	0.048	1,202 (12.6%)	2,187 (12.5%)	0.004
Anticoagulant medication	711 (7.4%)	1,458 (8.3%)	0.033	754 (7.9%)	1,401 (8.0%)	0.003

(Continued)

Table 1 (Cont'd). Baseline Characteristics of Study Patients Initiating Carvedilol and Metoprolol

Characteristic	Unweighted			Weighted		
	Carvedilol (n = 9,558)	Metoprolol (n = 17,506)	Std Diff[a]	Carvedilol (n = 9,533)	Metoprolol (n = 17,521)	Std Diff[a]
Midodrine	192 (2.0%)	350 (2.0%)	0.001	192 (2.0%)	352 (2.0%)	0.000
Use of ≥ 1 potent inhibitor of CYP2D6[e]	2,690 (29.5%)	5,162 (28.1%)	0.030	2,767 (29.0%)	5,090 (29.0%)	0.001

Note: All-covariates were measured during the baseline period before carvedilol or metoprolol initiation. Values are given as number (percent) for categorical variables and as mean ± standard deviation for continuous variables. The weighted cohort is the pseudo-population that was generated by the inverse probability of treatment weighting process.

Abbreviations: ACE, angiotensin-converting enzyme; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; CYP2D6, cytochrome P450 2D6; ESRD, end-stage renal disease; GI, gastrointestinal; IDH, intradialytic hypotension; std diff, standardized difference.

[a]A std diff > 0.1 represents meaningful imbalance between groups.[16]

[b]Claims-based definition of nonadherence included *International Classification of Diseases, Ninth Revision* discharge diagnosis codes V15.81 (personal history of noncompliance with medical treatment, presenting hazards to health) and V45.12 (noncompliance with renal dialysis).

[c]Patients were considered as having a recent history of frequent IDH if they had an intradialytic nadir systolic BP < 90 mm Hg in at least 30% of outpatient hemodialysis treatments during the last 30 days of the baseline period.[25]

[d]Other cholesterol medications included the following nonstatin cholesterol medications: bile acid sequestrants, cholesterol absorption inhibitors, fibrates, and niacin.

[e]Both carvedilol and metoprolol are metabolized by CYP2D6. Concomitant use of medications that are potent inhibitors of CYP2D6 may increase serum concentrations of both carvedilol and metoprolol, putting patients at increased risk for β-blocker–related adverse events such as hypotension. CYP2D6 inhibitors included amiodarone, bupropion, chloroquine, cinacalcet, diphenhydramine, fluoxetine, haloperidol, imatinib, paroxetine, propafenone, propoxyphene, quinidine, terbinafine, and thioridazine.

vs 85.1 events/1,000 person-years; adjusted HR, 1.18 [95% CI, 1.08-1.29]) (Figs 3 and S2).

Secondary Analyses

Secondary analyses assessing associations between carvedilol (vs metoprolol) initiation and mortality among individuals with hypertension, atrial fibrillation, heart failure, or a recent myocardial infarction produced results analogous to primary study findings (Tables 2 and S3).

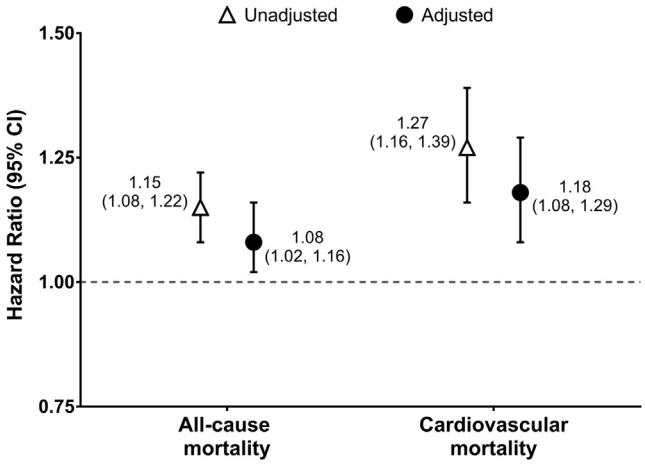

Figure 3. Association between carvedilol versus metoprolol initiation and 1-year mortality: intent-to-treat analysis. An intent-to-treat design was used in all analyses. Cox proportional hazards models were used to estimate the association between carvedilol (vs metoprolol) initiation and 1-year all-cause mortality. Fine and Gray proportional subdistribution hazards models were used to estimate the association between carvedilol (vs metoprolol) initiation and 1-year cardiovascular mortality. In cardiovascular mortality analyses, noncardiovascular death was treated as a competing risk. Inverse probability of treatment weighting was used in adjusted analyses to control for all baseline covariates listed in Table 1. Abbreviation: CI, confidence interval.

In secondary analyses evaluating the associations between study β-blockers and hospitalizations, individuals who initiated carvedilol (vs metoprolol) had similar rates of all-cause hospitalizations (2,383.8 vs 2,270.3 events/1,000 person-years; adjusted IRR, 1.00 [95% CI, 0.97-1.04]) and higher rates of cardiovascular hospitalizations (827.1 vs 726.5 events/1,000 person-years; adjusted IRR, 1.06 [95% CI, 1.01-1.12]) during the 1-year follow-up period.

Sensitivity Analyses

Sensitivity analyses comparing carvedilol initiators with metoprolol tartrate and metoprolol succinate treatment initiators (separately) generated results similar to primary analyses. Treatment with carvedilol (vs metoprolol) was associated with greater 1-year all-cause and cardiovascular mortality, regardless of the comparator metoprolol formulation (Table S4).

In sensitivity analyses using an on-treatment analytic paradigm, the study cohort was followed up for a total of 14,460 person-years (5,127 person-years for carvedilol-treated patients and 9,333 person-years for metoprolol-treated patients). During follow-up, there were 2,941 all-cause deaths (1,117 in the carvedilol group and 1,824 in the metoprolol group) and 1,341 cardiovascular deaths (544 in the carvedilol group and 797 in the metoprolol group). A total of 11,110 individuals discontinued index β-blocker therapy and 1,662 switched to a different β-blocker during follow-up. The average duration of continuous index medication use was 195 days for both carvedilol initiators and metoprolol initiators. Individuals who remained on carvedilol (vs metoprolol) treatment had nominally higher rates of all-cause mortality (217.9 vs 195.4 events/1,000 person-years; adjusted HR, 1.06 [95%, 0.98-1.14]) and higher rates of cardiovascular mortality (106.3 vs 85.4 events/1,000 person-years; adjusted HR, 1.15 [95% CI, 1.03-1.28]).

Sensitivity analyses assessing β-blocker–mortality associations among individuals who did not experience a

Table 2. Association Between Carvedilol Versus Metoprolol Initiation and 1-Year Mortality Among Clinically Relevant Subgroups: Intent-to-Treat Analysis[a]

β-Blocker	n	1-y All-Cause Mortality[a]		1-y Cardiovascular Mortality[b]	
		Rate per 1,000 p-y	Adjusted HR (95% CI)	Rate per 1,000 p-y	Adjusted HR (95% CI)
Patients with hypertension (n = 19,673)					
Metoprolol	12,652	234.7	1.00 (reference)	100.7	1.00 (reference)
Carvedilol	7,021	266.0	1.09 (1.02-1.17)	126.1	1.18 (1.07-1.31)
Patients with atrial fibrillation (n = 3,761)					
Metoprolol	2,525	406.1	1.00 (reference)	174.1	1.00 (reference)
Carvedilol	1,236	458.4	1.08 (0.94-1.23)	215.9	1.12 (0.94-1.35)
Patients with heart failure (n = 9,358)					
Metoprolol	5,251	336.7	1.00 (reference)	144.9	1.00 (reference)
Carvedilol	4,107	335.8	1.02 (0.94-1.11)	157.6	1.09 (0.96-1.23)
Patients with a recent MI (n = 1,793)					
Metoprolol	1,151	395.6	1.00 (reference)	187.1	1.00 (reference)
Carvedilol	642	443.6	1.02 (0.84-1.23)	244.7	1.19 (0.92-1.53)

Note: An intent-to-treat design was used in all analyses. Adjusted analyses controlled for baseline covariates listed in Table 1 using inverse probability of treatment weighting. Subgroups of interest were excluded in the corresponding propensity score models. For example, in subgroup analyses of patients with hypertension, the hypertension covariate was excluded from the propensity score model. Presented patient counts and outcome event rates are based on the unweighted cohort.
Abbreviations: CI, confidence interval; HR, hazard ratio; p-y, person-year; MI, myocardial infarction.
[a]Cox proportional hazards models were used to estimate the associations between carvedilol (vs metoprolol) initiation and 1-year all-cause mortality.
[b]Fine and Gray proportional subdistribution hazards models were used to estimate the associations between carvedilol (vs metoprolol) initiation and 1-year cardiovascular mortality. Noncardiovascular death was treated as a competing risk.

cardiovascular hospitalization in the last 30 days of the baseline period produced results analogous to primary study findings. Carvedilol (vs metoprolol) initiation was associated with higher 1-year all-cause and cardiovascular mortality in this patient subgroup (Table S5). In sensitivity analyses evaluating the study β-blocker–tracer outcome association, carvedilol (vs metoprolol) initiation was not associated with the occurrence of hospitalized bowel obstruction (rate of 30.3 vs 28.7 events/1,000 person-years; adjusted HR, 1.02 [95% CI, 0.86-1.20]).

Post Hoc Analyses

The rate of intradialytic hypotension (systolic blood pressure decrease ≥ 20 mm Hg during hemodialysis plus intradialytic saline solution administration) during study follow-up was higher among carvedilol (vs metoprolol) initiators (57.5 vs 55.2 episodes/1,000 person-treatments; adjusted IRR, 1.10 [95% CI, 1.09-1.11]). Similar findings were observed when an episode of intradialytic hypotension was defined as an intradialytic nadir systolic blood pressure < 90 mm Hg (comparing carvedilol with metoprolol initiators: rate of 144.4 vs 136.5 episodes/1,000-person-treatments; adjusted IRR, 1.02 [95% CI, 1.01-1.03]). In additional post hoc analyses, all-cause and cardiovascular mortality associations were higher among individuals with versus without a recent history of frequent intradialytic hypotension (Fig 4; Table S6).

Discussion

This observational study evaluated the comparative mortality risk of carvedilol and metoprolol initiation among individuals receiving maintenance hemodialysis. We found evidence that carvedilol (vs metoprolol) initiation was associated with greater 1-year all-cause and cardiovascular mortality. The associations were consistent within clinically relevant subgroups and robust across sensitivity analyses. We also found that carvedilol initiators experienced higher rates of intradialytic hypotension during follow-up compared with metoprolol initiators. In addition, the observed study β-blocker–mortality associations were more pronounced among individuals with versus without a recent history of frequent intradialytic hypotension.

To date, there have been no randomized clinical trials comparing the efficacy and safety of individual β-blockers in the dialysis population. Prior β-blocker clinical trials were either placebo controlled[6,26] or compared β-blockers with other antihypertensive medication classes (eg, angiotensin-converting enzyme inhibitors).[27] Existing observational investigations of β-blockers have predominantly focused on comparing β-blocker users with nonusers,[28-34] and only 2 observational studies have considered head-to-head β-blocker comparisons. Weir et al[5] assessed the association between β-blocker dialyzability and 180-day mortality in a cohort of 6,588 elderly Canadian hemodialysis patients. Initiation of a highly versus a minimally dialyzable β-blocker was associated with higher all-cause death. This study provided initial evidence that β-blocker heterogeneity may differentially affect clinical outcomes in the hemodialysis population; however, carvedilol (a minimally dialyzable β-blocker) and metoprolol succinate (a highly dialyzable β-blocker) were not considered. In the US, carvedilol and metoprolol succinate account for 50% of all β-blocker prescriptions.

In a second epidemiologic study, Shireman et al[35] evaluated the association between β-blocker selectivity

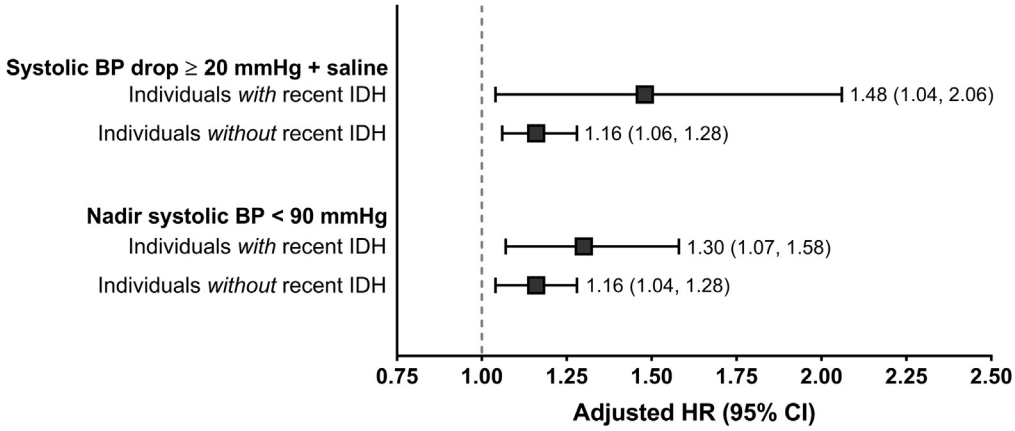

Figure 4. Association between carvedilol versus metoprolol initiation and 1-year cardiovascular mortality among individuals with and without a recent history of intradialytic hypotension (IDH): intent-to-treat analysis. An intent-to-treat design was used in all analyses. Fine and Gray proportional subdistribution hazards models were used to estimate the association between carvedilol (vs metoprolol) initiation and 1-year cardiovascular mortality. In these analyses, noncardiovascular death was treated as a competing risk. Inverse probability of treatment weighting was used in adjusted analyses to control for all baseline covariates listed in Table 1. Abbreviations: BP, blood pressure; CI, confidence interval; HR, hazard ratio; IDH, intradialytic hypotension.

and mortality in a cohort of 4,398 incident US hemodialysis and peritoneal dialysis patients with dual Medicare/Medicaid coverage and hypertension. Initiation of a cardioselective β-blocker (atenolol and metoprolol) versus a nonselective β-blocker (carvedilol and labetalol) was associated with greater survival. However, the relative contributions of carvedilol and metoprolol to the observed association are unclear, and this investigation relied on data from 2000 to 2005. In the last decade, carvedilol use has increased,[4,36] rendering a contemporary analysis important. International guideline bodies have called for additional comparative effectiveness research on putative cardioprotective drugs such as β-blockers in the hemodialysis population.[37]

To begin to address this evidence gap, we performed a head-to-head comparison of the 2 most commonly prescribed β-blockers in the United States; carvedilol and metoprolol. We found that carvedilol (vs metoprolol) initiation was associated with higher 1-year all-cause and cardiovascular mortality. Results were consistent among individuals with hypertension, atrial fibrillation, heart failure, and a recent myocardial infarction. Furthermore, the observed study β-blocker–mortality associations were robust across sensitivity analyses comparing carvedilol to immediate-release metoprolol tartrate and extended/controlled-release metoprolol succinate (separately). In post hoc analyses, we found that the association between carvedilol (vs metoprolol) initiation and mortality was more potent among individuals with a recent history of frequent intradialytic hypotension. In addition, the occurrence of intradialytic hypotension (defined 2 ways) was more common after carvedilol (vs metoprolol) initiation. Given that recurrent intradialytic hypotension is associated with increased morbidity and mortality in the hemodialysis population,[25,38-40] the results from our post hoc analyses support the notion that hemodynamic instability may play a mechanistic role in the observed association between carvedilol (vs metoprolol) initiation and greater mortality.

Pharmacologic and kinetic differences between carvedilol and metoprolol may plausibly explain the observed differences in mortality and intradialytic hypotension. First, the extent to which a β-blocker is removed from circulation by hemodialysis may affect intradialytic blood pressure. Carvedilol is minimally dialyzed, and metoprolol is highly dialyzed. As a result, carvedilol's antihypertensive effects are likely maintained over the course of dialysis, whereas metoprolol's antihypertensive effects may be diminished as serum drug concentrations decrease during treatment. Second, carvedilol and metoprolol differ with respect to their β-adrenergic receptor selectivity and vasodilatory capabilities. Carvedilol is a nonselective β-blocker (a β_1- and β_2-adrenergic receptor antagonist) with additional α-blocking activity (an α_1-adrenergic receptor antagonist). In contrast, metoprolol is a cardioselective β-blocker with high β_1-adrenergic receptor affinity. Both medications reduce heart rate and cardiac contractility, but due to its α-blocking effects, carvedilol is also a vasodilator. It is plausible that carvedilol-induced α-blockade may blunt compensatory sympathetic nervous system–mediated peripheral vasoconstriction during ultrafiltration, increasing the risk for intradialytic hemodynamic instability. These proposed clinical mechanisms likely act in concert in carvedilol-treated patients.

Ultimately, randomized controlled clinical trials are needed to definitively determine the relative safety and efficacy of carvedilol and metoprolol in the hemodialysis population. However, in the interim, our results suggest that the potential adverse hemodynamic effects of carvedilol (vs metoprolol) require consideration when

prescribing β-blockers to hemodialysis patients, particularly among individuals with a history of intradialytic hemodynamic instability. For example, it may be reasonable to: (1) consider metoprolol over carvedilol among individuals at higher risk for intradialytic hypotension, or (2) recommend that patients at higher risk for intradialytic hypotension withhold carvedilol doses before hemodialysis treatments to minimize potential intradialytic hypotensive effects. However, such decisions must be made carefully on an individual basis with consideration of comorbid cardiovascular conditions, historical blood pressure patterns, and concomitant antihypertensive medication use and dosing.

Our study has several strengths. First, we used a modern pharmacoepidemiologic study design to evaluate the comparative 1-year mortality risks associated with carvedilol and metoprolol initiation. To minimize the influence of bias due to confounding by indication or disease severity, we selected study medications with similar indications and therapeutic roles.[41] Notably, the carvedilol and metoprolol initiators were highly comparable, and all baseline covariate imbalances between treatment groups were diminished after IPT weighting. Additionally, we chose to study the 2 most commonly prescribed β-blockers to closely mirror a real-world clinical practice decision.[41] Second, unlike previous claims-based studies, we used a linked data set with detailed clinical data that enabled us to account for many important biochemical indexes and dialysis treatment parameters in our analyses. Finally, we performed multiple sensitivity analyses to test the robustness of our findings.

Our results should be considered within the context of study limitations. Because our study was observational, there may be residual confounding. However, we controlled for variables including albumin concentrations, phosphorus concentrations, and a history of nonadherence to treatment to minimize confounding from difficult-to-measure factors such as ambient health status. Reassuringly, carvedilol (vs metoprolol) initiation was not associated with the occurrence of the tracer outcome, hospitalized bowel obstruction. Second, although our linked data source contained detailed administrative and clinical data, information for some potentially important factors, such as the timing of medication dosing, subspecialty of the index β-blocker prescriber, and cardiac status (eg, ejection fraction and left ventricular hypertrophy) were not available. In particular, it is possible that a clinician's decision to prescribe carvedilol over metoprolol was influenced by left ventricular hypertrophy severity or other markers of cardiac function. As such, it is possible that residual confounding by indication (ie, indication bias)[41] may have influenced our results. Third, comorbid condition designations were based upon *International Classification of Diseases, Ninth Revision* diagnosis codes. Administrative claims data are generated for reimbursement and billing purposes. These data may not always reflect clinical subtleties and may not capture all patient characteristics, potentially affecting the accuracy of claims-identified comorbid conditions. For example, only a limited number of discharge diagnoses can be coded for each billable health care encounter, possibly reducing comorbid condition ascertainment. In addition, comorbid conditions not requiring a health care encounter during the 180-day baseline period may have been missed. Reassuringly, our approach facilitated capture of the most severe conditions and thus strongest potential confounders.[15,42] Fourth, our study population was composed of prevalent patients with ESRD receiving in-center hemodialysis. Our results may not be generalizable to excluded populations such as incident hemodialysis, home hemodialysis, or peritoneal dialysis patients. Understanding the relative risk-benefit profiles of carvedilol and metoprolol in these excluded patient populations is an area for future inquiry. Finally, our study evaluated a cohort of US hemodialysis patients. Our results may not apply to other countries that have national or regional prescription formularies which limit metoprolol and/or carvedilol prescribing.

In conclusion, we observed that carvedilol (vs metoprolol) initiation was associated with higher 1-year all-cause and cardiovascular mortality in a cohort of prevalent US hemodialysis patients. Data from our post hoc analyses suggest that one potential mechanism for the observed mortality associations may be an increased rate of intradialytic hypotension after carvedilol (vs metoprolol) initiation. Given the unique pharmacokinetic and hemodynamic considerations in the ESRD population, additional study of the efficacy and safety of β-blockers, as well as other cardioprotective medications with antihypertensive properties, is needed.

Supplementary Material

Figure S1: Propensity score distribution of patients treated with carvedilol and metoprolol.

Figure S2: The 1-year cumulative incidence of all-cause and CV mortality among carvedilol and metoprolol initiators: intent-to-treat analysis.

Table S1: Outcome definitions.

Table S2: Baseline covariate definitions.

Table S3: Association between carvedilol versus metoprolol initiation and 1-year mortality among clinically relevant subgroups: intent-to-treat analysis.

Table S4: Association between the initiation of carvedilol versus the initiation of the different metoprolol formulations and 1-year mortality: intent-to-treat analysis.

Table S5: Association between carvedilol versus metoprolol initiation and 1-year mortality among individuals who did not have a CV hospitalization during the last 30 days of the baseline period: intent-to-treat analysis.

Table S6: Association between carvedilol versus metoprolol initiation and 1-year mortality among individuals with and without a recent history of frequent IDH: intent-to-treat analysis.

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