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.

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

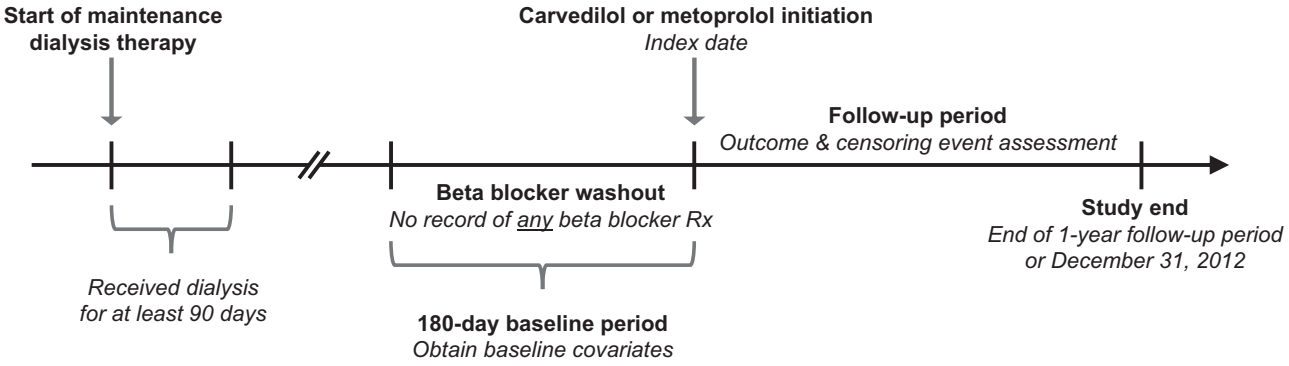

Figure 1. Study design. Carvedilol and metoprolol initiators were defined as hemodialysis patients who had no record of a β-blocker prescription in the previous 180 days (β-blocker washout period). Among these patients, the index date was defined as the date of carvedilol or metoprolol initiation. Baseline 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.