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

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Abstract

Background: Carvedilol and metoprolol are the beta-blockers most commonly prescribed to U.S. hemodialysis patients, accounting for approximately 80% of beta-blocker prescriptions. Despite well-established pharmacologic and pharmacokinetic differences between the two 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 U.S. dialysis organization who initiated carvedilol or metoprolol therapy from 01/01/2007 through 12/30/2012.

Predictor: Carvedilol versus metoprolol initiation.

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

Measurements: Survival models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) in mortality analyses. Poisson regression was used to estimate incidence rate ratios (IRR) 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.

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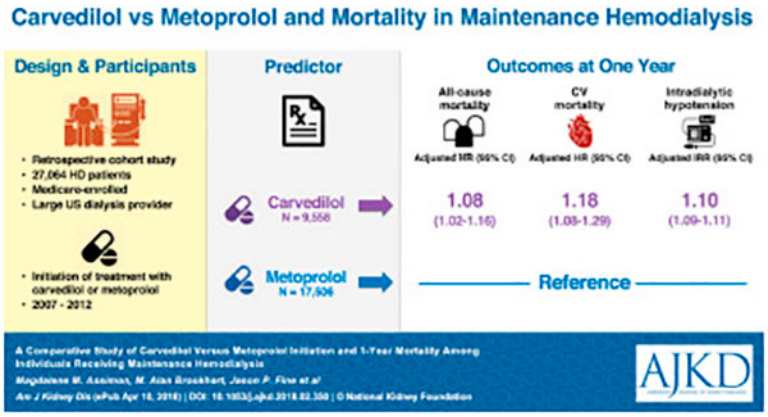
Results: 27,064 individuals receiving maintenance hemodialysis were included: 9,558 (35.3%) carvedilol initiators and 17,506 (64.7%) metoprolol initiators. Carvedilol (versus metoprolol) initiation was associated with greater all-cause mortality (adjusted HR, 1.08; 95% CI, 1.02–1.16) and cardiovascular 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 beta-blocker therapy. During follow-up, carvedilol (versus 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 (versus metoprolol) initiation.

Graphical Abstract



Index words:

beta-blocker; cardiovascular; carvedilol; hemodialysis; hypotension; metoprolol; mortality; blood pressure; intradialytic hypotension (IDH); dialyzability; end-stage renal disease (ESRD); pharmacoepidemiology

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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 beta-blockers, among others, are often prescribed to reduce cardiovascular risk. However, clinical trials establishing the cardioprotective nature and safety of beta-blockers largely excluded individuals with end-stage renal disease (ESRD).[2,3] Approximately 65% of the United States (U.S.) hemodialysis population is treated with a beta-blocker.[4] Despite widespread use, surprisingly little is known about the relative safety and efficacy of different beta-blockers in hemodialysis patients, a population with special drug dosing considerations.

Within the beta-blocker class, individual medications possess different pharmacologic and pharmacokinetic properties. Pharmacologically, beta-blockers differ with respect to their beta-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 beta-blocker clearance by the hemodialysis procedure (i.e. dialyzablity). These key differences may plausibly alter the hemodynamic and antiarrhythmic risk-benefit profiles of individual beta-blockers in the setting of ESRD.

In fact, observational data suggests that the potential survival benefit conferred by beta-blockers may differ across agents. In a Canadian cohort, Weir *et al.* found that the risk of all-cause death was significantly higher among hemodialysis patients treated with high dialyzability beta blockers (acebutolol, atenolol, metoprolol tartrate) as compared to patients treated with low dialyzablity beta-blockers (bisoprolol and propranolol).[5] However, carvedilol and metoprolol succinate, two commonly prescribed beta-blockers in the U.S.,[4] were not considered due to Canadian provincial prescription formulary restrictions. Carvedilol is a non-selective beta-blocker with alpha-blocking effects and is minimally cleared by hemodialysis. Metoprolol (tartrate and succinate) is a cardioselective beta-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.

While 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 U.S. 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

The study data were extracted from the clinical database of a large U. S. dialysis organization and the U.S. Renal Data System (USRDS). Data were linked at the patient level. The dialysis organization operates over 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 analog 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. Employing a new-user study design to evaluate the comparative safety and/or effectiveness of medications in retrospective investigations helps to 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 beta-blocker therapy from January 1, 2007 to December 30, 2012 following a 180-day baseline period free of any documented oral beta-blocker use (i.e. a beta-blocker washout period). We then applied the following exclusion criteria: 1) age <18 years old at the start of the baseline period, 2) dialysis vintage ≤90 days at the *start* of the baseline period (to ensure all potential study patients were eligible for Medicare coverage regardless of their age), 3) lack of continuous Medicare Part 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 <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 an oral beta-blocker other 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

The 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 renal 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 prior to 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 beta-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., Cary, NC). Baseline characteristics were described across carvedilol and metoprolol initiators as count (%) 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 (versus 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 beta-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 beta-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 (i.e. propensity score) of receiving carvedilol (versus 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, since the effect of metoprolol (versus 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 (i.e. per-protocol) approach. In these analyses, index beta-blocker discontinuation and switching to a non-index beta-blocker during follow-up were considered as additional censoring events. Third, to further minimize the influence of potential confounding by indication (i.e. indication bias), we evaluated the association between carvedilol (versus 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 (versus metoprolol) initiation and hospitalized bowel obstruction, a tracer (i.e. negative control) outcome that we did not expect to be influenced by the utilization of either of the study medications.

In secondary analyses, we evaluated the study beta-blocker–mortality associations within clinically relevant subgroups. We assessed the association between carvedilol (versus metoprolol) initiation and 1-year morality among individuals with hypertension, atrial fibrillation, heart failure and a recent myocardial infraction, the main cardiovascular indications for beta-blocker therapy. In additional analyses, we assessed the associations between carvedilol (versus 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 (versus 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 two different definitions: 1) a systolic blood pressure drop ≥20 mmHg during hemodialysis plus intradialytic saline administration (a guideline-based definition);[22–24] and 2) an intradialytic nadir systolic blood pressure <90 mmHg (a definition shown to associate with mortality).[25] We also evaluated study beta-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 female, 42.9% were black, 19.5% were Hispanic and the most common ESRD cause was diabetes (49.0%). Cardiovascular comorbidities 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 (Figure S1), indicating that the study groups were highly comparable. Patient baseline characteristics stratified by study beta-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 for a total of 20,863 person-years (7,219 person-years for carvedilol initiators and 13,644 person-years for metoprolol initiators). The average duration of follow-up was 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 (versus metoprolol) initiation and 1-year all-cause and cardiovascular mortality. Compared to individuals initiating metoprolol, individuals initiating carvedilol had a higher rate of all-cause mortality (225.1 versus 195.8 events/1,000 person-years; adjusted HR, 1.08 [95% CI, 1.02–1.16]) and cardiovascular

mortality (108.3 versus 85.1 events/100 person-years; adjusted HR, 1.18 [95% CI, 1.08–1.29]), Figure 3 and Figure S2.

Secondary analyses

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

In secondary analyses evaluating the associations between study beta-blockers and hospitalizations, individuals who initiated carvedilol (versus metoprolol) had similar rates of all-cause hospitalizations (2,383.8 versus 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 versus 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 to metoprolol tartrate and metoprolol succinate initiators (separately) generated results similar to primary analyses. Treatment with carvedilol (versus metoprolol) was associated 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 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 (554 in the carvedilol group and 797 in the metoprolol group). A total of 11,110 individuals discontinued index beta-blocker therapy and 1,662 switched to a different beta-blocker during follow-up. The average duration of continuous index medication use was 195 days for both carvedilol initiators metoprolol initiators. Individuals who remained on carvedilol (versus metoprolol) treatment had nominally higher rates of all-cause mortality (217.9 versus 195.4 events/1,000 person-years; adjusted HR, 1.06 [95%, 0.98–1.14]) and had higher rates cardiovascular mortality (106.3 versus 85.4 events/1,000 person-years; adjusted HR, 1.15 [95% CI, 1.03–1.28]).

Sensitivity analyses assessing beta-blocker–mortality associations among individuals who *did not* experience a cardiovascular hospitalization in the last 30 days of the baseline period produced results analogous to primary study findings. Carvedilol (versus 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 beta-blocker–tracer outcome association, carvedilol (versus metoprolol) initiation was not associated with the occurrence of hospitalized bowel obstruction (rate of 30.3 versus 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 (a systolic blood pressure drop ≥20 mmHg during hemodialysis plus intradialytic saline administration) during study follow-up was higher among carvedilol (versus metoprolol) initiators (57.5 versus 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 mmHg (comparing carvedilol to metoprolol initiators: rate of 144.4 versus 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 rates were higher among individuals with vs without a recent history of frequent intradialytic hypotension (Figure 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 (versus 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 to metoprolol initiators. In addition, the observed study beta-blocker–mortality associations were more pronounced among individuals with vs without a recent history of frequent intradialytic hypotension.

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

In a second epidemiologic study, Shireman *et al.* evaluated the association between beta-blocker selectivity and mortality in a cohort of 4,398 incident U.S. hemodialysis and peritoneal dialysis patients with dual Medicare/Medicaid coverage and hypertension.[35] Initiation of a cardioselective beta-blocker (atenolol, metoprolol) versus a non-selective beta-blocker (carvedilol, 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 2000–2005. In the last decade, carvedilol use has risen,[4,36]

rendering a contemporary analysis important. In fact, international guideline bodies have called for additional comparative effectiveness research on putative cardioprotective drugs such as beta-blockers in the hemodialysis population.[37]

To begin to address this evidence gap, we performed a head-to-head comparison of the two most commonly prescribed beta-blockers in the U.S., carvedilol and metoprolol. We found that carvedilol (versus 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 beta-blocker–mortality association was 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 (versus 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 two ways) was more common after carvedilol (versus 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 (versus 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 beta-blocker is removed from circulation by hemodialysis may impact 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 fall during treatment. Second, carvedilol and metoprolol differ with respect to their beta-adrenergic receptor selectivity and vasodilatory capabilities. Carvedilol is a non-selective beta-blocker (a β_1 and β_2 adrenergic receptor antagonist) with additional alpha-blocking activity (an α_1 adrenergic receptor antagonist). In contrast, metoprolol is a cardioselective beta-blocker with high β_1 adrenergic receptor affinity. Both medications reduce heart rate and cardiac contractility, but due to its alpha-blocking effects, carvedilol is also a vasodilator. It is plausible that carvedilol-induced alpha-blockade may blunt compensatory sympathetic nervous system-mediated peripheral vasoconstriction during ultrafiltration, increasing the risk of 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 (versus metoprolol) require consideration when prescribing beta-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 hold carvedilol doses prior to 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 treatment. 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 two most commonly prescribed beta-blockers to closely mirror a real-world clinical practice decision.[41] Second, unlike previous claims-based studies, we utilized a linked data set with detailed clinical data that enabled us to account for many important biochemical indices and dialysis treatment parameters in our analyses. Finally, we performed multiple sensitivity analyses to test the robustness of our findings.

However, these 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, phosphorus, and a history of non-adherence to treatment as a way to minimize confounding from difficult-to-measure factors such as ambient health status. Reassuringly, carvedilol (versus metoprolol) initiation was not associated with the occurrence of the tracer outcome, hospitalized bowel obstruction. Second, while our linked data source was comprised of detailed administrative and clinical data, information on some potentially important factors, such as the timing of medication dosing, subspecialty of the index beta-blocker prescriber, and cardiac status (e.g. ejection fraction, 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 (i.e. indication bias)[41] may have influenced results. Third, comorbid condition designations were based upon International Classification of Diseases, 9th Revision, diagnostic codes. Administrative claims data are generated for reimbursement and billing purposes. These data may not always reflect clinical subtleties and may not include 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 comorbidity ascertainment. In addition, comorbidities not requiring a healthcare 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 comprised of prevalent ESRD patients 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 U.S. hemodialysis patients. Our results may not apply to other countries where national or regional prescription formularies limit metoprolol and/or carvedilol prescribing.

In conclusion, we observed that carvedilol (versus metoprolol) initiation was associated with higher 1-year all-cause and cardiovascular mortality in a cohort of prevalent U.S. 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 (versus metoprolol) initiation. Given the unique pharmacokinetic and hemodynamic considerations in the ESRD population, additional study of the efficacy and safety of beta-blockers, as well as other cardioprotective medications with antihypertensive properties is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Authors' Contributions: Research idea and study design: MMA, MAB and JEF; data acquisition: MMA, MAB and JEF; data analysis/interpretation: MMA, MAB, JPF, GH, JBL and JEF; statistical analysis: MMA; and supervision or mentorship: MAB, JEF. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Disclaimer: Some of the data reported here have been supplied by DaVita Clinical Research. DaVita Clinical Research had no role in the design or implementation of this study or the in the decision to publish. Additionally, some of the data reported here have been provided by the United States Renal Data System. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as official policy or interpretation of the United States government.

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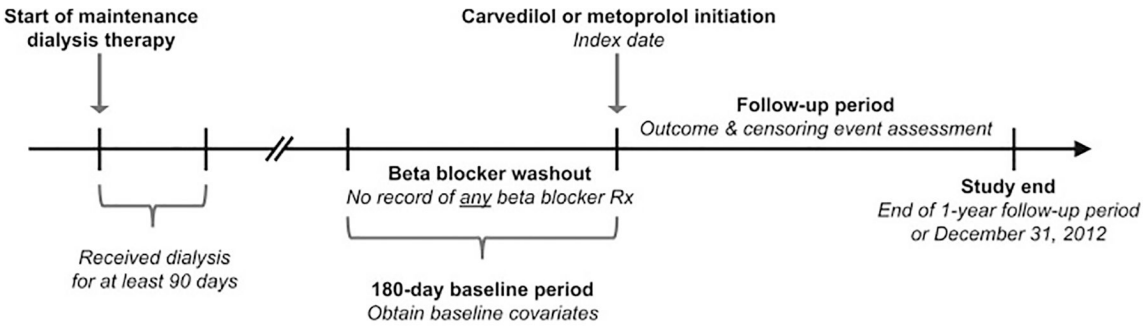

Figure 1. Study design

Carvedilol and metoprolol initiators were defined as hemodialysis patients who had no record of a beta-blocker prescription in the previous 180 days (beta-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 prior to the index date. Study follow-up began immediately after the index date. To ensure all potential study patients were eligible for Medicare coverage regardless of their age, individuals needed to have a dialysis vintage > 90 days at the start of the baseline period.

Abbreviations: Rx, prescription

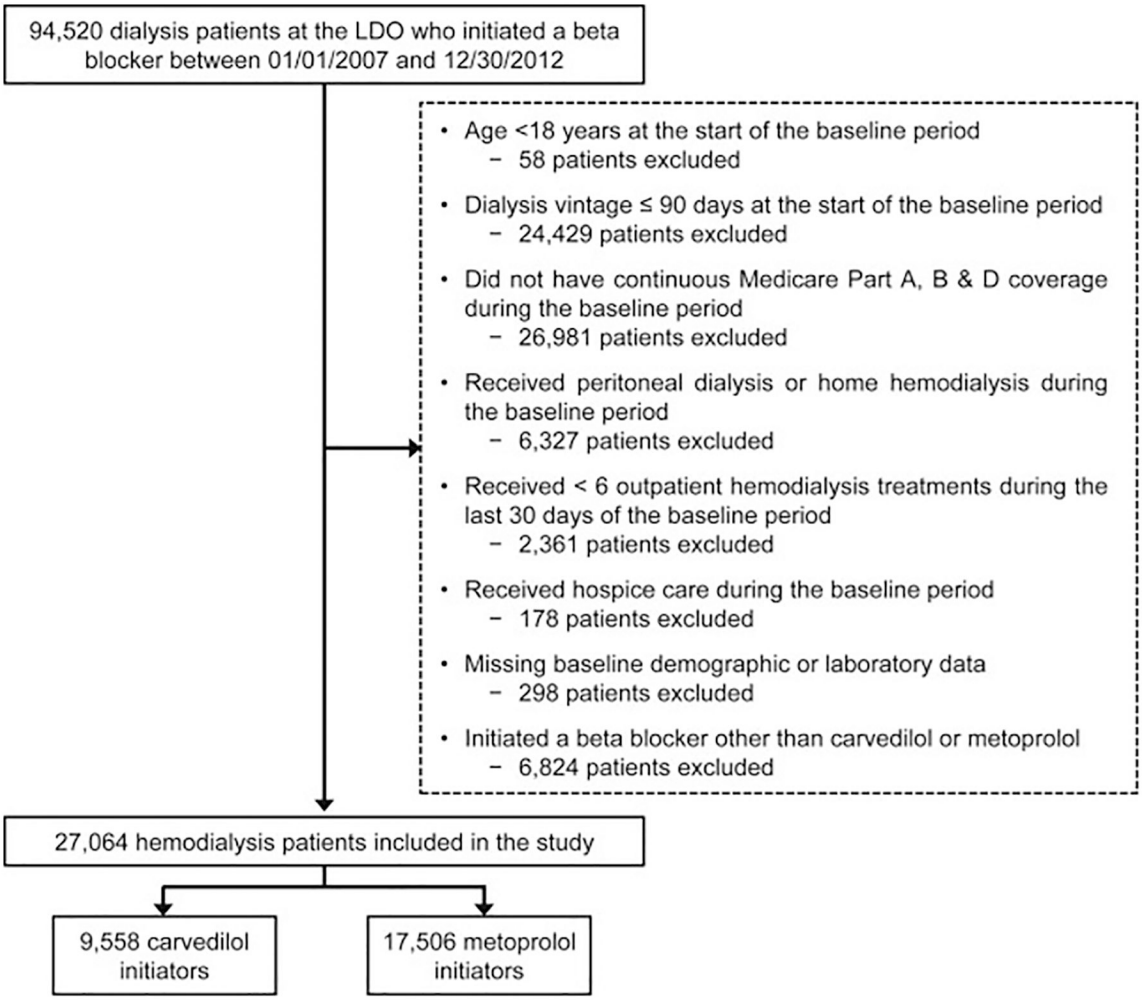

Figure 2. Flow diagram depicting the assembly of the study cohort
Abbreviations: LDO, large dialysis organization

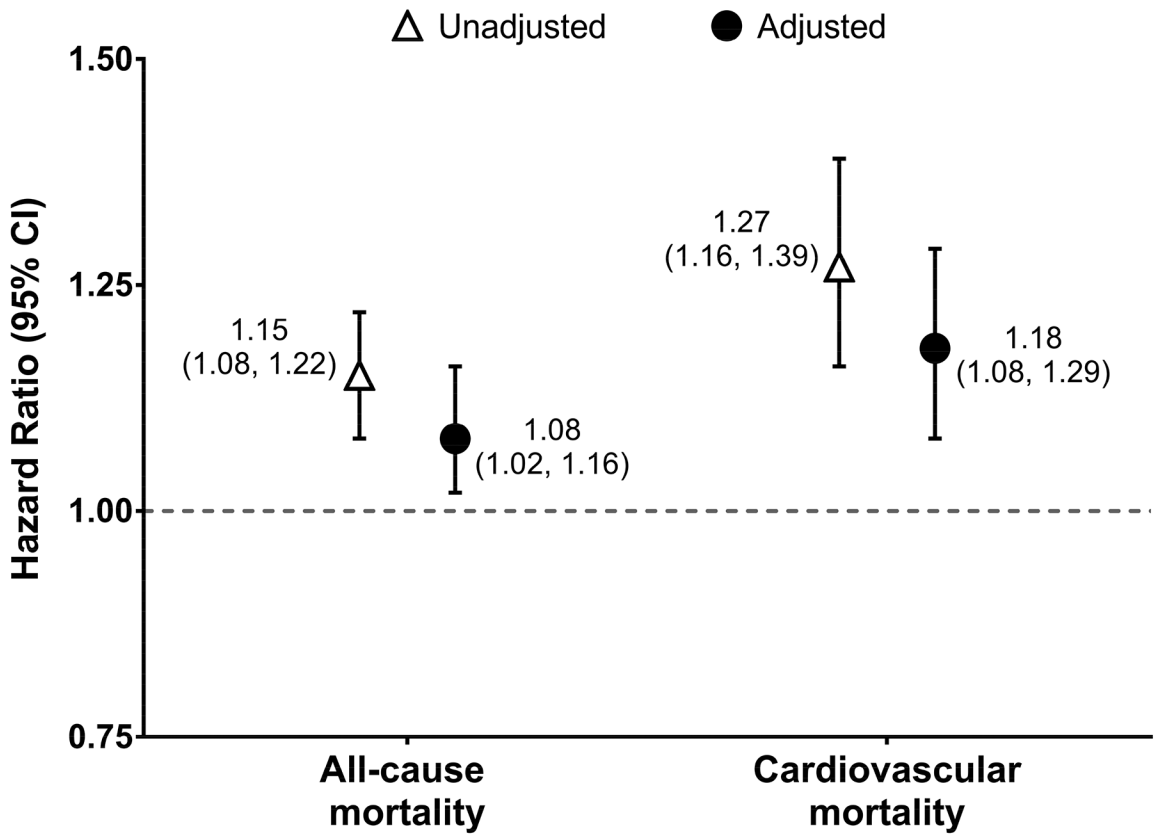

Figure 3. Association between carvedilol versus metoprolol initiation and 1-year mortality: intent-to-treat analysis

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

Abbreviations: CI, confidence interval; HR, hazard ratio; ref., referent

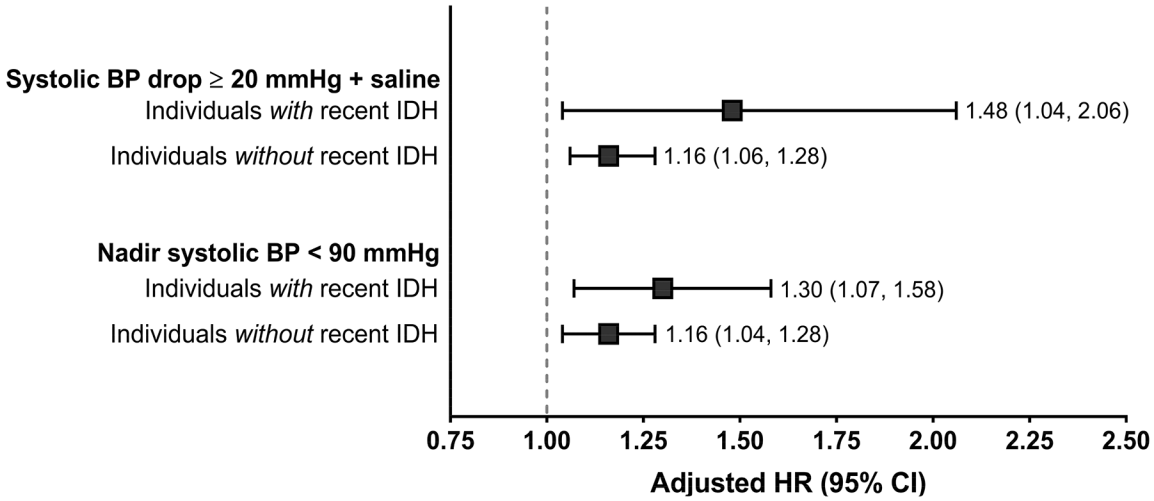

Figure 4. Association between carvedilol versus metoprolol initiation and 1-year cardiovascular mortality among individuals with and without a recent history of intradialytic hypotension: intent-to-treat analysis

An intent-to-treat design was employed in all analyses. Fine and Gray proportional subdistribution hazards models were used to estimate the association between carvedilol (versus metoprolol) initiation and 1-year cardiovascular mortality. In these analyses, non-cardiovascular death was treated as a competing risk. Inverse probability of treatment weighting was used in adjusted analyses to control for all the baseline covariates listed in Table 1.

Abbreviations: CI, confidence interval; HR, hazard ratio; ref., referent

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 beta-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

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 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 years	595 (6.2%)	935 (5.3%)	0.038	536 (5.6%)	988 (5.6%)	0.001
1.0 – 1.9 years	2,118 (22.2%)	3,705 (21.2%)	0.024	2,053 (21.5%)	3,778 (21.6%)	0.001
2.0 – 2.9 years	1,668 (17.5%)	2,778 (15.9%)	0.042	1,556 (16.3%)	2,875 (16.4%)	0.002
≥ 3.0 years	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
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

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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]
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
Pre-dialysis systolic BP						
< 130 mmHg	1,384 (14.5%)	2,159 (12.3%)	0.063	1,241 (13.0%)	2,289 (13.1%)	0.001
130 – 149 mmHg	2,696 (28.2%)	4,744 (27.1%)	0.025	2,621 (27.5%)	4,808 (27.4%)	0.001
150 – 169 mmHg	3,175 (33.2%)	6,084 (34.8%)	0.032	3,253 (34.1%)	5,997 (34.2%)	0.002
≥170 mmHg	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

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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]
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
Number of medications in last 30 days of baseline	5.5 ± 3.8	5.5 ± 3.9	0.014	5.5 ± 3.9	5.5 ± 3.9	0.014
Alpha 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 alpha 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
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

Abbreviations: Std diff, standardized difference; CV, cardiovascular; IDH, intradialytic hypotension; BP, blood pressure.

All-covariates were measured during the baseline period prior to carvedilol or metoprolol initiation. Values for categorical variables are given as number (%) 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.

[a] A standardized difference > 0.1 represents meaningful imbalance between groups.[16]

[b] Claims-based definition of nonadherernce included ICD-9 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 IDHBP if they had an intradialytic nadir systolic BP < 90 mmHg 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 non-statin cholesterol medications: bile acid sequestrants, cholesterol absorption inhibitors, fibrates and niacin.

[e]Both carvedilol and metoprolol are metabolized by cytochrome P450 2D6. Concomitant use of medications that are potent inhibitors cytochrome P450 2D6 of may increase serum concentrations of both carvedilol and metoprolol, putting patients at increased risk for beta-blocker—related adverse events such as hypotension. Cytochrome P450 2D6 inhibitors included: amiodarone, bupropion, chloroquine, cinacalcet, diphenhydramine, fluoxetine, haloperidol, imatinib, paroxetine, propafenone, propoxyphene, quinidine, terbinafine and thioridazine.

Abbreviations: COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; GI, gastrointestinal

Table 2.

Association between carvedilol versus metoprolol initiation and 1-year mortality among clinically relevant subgroups: intent-to-treat analysis[a]

		1-year all-cause mortality[b]			1-year cardiovascular mortality[c]	
Beta-blocker	**N**	**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 (ref.)		100.7	1.00 (ref.)
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 (ref.)		174.1	1.00 (ref.)
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 (ref.)		144.9	1.00 (ref.)
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 (ref.)		187.1	1.00 (ref.)
Carvedilol	642	443.6	1.02 (0.84, 1.23)		244.7	1.19 (0.92, 1.53)

An intent-to-treat design was employed in all analyses. Adjusted analyses controlled for baseline covariates listed in Table 1 using inverse probability of treatment weighting. Subgroups of interest were excluded the corresponding propensity score models. For example, in subgroup analyses of patients with hypertension, the hypertension covariate was excluded from the propensity score model.

[a]Presented patient counts and outcome event rates are based on the unweighted cohort.

[b]Cox proportional hazards models were used to estimate the associations between carvedilol (versus metoprolol) initiation and 1-year all-cause mortality.

[c]Fine and Gray proportional subdistribution hazards models were used to estimate the associations between carvedilol (versus metoprolol) initiation and 1-year cardiovascular mortality. Non-cardiovascular death was treated as a competing risk.

Abbreviations: CI, confidence interval; HR, hazard ratio; no., number; p-y, person-year; MI, myocardial infarction