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Relationship between calcium channel blocker class and mortality in dialysis

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Abstract

Background and objective—The comparative effectiveness of dihydropyridine (DHP) and non-DHP calcium channel blockers (CCBs) in maintenance dialysis patients has not been well-studied

Methods—A retrospective cohort of hypertensive patients initiating dialysis was created. New CCB initiators, defined as individual who had no evidence of CCB use in the first 90 days of dialysis but who were initiated by day 180, were followed from their first day of medication exposure until event or censoring; events consisted of all-cause mortality (ACM) and a combined endpoint of cardiovascular morbidity or mortality (CVMM). Cox proportional hazards models were used to determine adjusted hazard ratios (AHRs) comparing the effect of DHPs vs. non-DHPs.

Results—There were 2900 and 2704 new initiators of CCBs in the ACM and CVMM models, respectively. Adjusted for other factors, use of DHPs, compared to non-DHPs, was associated with an AHR of 0.77 (99% confidence intervals, 0.64 – 0.93, $P = 0.0004$) for ACM and 0.86 (0.72 – 1.02, $P = 0.024$) for CVMM. Results were similar when individuals who initiated therapy at any point after the cohort inception were included, with AHRs of 0.60 (0.53 – 0.69, $P < 0.0001$) and 0.77 (0.67 – 0.89, $P < 0.0001$) for ACM and CVMM, respectively. Further, elimination of

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individuals with chronic atrial fibrillation resulted in AHRs of 0.71 and 0.70 for ACM and CVVM, respectively.

Conclusion—DHPs, as compared to non-DHPs, were associated with reduced hazard of death or cardiovascular morbidity and mortality; potential mechanisms of action require further study.

Keywords

Dialysis; end stage renal disease; hypertension; mortality; calcium channel blockers; comparative effectiveness

INTRODUCTION

Patients with end-stage renal disease (ESRD) on maintenance dialysis have high rates of hypertension and cardiovascular disease (CVD).¹ As a result, antihypertensive medications with “cardioprotective” properties²⁻⁵ are commonly used in this population.^{6, 7} However, because patients on dialysis are not typically enrolled in randomized clinical trials (RCTs), prescribing decisions are often based upon extrapolation from what is known from the general population, despite stark differences in physiology and health status in the dialysis and non-dialysis populations.

One commonly used class of medications used to treat hypertension is the calcium channel blockers (CCBs), which can be further classified into dihydropyridines (DHPs) and non-DHPs. CCBs have often been compared to other antihypertensive agents in the non-dialysis population,^{8, 9} but little, if any, work has been done to compare the effects of DHPs to non-DHPs in the maintenance dialysis population. Further, while observational evidence exists that CCBs as a whole may confer mortality benefits in dialysis patients,¹⁰⁻¹⁵ and a randomized clinical trial demonstrated mortality benefits in amlodipine compared to placebo,¹⁶ there do not appear to be any comparative effectiveness studies of CCB subclasses in dialysis patients. This within-class distinction could be important because CCBs differ in their effects on cardiac inotropy, cardiac chronotropy, and vascular relaxation.^{17, 18} For example, the non-DHPs have roughly equal effects on vascular selectivity and negative inotropy, while the DHPs more strongly affect the former relative to the latter.¹⁹⁻²¹ Additionally, non-DHPs tend to affect chronotropy more so than do DHPs.^{17, 21} As such, the varying physiologic effects of CCBs may provide a therapeutic rationale for prescribing decisions favoring one type over another.

Given the dearth of comparative effectiveness data relevant to the maintenance dialysis population regarding CCBs in the treatment of hypertension, and given mechanistic differences between DHPs and not DHPs,^{17, 18} our goal was to compare mortality and morbidity outcomes across two major subclasses of CCBs. To do so, we utilized a novel linkage of the United States Renal Data System (USRDS) with Medicaid pharmacy claims^{6, 22} to link detailed longitudinal medication exposure data with clinical outcomes in a large cohort of incident dialysis patients. We hypothesized that agents with less of an effect on cardiac inotropy, such as DHPs, might confer benefits not seen when non-DHPs are used.

METHODS

Study design and data sources

We performed a retrospective cohort analysis of incident, Medicare and Medicaid (dually eligible) maintenance dialysis patients, quantifying their exposure to the two subclasses of CCBs and assessing their outcomes over six years (2000-2005).^{6, 22} Outcomes assessed were all-cause mortality and a combined outcome that included cardiovascular mortality and morbidity. The comparative effectiveness of new DHP use relative to new non-DHP use was analyzed as described below.

Data were from two primary sources. First, we utilized the USRDS, a national system that collects data on virtually all patients undergoing maintenance dialysis in the U.S. From the USRDS core files, we utilized information on demographics, comorbidities, functional status, and dialysis modality (from the Medical Evidence Form, or CMS 2728) recorded at the time of dialysis commencement. The USRDS also incorporates inpatient and outpatient medical claims paid by Medicare, a federally-funded program for which nearly all adults with end stage renal disease are entitled, regardless of age.^{1, 23} Medicaid, a joint federal-state program designed to provide prescription drug coverage to low-income persons was required so as to be able to track prescription medication exposure. (Of note, outpatient prescription medications were not covered under Medicare during this period.)

To make possible the study of dually eligible individuals, the USRDS performed a deterministic match, permitting us to link USRDS data with Centers for Medicare & Medicaid Services (CMS) Medicaid Analytic eXtract Personal Summary Files and the final action prescription drug claims files, as described previously.^{22, 24}

Cohort creation

We created a cohort consisting of hypertensive individuals who were new initiators of CCBs, defined as those who had at least one prescription for a CCB during the study period, no use during the first 90-day run-in period, initiation within the next 90 days (i.e., within the first 180 days of starting dialysis), and no cross-subclass CCB crossover (i.e., DHP to non-DHP, or vice versa). To assure complete observability of the cohort, we employed several criteria.²² First, we limited the cohort to persons enrolled in a single state's Medicaid fee-for-service program. Persons with coverage through the Veterans Administration and those who had previously been transplanted with a kidney were excluded. Persons who received a kidney transplant, died, or were not continuously eligible for Medicare and Medicaid during the first 90 days on dialysis were excluded. Additionally, persons who did not fill any prescriptions during the first 90 days were excluded (as this lack of prescriptions might reflect the Medicaid's spend-down requirements). Ohio residents were excluded since their claims do not include the days supplied of medication. We also excluded persons who were institutionalized during their entire follow-up period because such patients would typically have received their medications from the institutionalizing facility (constituting unobservable prescriptions in our approach) and because any appearance of outpatient prescriptions would have been difficult to interpret clinically. Additionally, we excluded persons who were missing multiple data fields from their CMS 2728 form (other than for

hemoglobin and body mass index), and/or did not have hypertension documented on this form. Finally, we selected individuals who received at least one CCB during their follow-up period.

The observation window began at the date the first CCB prescription was dispensed. Subjects were then followed until they incurred a first outcome event (death or cardiovascular event). They were censored when they lost Medicare or Medicaid eligibility, received a kidney transplant, or reached the end of the observation window (December 31, 2005).

Covariates and descriptive variables

Demographic and clinical variables, drawn from the CMS 2728 form, included age, sex, race by ethnicity, employment status, smoking, substance abuse (alcohol or illicit drugs), ability to ambulate and to transfer, body mass index (BMI), cause of ESRD, comorbidities, dialysis duration (before medication initiation) and dialysis modality. Ethnicity was categorized into one of four mutually exclusive groups: non-Hispanic Caucasians, non-Hispanic African-Americans, Hispanics, and Others. Body mass index (BMI) was classified into 4 categories: $< 20 \text{ kg/m}^2$, $20\text{-}24.99 \text{ kg/m}^2$, $25\text{-}29.99 \text{ kg/m}^2$, 30 kg/m^2 . Cause of ESRD was categorized as diabetes, hypertension, glomerulonephritis, or other. Comorbidities consisted of diabetes, congestive heart failure, coronary artery disease, cerebrovascular disease, and peripheral vascular disease. Because the CMS 2728 form is structured such that diabetes and hypertension may be considered as both a cause of ESRD and/or a comorbidity, for the purposes of the present analysis, these two covariates were each considered a comorbidity if they were listed as either on the CMS 2728 form.^{25, 26} Dialysis modality at time of dialysis initiation was categorized as in-center hemodialysis or self-care dialysis (home hemodialysis or peritoneal dialysis). In the case of missing data ($<1.5\%$ for BMI in all cases and $< 10.0\%$ for hemoglobin in all cases), a separate category was created for the analysis described below. Additionally, we examined concomitant use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers (ACEI/ARBs) and β -adrenergic blockers (β -blockers), for both outcomes.

Medication Exposure

CCBs were divided into two subclasses: dihydropyridines (e.g., amlodipine, felodipine, nisoldipine, isradipine, nicardipine, nimodipine, and long-acting nifedipine) and non-DHPs (diltiazem and verapamil). New CCBs users were those who did not have any prescriptions for a CCB in the first 90 days following dialysis initiation. Persons were assigned to a single CCB subclass: anyone who used medications from both subclasses was excluded; this exclusion amounted to 21 out of 589 total non-DHP users (3.6%) and 22 of 2922 DHP users (0.8%), or 1.2% of the total cohort.

In order to determine whether the durations of exposure were comparable between CCB subclasses, we examined their proportion of days covered (PDC).²⁷ The PDC is computed from converting days supplied and dates from individual drug claims to a daily array. The PDC was adjusted for prescription overlaps, as well as hospital and skilled nursing facility

days (since medications administered throughout the institutionalization would not result in an outpatient drug claim).

Outcomes

All-cause mortality (ACM) was ascertained from the USRDS Core CD, which specifies date and cause of death. In addition, we created a combined cardiovascular morbidity and mortality (CVMM) event outcome, capturing the first event per person. CVMM was defined as an inpatient hospitalization (Medicare Part A claims), occupying the first (primary) position on the claim, for myocardial infarction (ICD-9 codes 410.x0, 410.x1), ischemic heart disease (411.xx), revascularization (ICD9 procedure codes 36.xx except 36.9), congestive heart failure (428.xx, 402.x1, 404.x1, or 404.x3), cerebrovascular accident (433.xx, 434.xx, 435.x), or peripheral vascular disease (440.2-4, 443.1, 443.81, 443.9, 444.2x, 444.81, 445.0x). Cardiac-related mortality was derived from the USRDS listed cause of death (myocardial infarction, atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest, cerebrovascular accidents). Outcome events were quantified as time from initiation of their CCB to either the event or censoring.

Statistical Analyses

To examine balance between CCB subclasses, we generated contingency tables using Pearson's chi-square test and assessing validity by examining expected cell counts for categorical measures. For continuous measures, descriptive statistics were generated, stratified histograms were examined, and two-sample t-tests performed. To investigate within-class comparative effectiveness, we examined these data using Kaplan-Meier survival curves for an unadjusted comparison. We then fit Cox proportional hazards regression models to compare these subgroups adjusted for other potential confounding and estimate for these other factors potential associations with ACM and CVMM. Exponentiation of the parameter estimates obtained from these models using appropriate contrast statements allowed us to calculate the hazard ratios (HRs) for evaluating DHPs relative to non-DHPs. Cox proportionality assumptions were ascertained through visual assessment of the complementary log-log survival plots.

Statistical significance was inferred when $P < 0.01$. Statistical analyses were done with SAS 9.2 (SAS Institute, Inc., www.sas.com).

Sensitivity Analyses

To test the robustness of our results, we performed several sensitivity analyses. First, we examined all new users of CCBs (i.e., those with no evidence of use within the first 90 days of dialysis but who initiated at any time during follow-up). Second, using the primary model as the basis for further analyses, we eliminated individuals who had chronic AF at any time during follow-up (using a previously developed algorithm²⁸) in order to explore the potential impact of chronic atrial fibrillation (AF) on our results. The decision to eliminate individuals who ever appeared to have chronic AF was undertaken because dating the onset of a chronic and typically stable medical condition such as AF can be particularly challenging. Third, we created a further restricted model that eliminated individuals with chronic AF and included interactions between CCB subclass and heart failure (since CCB

subclass use could vary by the presence of heart failure, as defined on the CMS 2728 form), and between CCB subclass and age. Fourth, to examine whether use β -adrenergic antagonists (“ β -blockers”) might be potential confounders (and therefore partially responsible for any findings), we explicitly modeled β -blocker use. Finally, we specifically tested for an interaction between CCB subclass and β -blocker use.

Compliance and Research Participant Protection

The research protocol was approved by the institutional review board at the University of Kansas Medical Center (KUMC). Data Use Agreements between KUMC and the USRDS and CMS permitted the data linking across the USRDS, Medicare and Medicaid files.

RESULTS

Figure 1 demonstrates the construction of the study cohort. Of the initial 84,670 cohort, there were 52,922 with hypertension who met other criteria for this study. Over one-half ($n = 28,677$) received a CCB prescription during their first 90 days on dialysis. From the remaining 24,245 eligible patients, there were 2,900 new CCB initiators included in the ACM model and 2,704 in the CVMM model. (Model totals were different since, for example a patient could have had a cardiovascular event before receiving a CCB, thus being eligible for the ACM model but not the CVMM model. Alternatively, a patient could have been on both a DHP and a non-DHP during his or her time to mortality, but only a DHP during his or her time to CVMM, thus being eligible for the CVMM model but not the ACM model.)

Table 1 shows bivariate comparisons of users of DHPs vs non-DHPs at baseline. In both analytic cohorts (ACM and CVMM), DHP users were significantly younger by about 4 years, less likely to be Caucasian, and less likely to be female. In general, other comorbidities and causes of ESRD, were relatively well-balanced different between groups. PDCs did not differ by subclass for either outcome, signaling comparable exposure during the observation window.

Survival by the Kaplan-Meier method is shown graphically in Figure 2. For both ACM and CVMM, individuals prescribed DHPs had superior outcomes compared to those prescribed non-DHPs. In the case of ACM, 50% mortality was reached approximately 42.8 months for DHP users, but at only about 28.6 months for non-DHP users. For CVMM, 50% had reached the endpoint by about 20.5 months among DHP users, but by only about 17.2 months among non-DHP users.

The modeled effects of the medications for both ACM and CVMM are shown in Table 2. Adjusted for all other factors, use of DHPs, compared to non-DHPs, was associated with an AHR of 0.77 (99% CIs, 0.64 – 0.93, $P = 0.0004$) for ACM and 0.86 (0.72 – 1.02, $P = 0.024$) for CVMM. In addition, older age and Caucasian (compared to African-American) race were significantly associated with increase in both ACM and CVMM. For ACM, mortality was increased for individual in the lowest BMI category and decreased in those in the highest, as expected; there was a trend towards this finding for CVMM.

In a sensitivity analysis including individuals who initiated a CCB at any point after day 90 of dialysis, DHPs were associated with an AHR of 0.60 (99% CIs, 0.53 – 0.69, $P < 0.0001$) for ACM and 0.77 (0.67 – 0.89, $P < 0.0001$) for CVMM. Elimination of individuals with chronic AF resulted in an AHR of 0.71 (0.57 – 0.89, $P < 0.0001$) for ACM and 0.70 (0.56 – 0.89, $P = 0.0001$) for CVMM. When interaction terms were incorporated into the ACM model restricted to individuals without chronic AF, interaction of DHP with neither age ($P = 0.87$) nor HF ($P = 0.76$) were significant. Likewise, for the corresponding CVMM model, interactions were not significant for DHP with age ($P = 0.42$) and DHP with HF (0.86).

We also examined concomitant use of ACEI/ARBs and β -blockers, for both outcomes, in this group. Differential use of these agents across CCB subclasses were consistently $< 10\%$: for the ACM model, use of ACEI/ARBs in patients prescribed DHPs was 35.3% versus 40.5% ($P = 0.047$), while use of β -blockers in DHP patients was 38.6%, versus 29.8% in non-DHP patients ($P = 0.0008$). For the CVMM model, corresponding percentages for ACEI/ARBs were 35.5% versus 40.8% ($P = 0.031$), and for β -blockers 38.0% versus 29.0% ($P = 0.0015$). In the models which included prevalent β -blocker use, the β -blocker effect was not significant for ACM ($P = 0.14$; AHR 0.94 [0.83-1.05]), and the benefit associated with DHPs, as compared with non-DHPs, remained similar in magnitude and direction ($P = 0.0007$; AHR 0.78 [0.64-0.94]). Analogously, for the CVMM model, the effect of β -blockers was not significant at the $P = 0.01$ level ($P = 0.05$; AHR=0.91 [0.80-1.03]) and the advantage associated with DHPs was, if anything, strengthened ($P = 0.0008$; AHR=0.77 [0.63-0.94]). When β -blocker use was tested for an interaction with CCB subclass, the interaction P -values were 0.08 for ACM and 0.32 for CVMM.

DISCUSSION

In this study, we compared new users of DHPs and non-DHPs for differences in all-cause mortality and a combined endpoint of cardiovascular events and death in patients on maintenance dialysis. We found that, after adjustment for a wide variety of other factors, DHPs were associated with reductions of ACM by 23% and of CVMM by 14% compared to non-DHPs. This suggests that use of DHPs may confer benefits not seen with non-DHPs when the medications are used in otherwise similar maintenance dialysis patients.

While differences in dialytic clearance are unlikely to be responsible for our findings, given that neither DHPs nor non-DHPs are significantly cleared by hemodialysis,²⁹ pharmacological differences on cardiovascular physiology such as systolic function, diastolic function, and electrical conduction may well be operative in dialysis patients. While both DHP's and non-DHPs were studied in previous decades to determine their effects on heart failure,³⁰⁻³³ recent guidelines³⁴ have affirmed that in the setting of heart failure with reduced ejection fraction (classically, left ventricular systolic dysfunction), CCBs are likely harmful. The sole exception is amlodipine, which, while not recommended, is not actively discouraged. CCBs differ in their spectrums of activity in both vasoconstriction and negative inotropy,^{17, 18} varying in their ratio of vascular selectivity to negative inotropy.¹⁹⁻²¹ This ratio is 1:1 for diltiazem and verapamil, but is thought to be 10:1 for nifedipine and perhaps as high as 1000:1 for amlodipine,²⁰ suggesting a possible mechanism³⁵ for the putative superiority of DHPs in this population. Given the high

prevalence of systolic dysfunction in maintenance dialysis patients,³⁶ it is possible that the effect we observed was due not to any salutary effect of DHPs, but rather the potential of non-DHPs to worsen CV function. Although we failed to detect an interaction effect between heart failure and CCB subclass, our database did not allow us to specifically uniquely identify patients with heart failure due to systolic dysfunction.

Another possible reason for our findings relates to differential effects on cardiac conduction of DHPs and non-DHPs. Diastolic dysfunction (now termed heart failure with preserved ejection fraction, or HFpEF³⁷) appears to be common in dialysis patients.^{36, 38, 39} While AHA guidelines make no additional specific recommendations for the treatment of HFpEF, they warn about chronotropic “incompetence” in this setting.³⁷ Verapamil and diltiazem decrease conductivity through the sinoatrial and atrioventricular nodes,²¹ a property which is at least in part responsible for their effects on inotropy and which also provides the rationale for their use in tachyarrhythmias. However, an intact chronotropic response is important for hemodialysis patients, who frequently experience profound intradialytic hypotension during a HD treatment session. It is not unusual for HD patients to experience decreases in systolic blood pressure of 50mmHg or more over hours or even minutes during aggressive intravascular fluid removal. When exposed to agents which blunt the chronotropic response, patients may not be able to adequately respond to this hemodynamic stress. Whether differences in effects on chronotropy between types of CCBs may be responsible, directly or indirectly, for an increase in cardiovascular events is speculative, but should be further studied.

Our study has several important limitations. First, as an observational study, our investigation cannot prove causality. Only a randomized clinical trial (RCTs) would be able to definitively eliminate the selection bias present in all observational studies in order to answer whether DHPs are truly superior to non-DHPs in reducing overall mortality and cardiovascular events. Second, we lack important patient-level factors such as severity of disease or level of blood pressure control. These factors might be unbalanced between the treatment groups, and therefore could be a source of residual confounding resulting from non-random treatment allocation. Additionally, a whole host of factors influence prescribing decisions among physicians, including physician demographics, physician years since training, care environment, confidence in managing disorders, and aspects of the physician-patient relationship;⁴⁰⁻⁴² these cannot be accounted for in an observational study. Nevertheless, among the factors we could measure, the observed differences between treatment groups at baseline were modest. Any unmeasured residual confounders (e.g., the modestly different rates of ~10% in use of ACEI/ARBs or β -blockers) would need to be both very common and extremely powerful to fully account for the large effect size that we observed. We also limited the look-back period for prior CCB use to 90 days to establish new use; this may be an imperfect approach, since patients may have been exposed to CCBs in their more distant medical history, and therefore not been truly treatment naïve. Finally, we studied only dually eligible individuals, who have lower socioeconomic status than others. How our results might be generalized to other individuals, such as those with private insurance, is unknown, although from a purely physiologic perspective, drug efficacy would not be expected to be dependent on socioeconomic status. However, our study had important strengths, including use of a large sample size, demonstration of comparable levels of

exposure between DHPs and non-DHPs, and use of multiple sensitivity analyses which, overall, supported the findings of the primary analytic approach. Additionally, we specifically employed a design which focused not only new users of the medications but also on “early initiators” (that is, individuals starting the drugs within the first 90 days of follow up), which would likely have the effect of attenuating confounding-by-indication that might result from the accumulation of additional comorbid events over time on dialysis.

In conclusion, we found that DHPs are associated with lower risk of ACM and CVMM, compared to non-DHPs, in a large cohort of incident dialysis patients newly starting these agents. These findings may reflect the different mechanisms of action of these two medication subclasses. The initiation of dialysis is an appropriate time for providers to reconsider the ideal antihypertensive regimen for their patients. It is unlikely that a controlled clinical trial will actually be performed in the near future that compares subclasses of CCBs in the dialysis population, given little financial incentive to do so. As such, clinicians should carefully consider the possibility that non-DHP CCBs may be problematic in patients receiving maintenance dialysis.

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Take-Home Points

- Comparative effectiveness of calcium channel blocker classes (dihydropyridines, or DHPs, versus non- dihydropyridines, or non-DHPs) has not been examined in a large retrospective cohort of maintenance dialysis patients.
- New initiators of DHPs and of non-DHPs were compared for the outcomes of all-cause mortality (ACM) and a combined endpoint of cardiovascular morbidity and mortality (CVMM).
- Adjusted for other factors, use of DHPs, compared to non-DHPs, was associated with an adjusted hazard ratio of 0.77 ($P = 0.0004$) for ACM and 0.86 ($P = 0.024$) for CVMM.
- Results of sensitivity analyses, which included individuals who initiated therapy at any point after the cohort inception and which further eliminated individuals with chronic atrial fibrillation, were similar.
- DHPs may therefore confer a survival advantage in dialysis patients prescribed CCBs.

*Total individuals included differed in the models due to specific aspects of the study design. Thus some individuals could be in one model and not the other. For example, a person could be in the ACM model but not the CVMM model if they started a CCB prescription after a cardiovascular event; in distinction, a person could be in the CVMM model but not the ACM model if they switched CCB classes between a cardiovascular event and death (thus causing elimination from the ACM model).

Abbreviations: Rx, prescription; CMS, Centers for Medicare and Medicaid Services; CCB, calcium channel blockers; ACM, all-cause mortality; CVMM, cardiovascular morbidity and mortality

Figure 1.
Flowchart demonstrating creation of the study cohort.

A. **No. of participants at risk over time**

DHP	2900	1372	637	215	28
Non-DHP	568	242	113	26	5

Solid line, dihydropyridine (DHP); broken line, non-dihydropyridines (Non-DHP)

B. **No. of participants at risk over time**

DHP	2704	882	324	96	10
Non-DHP	527	149	51	12	1

Solid line, dihydropyridine (DHP); broken line, non-dihydropyridines (Non-DHP)

Figure 2.

Kaplan-Meier survival curves of new users of calcium channel blockers.

(A) All-cause mortality model

(B) Cardiovascular morbidity and mortality model

Descriptive characteristics of new users of calcium channel blockers among hypertensive dialysis patients, by modeled cohort.

Table 1

	All-cause mortality		Cardiovascular morbidity and mortality	
	Dihydropyridines	Non-dihydropyridines	Dihydropyridines	Non-dihydropyridines
Number of cases	2900	568	2704	527
Age, mean years $\pm$ SD	58.50 $\pm$ 15.5 *	62.5 $\pm$ 15.5 *	58.2 $\pm$ 15.5 *	61.9 $\pm$ 15.7 *
Females, <i>n</i> (%)	1667 (57.5)	341 (60.0)	1545 (57.1)	318 (60.3)
Race/Ethnicity, <i>n</i> (%) *				
African-American	1324 (45.7)	257 (45.3)	1238 (45.8)	245 (46.5)
Caucasian	806 (27.8)	193 (34.0)	750 (27.7)	174 (33.0)
Hispanic	600 (20.7)	76 (13.4)	554 (20.5)	70 (13.3)
Other	170 (5.9)	42 (7.4)	162 (6.0)	38 (7.2)
BMI category, <i>n</i> (%) *				
< 20 kg/m ²	295 (10.2)	65 (11.4)	271 (10.0)	61 (11.6)
20-24.9 kg/m ²	863 (30.0)	160 (28.2)	803 (29.7)	149 (28.3)
25-29.9 kg/m ²	784 (27.0)	157 (27.6)	736 (27.2)	140 (26.6)
30 kg/m ²	934 (32.2)	182 (32.0)	870 (32.2)	173 (32.8)
Missing	24 (0.8)	4 (0.7)	24 (0.9)	4 (0.8)
Smoker, <i>n</i> (%)	188 (6.5)	37 (6.5)	171 (6.3)	34 (6.5)
Substance abuser, <i>n</i> (%)	100 (3.5)	13 (2.3)	96 (3.6)	13 (2.5)
Unemployed, <i>n</i> (%)	2808 (96.8)	557 (98.1)	2616 (96.8)	516 (97.9)
Unable to ambulate, <i>n</i> (%)	131 (4.5)	34 (6.0)	126 (4.7)	30 (5.7)
Unable to transfer, <i>n</i> (%)	50 (1.7)	13 (2.3)	48 (1.8)	11 (2.1)
Cause of ESRD, <i>n</i> (%)				
Diabetes	1552 (52.1)	306 (53.9)	1399 (51.7)	282 (53.5)
Hypertension	873 (30.1)	165 (29.1)	822 (30.4)	152 (28.8)
Glomerulonephritis	240 (8.3)	38 (6.7)	230 (8.5)	38 (7.2)
Other	275 (9.5)	59 (10.4)	253 (9.4)	55 (10.4)
Comorbidities, <i>n</i> (%)				
Diabetes	1813 (62.5)	357 (62.9)	1679 (62.1)	328 (62.2)

	All-cause mortality		Cardiovascular morbidity and mortality	
	Dihydropyridines	Non-dihydropyridines	Dihydropyridines	Non-dihydropyridines
Coronary artery disease	645 (22.2)	121 (21.3)	580 (21.5)	109 (20.7)
Congestive heart failure	962 (33.2)	192 (33.8)	884 (32.7)	172 (32.6)
Cerebrovascular disease	312 (10.8)	70 (12.3)	279 (10.3)	63 (12.0)
Peripheral vascular disease	395 (13.6)	85 (15.0)	361 (13.4)	73 (13.9)
In-center hemodialysis	2774 (95.7)	543 (95.6)	2582 (95.5)	502 (95.3)
Hemoglobin				
< 11 g/dL	2036 (70.2)	396 (69.7)	1904 (70.4)	366 (69.5)
11 g/dL	628 (21.7)	125 (22.0)	581 (21.5)	119 (22.6)
missing	236 (8.1)	47 (8.3)	219 (8.1)	42 (8.0)
PDC, mean $\pm$ SD	0.52 $\pm$ 0.27	0.50 $\pm$ 0.30	0.52 $\pm$ 0.27	0.51 $\pm$ 0.29
Yrs of followup, mean $\pm$ SD	1.73 $\pm$ 1.41 [*]	1.50 $\pm$ 1.37 [*]	1.74 $\pm$ 1.42	1.64 $\pm$ 1.39
Dialysis duration ^J , yrs	0.09 $\pm$ 0.07	0.10 $\pm$ 0.07	0.09 $\pm$ 0.07	0.09 $\pm$ 0.07
Comorbidity Index	6.1 $\pm$ 3.7 [*]	7.0 $\pm$ 4.0 [*]	5.9 $\pm$ 3.6 [*]	6.8 $\pm$ 3.9 [*]

Abbreviations: SD, standard deviation; BMI, body mass index; ESRD, end stage renal disease; PDC, proportion of days covered; CVM, cardiovascular morbidity and mortality.

^{*} $P < 0.01$

^J At time of initial calcium channel blocker prescription

Adjusted hazard ratios of use of calcium channel blockers on the outcomes of all-cause mortality and cardiovascular morbidity and mortality, adjusted for other factors.

Table 2

	Cardiovascular morbidity and mortality		Cardiovascular morbidity and mortality	
	AHR (99% CIs)	P-value	AHR (99% CIs)	P-value
DHPs (vs non-DHPs)	0.77 (0.64 – 0.93)	0.0004	0.86 (0.72 – 1.02)	0.024
Age, per decade	1.29 (1.21 – 1.38)	< 0.0001	1.03 (0.98 – 1.09)	0.11
Female sex	0.96 (0.81 – 1.13)	0.51	1.08 (0.94 – 1.25)	0.15
Race/Ethnicity, <i>n</i> (%)				
African-American	–	–	–	–
Caucasian	1.24 (1.03 – 1.49)	0.0025	1.10 (0.93 – 1.29)	0.15
Hispanic	0.91 (0.74 – 1.13)	0.28	0.90 (0.75 – 1.08)	0.13
Other	0.72 (0.51 – 1.01)	0.013	0.96 (0.72 – 1.28)	0.72
BMI category, <i>n</i> (%)				
< 20 kg/m ²	1.56 (1.22 – 1.99)	< 0.0001	1.04 (0.82 – 1.33)	0.65
20–24.9 kg/m ²	–	–	–	–
25–29.9 kg/m ²	0.95 (0.77 – 1.16)	0.49	1.02 (0.86 – 1.22)	0.74
30 kg/m ²	0.71 (0.58 – 0.88)	< 0.0001	0.85 (0.71 – 1.01)	0.018
Missing	0.60 (0.24 – 1.52)	0.16	1.11 (0.58 – 2.10)	0.68
Smoking	1.03 (0.73 – 1.46)	0.81	0.96 (0.71 – 1.30)	0.72
Substance abuse	0.91 (0.53 – 1.55)	0.63	0.80 (0.52 – 1.23)	0.18
Unemployed	1.46 (0.69 – 3.11)	0.20	0.95 (0.61 – 1.47)	0.75
Unable to ambulate	1.26 (0.86 – 1.83)	0.12	1.01 (0.69 – 1.46)	0.96
Unable to transfer	1.69 (1.00 – 2.85)	0.010	1.45 (0.82 – 2.57)	0.092
Comorbidities				
Diabetes	0.98 (0.81 – 1.18)	0.79	1.06 (0.90 – 1.25)	0.37
Coronary artery disease	1.06 (0.88 – 1.28)	0.42	1.11 (0.94 – 1.32)	0.11
Congestive heart failure	0.93 (0.78 – 1.12)	0.31	1.06 (0.90 – 1.25)	0.37
Cerebrovascular disease	0.94 (0.75 – 1.18)	0.48	0.87 (0.69 – 1.08)	0.096
Peripheral vascular disease	0.87 (0.70 – 1.09)	0.11	0.91 (0.74 – 1.12)	0.26
Liu comorbidity index	1.09 (1.06 – 1.12)	< 0.0001	1.09 (1.05 – 1.11)	< 0.0001

	Cardiovascular morbidity and mortality		Cardiovascular morbidity and mortality	
	AHR (99% CIs)	P-value	AHR (99% CIs)	P-value
Self-care dialysis	1.22 (0.81 – 1.86)	0.22	0.97 (0.69 – 1.37)	0.82
Dialysis duration [†] , yrs	1.71 (0.57 – 5.11)	0.21	0.78 (0.29 – 2.04)	0.50
Hemoglobin				
< 11 g/dL	–	–	–	–
11 g/dL	1.05 (0.87 – 1.27)	0.49	1.05 (0.89 – 1.24)	0.47
Missing	1.04 (0.80 – 1.37)	0.69	0.87 (0.68 – 1.12)	0.16

AHR, adjusted hazards ratio; CI, confidence interval; DHP, dihydropyridine; BMI, body mass index

[†] At time of initial calcium channel blocker prescription