Kidney International, Vol. 61 (2002), pp. 2157–2164

Calcium channel blocker use and mortality among patients with end-stage renal disease

BRYAN KESTENBAUM, DANIEL L. GILLEN, DONALD J. SHERRARD, STEVEN SELIGER, ADRIANNE BALL, and CATHERINE STEHMAN-BREEN

Division of Nephrology, School of Public Health and Community Medicine, and Department of Biostatistics, University of Washington; and Division of Nephrology, Puget Sound Health Care System, Seattle, Washington, USA

Calcium channel blocker use and mortality among patients with end-stage renal disease.

Background. Patients on dialysis suffer from alarming rates of cardiovascular disease. While calcium channel blockers (CCBs) are prescribed widely to patients with end-stage renal disease (ESRD) for the treatment of hypertension, the long-term outcomes associated with the use of these medications are not known. We sought to determine the association between CCB use and mortality among a cohort of ESRD patients.

Methods. Data were utilized from the United States Renal Data System Dialysis Morbidity and Mortality Wave II, a randomly selected prospective cohort of 4065 ESRD patients who began dialysis in 1996. Clinical data, including medication information, were collected 60 days after the start of dialysis. Subsequent survival status and cause of death were ascertained. The Cox proportional hazards model was used to estimate the relative risk of death associated with CCB use.

Results. Data from 3716 patients (91.4%) were available for analysis. Fifty-one percent of the study patients were prescribed a CCB. The use of a CCB was associated with a 21% lower risk of total mortality (RR 0.79, CI 0.69 to 0.90) and a 26% lower risk of cardiovascular specific mortality (RR 0.74, CI 0.60 to 0.91). For patients with pre-existing cardiovascular disease, CCB use was associated with a 23% (RR 0.77, CI 0.65 to 0.91) and 32% (RR 0.68, CI 0.53 to 0.87) lower risk of total and cardiovascular mortality, respectively.

Conclusion. After controlling for known risk factors and potential confounders, CCBs were found to be associated with a lower risk of mortality among ESRD patients.

The risk of cardiovascular disease among patients with end-stage renal disease (ESRD) is 10 times higher than the general population [1]. While cardiovascular disease remains the leading cause of death and disability for patients with renal failure, few studies have investigated whether cardiac medications can improve clinical outcomes for dialysis patients.

Among the general population, studies examining calcium channel blocker (CCB) use have reached mixed conclusions with regard to their effects on patient outcome [2–8]. Short acting dihydropyridines have been associated with an increased risk of myocardial infarction, while longer acting CCBs hold mortality risks similar to other antihypertensive medications. Although calcium channel blockers are prescribed widely to patients with ESRD, principally for the treatment of hypertension, the impact of CCB use on survival has never been evaluated in this population. CCBs may have different effects in ESRD patients. Chronic renal failure (CRF) generates a unique biochemical milieu characterized by derangements in calcium metabolism. In the setting of renal failure, calcium channel blockers reverse pathologic levels of intracellular calcium that may contribute to the development of accelerated cardiovascular disease [9–11]. Therefore, generalization of results from non-uremic patients to those with renal failure should be done with caution.

Based on the experimental benefit of CCBs in uremia, we hypothesized that these medications would be beneficial to patients with renal failure. We conducted a cohort study using data from the United States Renal Database System Dialysis Morbidity and Mortality Study Wave II (USRDS DMMS II) to estimate the risk of death associated with CCB use among ESRD patients.

METHODS

Patient population

Details of the USRDS DMMS II are described in detail elsewhere [12]. Briefly, the USRDS collects demographic and clinical data on all patients who have survived more than 90 days on dialysis. DMMS II was a prospective study containing a random sample of 4065 incident hemodialysis (HD) and peritoneal dialysis (PD)

Key words: calcium channel blocker, dialysis, mortality, cardiovascular disease, hypertension, dihydropyridines, USRDS DMMS II.

Received for publication May 24, 2001
and in revised form January 10, 2002
Accepted for publication January 11, 2002

patients initiating dialysis in 1996 and early 1997 from 25% of United States dialysis facilities ($N = 799$). To obtain comparable numbers of PD and HD patients for the study, PD patients were over sampled. All incident PD patients were included whereas only 20% of all HD patients were selected. Patients were excluded from DMMS II if they were younger than 18 years, home dialysis patients, or previously transplanted. For the purposes of this analysis, all subjects who participated in DMMS II were included.

Data collection

Dialysis center personnel collected baseline and follow-up patient data using medical records from dialysis centers, hospitalizations, and personal physicians, and by directly interviewing patients. Dialysis modality was determined on day 60 of ESRD. Baseline data were collected 60 days after the start of dialysis. Variables used for the purpose of this analysis were patient gender, age, race (black, white, and other), smoking status (never, former, or current smoker), treatment modality (hemodialysis, peritoneal dialysis, transplant), medications, serum albumin, pre-dialysis blood pressure (systolic and diastolic), history of diabetes (yes, no), clinical determination of malnourishment (yes, no), and history of the following specific medical conditions: coronary artery disease, myocardial infarction, coronary angioplasty, coronary artery bypass surgery, cardiac arrest, and stroke. These clinical conditions, including cardiac history, were determined by dialysis personnel through review of notation in the patients' medical charts and through interviews with the patients themselves. A maximum of 15 medications per patient were recorded. We determined if CCBs, angiotensin-converting enzyme (ACE) inhibitors, β blockers and aspirin had been prescribed by comparing patients' recorded medications to a list of known generic and brand names. CCBs were classified into four groups: group 1, short acting nifedipine; group 2, long acting dihydropyridines; group 3, diltiazem; and group 4, verapamil. Changes in treatment modality during follow-up were obtained from the Treatment History File, which is maintained by the USRDS.

Ascertainment of outcome

Survival status and cause of death were linked to the Wave 2 data from the USRDS Patients Standard Analysis File (SAF) via unique patient identifiers assigned by the USRDS. Patient survival status is periodically updated in the SAF and at the time of analysis was complete through July 1998. The date and cause of death listed in the SAF were obtained by the USRDS from HCFA form #2746, which is completed by the primary nephrologist following the death of any dialysis patient. For the purposes of this analysis, death from cardiovascular disease was defined a priori as death from myocardial infarction, atherosclerotic heart disease, cardiomyopathy, cerebrovascular accident, cardiac arrhythmia and cardiac arrest of unknown cause.

Statistical analysis

The association between baseline CCB use and time to death was analyzed using the Cox proportional hazards model for censored failure times. In this model, the hazard or the instantaneous probability of death, was modeled as a function of the predictor covariates. The relative risk (RR) or hazard ratio was then estimated for each covariate as the proportionate change in the instantaneous probability of death for two individuals differing only by a single unit of that covariate. A relative risk less than one suggests that a one-unit increase in a covariate is associated with a longer time to death. Alternatively, a relative risk greater than one suggests a shorter time to death. Variables used in the multivariate model were chosen a priori and retained in the model if there was biological plausibility or if exploratory analyses suggested that the covariate of interest may be associated with death or may confound the relationship between CCB use and death. Variables used for adjustment in the models included age, sex, race, treatment modality, diabetes, pre-existing cardiovascular disease, undernourishment, serum albumin, pre-dialysis systolic and diastolic blood pressure, and the use of an ACE inhibitor, β blocker, and aspirin. Formal tests as well as graphical methods were used to verify the existence of proportional hazards. Further, residual diagnostics were used to identify outlying points and to model the correct functional form of adjustment variables. Estimated RR along with corresponding 95% confidence intervals and P values for two-sided tests of association are reported for all regression covariates.

To improve generalization of our results, patients were not censored at the time of transplant. Since transplant patients are generally healthier, censoring patients at the time of transplant would have made our results applicable only to less healthy ESRD patients. Because the dialysis modality administered to a patient can change over time, treatment modality was entered into all analyses as a time dependent covariate. The use of the time-dependent covariate allowed patients to continue to contribute time at risk for a given modality for the amount of time they underwent that particular modality.

RESULTS

A total of 4065 patients were included in DMMS II. Of these, 349 patients were excluded from our analysis because they did not receive a valid USRDS patient identifier, making follow-up impossible. Therefore, 3716 patients were available for analysis. There were no notable differences in clinical characteristics between patients included and excluded from the study.

Table 1. Patient characteristics at the time of data collection

Characteristic	No calcium channel blocker use (N = 1814)	Calcium channel blocker use (N = 1902)
Age *years*	59.9 (15.7)	58.2 (15.8)
Female sex	857 (47.2%)	890 (46.8%)
Race		
White	1211 (67.5%)	1147 (60.8%)
Black	450 (25.1%)	567 (30.0%)
Other	134 (7.5%)	173 (9.2%)
Smoking status		
Never	960 (57.7%)	991 (55.5%)
Former	509 (28.5%)	510 (30.5%)
Current	196 (11.8%)	286 (16.0%)
History of cardiovascular disease[a]	795 (49.4%)	833 (48.3%)
Undernourished	376 (21.6%)	326 (17.7%)
History of diabetes	874 (49.1%)	951 (50.9%)
Mean serum albumin *mg/dL*	3.42 (0.58)	3.50 (0.58)
Mean serum cholesterol	188.6 (54.7)	198.4 (56.7)
Mean serum triglycerides	190.5 (145.3)	206.5 (142.1)
Mean pre-dialysis diastolic BP *mm Hg*	78.5 (11.9)	81.8 (11.9)
Mean pre-dialysis systolic BP *mm Hg*	141.7 (21.1)	150.9 (19.0)
Aspirin use (yes vs. no)	247 (13.6%)	317 (16.7%)
ACE inhibitor use (yes vs. no)	413 (22.8%)	446 (23.4%)
β blocker use (yes vs. no)	289 (15.9%)	372 (19.6%)

Data are mean (SD) or N (%)

[a] Defined as a prior diagnosis of coronary heart disease, coronary artery disease, myocardial infarction, coronary artery bypass surgery, angioplasty, cardiac arrest, cerebrovascular accident, or congestive heart failure

Table 2. Prevalence of calcium channel blocker use (N = 3716)

Calcium channel blocker class	*N (%)*
Any calcium channel blocker	1902 (51.2%)
Class I	351 (9.5%)
Nifedipine (Procardia)	351 (9.5%)
Class II	1162 (31.3%)
Nifedipine (Procardia, Adalat) XL, CC, or GITS	449 (12.1%)
Amlodipine (Norvasc)	637 (17.1%)
Felodipine (Plendil)	40 (1.1%)
Isradipine (Dynacirc)	35 (0.9%)
Nicardipine (Cardene)	10 (0.3%)
Nisoldipine	0 (0%)
Lacidipine	0 (0%)
Class III	363 (9.8%)
Diltiazem (Cardizem, Dilacor)	363 (9.8%)
Class IV	76 (2.0%)
Verapamil (Isoptin)	76 (2.0%)
Combination of 2 classes	50 (1.4%)

The baseline characteristics of the study patients are shown in Table 1. Fifty-one percent of our cohort reported taking a CCB 60 days after the start of dialysis. There were no important differences in baseline clinical characteristics between patients who reported using a CCB, and those who did not.

Table 2 describes the proportion of patients using CCBs stratified by CCB group. The majority of subjects prescribed CCBs were receiving long acting dihydropyridines, particularly amlodipine and long acting nifedipine. Diltiazem was prescribed to approximately 10% of the cohort, while verapamil was rarely used. A few patients (1.4%) reported using a combination of two CCBs. The most frequent combinations reported were a dihydropyridine plus diltiazem, followed by a dihydropyridine plus short acting nifedipine.

There were 1232 total deaths during the follow-up period. Table 3 presents adjusted and unadjusted relative risks of total mortality associated with the covariates of interest. Among CCB users, the total mortality rate was 169.8 deaths/1000 person-years compared to 225.6 deaths/1000 person-years among non-users. The use of a beta-blocker, aspirin, or an ACE inhibitor was not associated with a difference in the adjusted risk of death from all causes, while the use of a CCB was significantly associated with a lower risk of total mortality. For patients reporting the use of any CCB, the adjusted relative risk for total mortality was 0.79 (CI 0.69 to 0.90) when compared to patients that did not report CCB use, while for patients reporting diltiazem use the adjusted relative risk was estimated to be 0.63 (CI 0.49 to 0.81). Of the clinical characteristics we studied, advancing age, low serum albumin, diabetes, pre-existing cardiac disease, and Caucasian race were all significantly associated with higher risks of total mortality. Blood pressure had a U-shaped relationship with mortality; pre-dialysis systolic pressures less than 130 and greater than 160 were associated with a higher risk of death. Similarly, pre-dialysis diastolic pressures less than 60 and greater than 90 were associated with a higher risk of mortality. We tested several interaction terms, including an interaction between CCB use and treatment modality, and an interaction between CCB use and race. These interaction terms were found not to be statistically significant.

Table 4 lists the adjusted and unadjusted relative risks for cardiovascular specific mortality associated with the identified baseline characteristics. There were 72.45 cardiovascular related deaths/1000 person-years among CCB users as compared to 107.75 CV related deaths/1000 person-years among non-users. After adjustment, the use of a β blocker, ACE inhibitor, or aspirin was not associated with a difference in cardiovascular specific mortality. In contrast, many of the calcium channel blockers were associated with a significantly lower risk of cardiovascular death. For example, the use of any calcium channel blocker was associated with a 26% lower risk of cardiovascular specific death (aRR 0.74, CI 0.60 to 0.91). Similarly, the use of the non-dihydropyridine, diltiazem was associated with 38% lower risk of cardiovascular mortality (aRR 0.62, CI 0.42 to 0.90). We did not observe a higher risk of CV mortality associated with the prescription of short acting nifedipine. Pre-existing cardiovascular disease, low serum albumin, undernourishment, and diabetes were associated with higher risks of cardiovascular specific death.

Table 5 illustrates the results of our analysis after stratifying by previous history of cardiovascular disease. For

Table 3. Cox regression results for all-cause mortality

Covariate	Deaths ($N = 1232$)	Unadjusted RR (95% CI)	P value	Adjusted RR (95% CI)	P value
Age *per decade*	1225	1.48 (1.42, 1.55)	<0.001	1.30 (1.23, 1.38)	<0.001
Female sex	601	1.09 (0.97, 1.21)	0.147	1.12 (0.98, 1.29)	0.104
Race					
White	897	1.0		1.0	
Black	267	0.62 (0.54, 0.71)	<0.001	0.74 (0.63, 0.88)	<0.001
Other	63	0.48 (0.37, 0.62)	<0.001	0.58 (0.43, 0.78)	<0.001
Modality					
HD	720	1.0		1.0	
PD	468	0.96 (0.86, 1.08)	0.550	1.07 (0.92, 1.23)	0.374
Transplant	15	0.17 (0.10, 0.28)	<0.001	0.29 (0.15, 0.57)	<0.001
Smoking Status					
Never	608	1.0		1.0	
Former	387	1.28 (1.13, 1.46)	<0.001	0.99 (0.85, 1.16)	0.928
Current	142	0.96 (0.80, 1.15)	0.652	1.22 (0.99, 1.51)	0.063
History of CVD[a]	750	2.79 (2.45, 3.17)	<0.001	1.66 (1.42, 1.94)	<0.001
Undernourished (yes vs. no)	360	2.19 (1.93, 2.48)	<0.001	1.43 (1.23, 1.67)	<0.001
History of diabetes	712	1.52 (1.36, 1.70)	<0.001	1.31 (1.14, 1.52)	<0.001
Albumin *1 g/dL decrease*	1126	1.82 (1.67, 2.00)	<0.001	1.43 (1.26, 1.62)	<0.001
Diastolic BP *mm Hg*					
60 to 90	946	1.0		1.0	
Less than 60	132	2.67 (2.23, 3.21)	<0.001	1.36 (1.07, 1.74)	0.013
Greater than 90	123	0.55 (0.45, 0.66)	<0.001	0.98 (0.77, 1.24)	0.842
Systolic BP *mm Hg*					
130 to 160	564	1.0		1.0	
Less than 130	349	1.86 (1.63, 2.13)	<0.001	1.53 (1.28, 1.82)	<0.001
Greater than 160	288	1.11 (0.96, 1.28)	0.154	1.13 (0.95, 1.33)	0.168
Aspirin (yes vs. no)	234	1.41 (1.22, 1.62)	<0.001	0.95 (0.79, 1.13)	0.544
ACE inhibitors (yes vs. no)	270	0.94 (0.82, 1.08)	0.365	0.96 (0.82, 1.13)	0.637
β Blockers (yes vs. no)	207	0.94 (0.81, 1.09)	0.419	1.03 (0.87, 1.22)	0.749
CCB use (yes vs. no)	561	0.74 (0.67, 0.83)	<0.001	0.79 (0.69, 0.90)	0.001
No reported use	672	1.0		1.0	
Class I	92	0.70 (0.56, 0.87)	0.001	0.73 (0.56, 0.96)	0.022
Class II	340	0.77 (0.68, 0.88)	<0.001	0.89 (0.76, 1.04)	0.157
Class III	95	0.71 (0.57, 0.88)	0.002	0.63 (0.49, 0.81)	<0.001
Class IV	19	0.72 (0.46, 1.14)	0.163	0.48 (0.24, 0.97)	0.040
Combination of 2	15	0.77 (0.46, 1.29)	0.327	0.65 (0.36, 1.19)	0.165

[a] Defined as prior Dx of CHD/CAD, MI, bypass, angioplasty, cardiac arrest, cerebrovascular accident or congestive heart failure

patients without a prior history of cardiovascular disease, the use of a CCB was not associated with a significant change in the risk of total or cardiovascular related death. In contrast, a lower risk of mortality was found among patients with pre-existing CVD who reported using a calcium channel blocker. After adjustment, the use of any CCB was associated with a 32% lower risk of death from cardiovascular disease (aRR 0.68, CI 0.53 to 0.87) and a 23% lower risk of death from all causes (aRR 0.77, CI 0.65 to 0.91). The lowest associated risk was observed for the more cardiac selective calcium channel blockers, diltiazem, and verapamil. For patients with a prior history of cardiovascular disease, diltiazem was associated with a 48% lower risk of cardiovascular specific death (aRR 0.52, CI 0.33 to 0.82) and 38% lower risk of death from all causes (aRR 0.62, CI 0.46 to 0.84).

DISCUSSION

Greater than half of the ESRD patients under study reported taking a calcium channel blocker. The use of any CCB was associated with a 21% lower risk of all-cause mortality and a 26% lower risk of cardiovascular specific mortality. After stratifying by history of cardiovascular disease, no association was found between CCB use and mortality for patients without a previous history of CVD. In contrast, CCB use was associated with a 32% lower risk of cardiovascular mortality for patients who reported a prior history of CVD.

There was a lower risk of total and cardiovascular mortality associated with CCB use. While our study design is observational, these results are consistent with those from randomized trials among the general population comparing CCBs to placebo for the treatment of hypertension [5, 7]. For example, nitrendipine was found to reduce total mortality by 55% versus placebo when prescribed to 492 elderly, hypertensive diabetic patients [7]. When felodipine was used as primary therapy to treat 18,790 hypertensive patients in the Hypertension-Optimal-Therapy trial, a trend toward decreased cardiovascular mortality was observed as blood pressures were lowered [5]. We found a lower relative risk of mortality associated with CCB use among our cohort than generally reported among patients without renal failure. It is

Table 4. Cox regression results for CV/stroke-related mortality

Covariate	Deaths ($N = 560$)	Unadjusted RR *95% CI*	*P* value	Adjusted RR *95% CI*	*P* value
Age *per decade*	555	1.56 (1.47, 1.67)	<0.001	1.35 (1.23, 1.47)	<0.001
Female sex	256	0.96 (0.81, 1.14)	0.650	1.03 (0.84, 1.27)	0.756
Race					
White	409	1.0		1.0	
Black	117	0.60 (0.49, 0.74)	<0.001	0.78 (0.61, 1.01)	0.055
Other	31	0.52 (0.36, 0.75)	<0.001	0.59 (0.38, 0.92)	0.021
Modality					
HD	321	1.0		1.0	
PD	229	1.03 (0.87, 1.22)	0.745	1.24 (1.00, 1.53)	0.047
Transplant	3	0.09 (0.03, 0.27)	<0.001	0.11 (0.02, 0.74)	0.023
Smoking Status					
Never	279	1.0		1.0	
Former	185	1.33 (1.10, 1.60)	0.003	0.97 (0.78, 1.21)	0.791
Current	51	0.73 (0.54, 0.98)	0.035	0.93 (0.65, 1.32)	0.682
History of CVD[a]	295	3.54 (2.89, 4.33)	<0.001	1.89 (1.49, 2.41)	<0.001
Undernourished (yes vs. no)	146	1.87 (1.55, 2.26)	<0.001	1.20 (0.94, 1.52)	0.138
History of diabetes	342	1.73 (1.46, 2.06)	<0.001	1.59 (1.28, 1.97)	<0.001
Albumin *1 g/dL decrease*	515	1.64 (1.43, 1.89)	<0.001	1.22 (1.00, 1.48)	0.046
Diastolic BP *mm Hg*					
60 to 90	433	1.0		1.0	
Less than 60	69	2.96 (2.29, 3.81)	<0.001	1.64 (1.17, 2.31)	0.004
Greater than 90	45	0.44 (0.33, 0.60)	<0.001	0.83 (0.56, 1.22)	0.335
Systolic BP *mm Hg*					
130 to 160	245	1.0		1.0	
Less than 130	165	2.00 (1.64, 2.44)	<0.001	1.58 (1.21, 2.06)	0.001
Greater than 160	137	1.22 (0.99, 1.50)	0.064	1.32 (1.03, 1.69)	0.030
Aspirin (yes vs. no)	125	1.71 (1.40, 2.08)	<0.001	1.13 (0.88, 1.44)	0.342
ACE inhibitors (yes vs. no)	121	0.92 (0.75, 1.13)	0.431	0.90 (0.71, 1.14)	0.391
Beta-blockers (yes vs. no)	97	0.97 (0.78, 1.21)	0.804	1.02 (0.79, 1.31)	0.876
CCB use (yes vs. no)	239	0.67 (0.57, 0.79)	<0.001	0.74 (0.60, 0.91)	0.004
No reported use	321	1.0		1.0	
Class I	39	0.63 (0.45, 0.87)	0.006	0.75 (0.51, 1.11)	0.155
Class II	143	0.68 (0.56, 0.83)	<0.001	0.80 (0.63, 1.02)	0.07
Class III	45	0.71 (0.52, 0.97)	0.029	0.62 (0.42, 0.90)	0.013
Class IV	5	0.40 (0.17, 0.97)	0.042	0.27 (0.07, 1.07)	0.063
Combination of 2	7	0.77 (0.36, 1.62)	0.486	0.82 (0.36, 1.85)	0.628

[a] Defined as prior Dx of CHD/CAD, MI, bypass, angioplasty, cardiac arrest, cerebrovascular accident, or congestive heart failure

Table 5. Cox regression results stratified by history of CVD

Covariate	No prior history aRR[a] (*95% CI*)	*P* value	Prior history aRR[a] (*95% CI*)	*P* value
CV-related mortality				
CCB use (yes vs. no)	0.86 (0.58, 1.27)	0.434	0.68 (0.53, 0.87)	0.002
No reported use	1.0		1.0	
Class I	1.04 (0.53, 2.05)	0.901	0.65 (0.40, 1.06)	0.085
Class II	0.79 (0.50, 1.25)	0.316	0.78 (0.59, 1.03)	0.078
Class III	0.98 (0.49, 1.93)	0.944	0.52 (0.33, 0.82)	0.005
Class IV	0.44 (0.06, 3.19)	0.413	0.19 (0.03, 1.38)	0.101
Combination of 2	1.06 (0.14, 7.81)	0.953	0.68 (0.28, 1.67)	0.397
All-cause mortality				
CCB use (yes vs. no)	0.79 (0.62, 1.01)	0.062	0.77 (0.65, 0.91)	0.002
No reported use	1.0		1.0	
Class I	0.96 (0.63, 1.47)	0.856	0.64 (0.45, 0.90)	0.011
Class II	0.81 (0.61, 1.07)	0.137	0.90 (0.75, 1.09)	0.299
Class III	0.65 (0.39, 1.06)	0.082	0.62 (0.46, 0.84)	0.002
Class IV	0.68 (0.25, 1.86)	0.451	0.37 (0.14, 1.00)	0.050
Combination of 2	0.60 (0.15, 2.46)	0.480	0.62 (0.32, 1.21)	0.161

[a] Adjusted for age, sex, race, treatment modality, smoking status, history of CVD, undernourished, albumin, diastolic BP, systolic BP, aspirin use, ACE inhibitor use and beta blocker use

possible that the actions of CCBs, such as reduction in blood pressure, attenuation of left ventricular hypertrophy (LVH), and restoration of intracellular calcium are of particular benefit to patients with ESRD.

In contrast to some reports, which have suggested that CCBs increase the risk of myocardial infarction and death among selected patient groups when compared to other antihypertensive agents [3, 6, 8], there was no

association between the use of a CCB and a greater risk of mortality among ESRD patients. Recently published randomized trials, such as the International Nifedipine GITS Study and the Nordic Diltiazem Study, have found similar mortality rates among users of CCBs, β blockers and diuretics [2, 4]. The more gradual reduction in blood pressure produced by newer, long acting forms of calcium channel blockers may account for their enhanced safety.

We found a particularly strong association between CCB use and lower mortality among patients with prior cardiovascular disease (CVD). Studies from the general population have reached differing conclusions regarding CCB therapy among patients who have suffered acute MI [8, 13–17]. The Multi-Center Diltiazem Post Infarction Trial (MDPIT) found no difference in survival for 2466 patients assigned diltiazem or placebo following MI [13]. However, subsets of MDPIT subjects, such as those without pulmonary congestion at presentation and those with hypertension, experienced a reduction in cardiac death or re-infarction with diltiazem use [18]. The Danish Verapamil Infarction Trial II (DAVIT II), examining verapamil therapy following acute MI, found a non-significant 20% reduction in death or re-infarction for patients randomized to verapamil versus placebo [14]. When similar patients from MDPIT and DAVIT II, with non-Q wave MI and without pulmonary congestion, were combined, the relative risk of mortality for users of diltiazem and verapamil was 0.65 (CI 0.40 to 1.05) [15], similar to our estimates among ESRD patients. There were no statistically significant associations between CCB use and mortality among patients without prior CVD in our cohort. It is possible that CCBs are of particular benefit for ESRD patients with CVD. Alternatively, we may have lacked the statistical power to detect significant associations among patients without prior CVD because these patients experienced fewer events, though the estimated relative risks associated with CCB use suggests the former.

No significant interaction was found between CCB use, race, and mortality, implying that the lower risk of death associated with CCB use was similar among white and African American patients under this study. Among African American patients with hypertension and renal insufficiency participating in the African American Study of Kidney Disease and Hypertension (AASK) trial, the risk of death was not statistically different among subjects treated with CCBs as compared to ACE inhibitors [19]. However, the population studied and end points used for the AASK trial were different from the present study, limiting direct comparisons.

While most studies have found long acting CCBs to be safe for the treatment of hypertension, short acting nifedipine was reported to increase the risk of MI for patients with hypertension, as well as for patients with a recent MI [3, 20]. In contrast, our results show a lower mortality for ESRD patients who reported taking short acting nifedipine. It is possible that the results of previous studies do not apply directly to our cohort, either because of differences in design or because of differences in the response of ESRD patients to this medication. Additionally, it is possible that complete medication names, such as XL, GITS, or CC were not accurately reported in the USRDS, resulting in misclassification and reducing our ability to detect changes in mortality associated with short acting nifedipine use.

Our data do not show an association between the use of ACE inhibitors, β blockers, or aspirin and the risk of mortality among ESRD patients. Patients with renal failure have unique physiologic characteristics, which may lead to unpredictable responses to traditional cardiac medications. For example, low renin levels found in many dialysis patients could attenuate the benefit from ACE inhibition and explain the lack of association observed between ACE inhibitor use and mortality among our cohort. Similarly, the significant platelet dysfunction induced by renal failure could be responsible for the lack of association detected between aspirin use and mortality. Finally, a blunted response to sympathetic stimulation might explain a lack of association between beta-blocker use and mortality among patients with renal failure. Further exploration of this complex issue is necessary to optimize antihypertensive therapy among patients with ESRD.

Calcium channel blockers possess a variety of potential therapeutic properties in dialysis patients. Traditional mechanisms by which CCBs are believed to act include relaxation of vascular smooth muscle, control of blood pressure, and attenuation of heart rate and contractility. These properties may be of special importance to dialysis patients, who have strikingly high rates of hypertension and LVH [21, 22]. For example, nifedipine suppresses surges in fibrinogen and von Willebrand factor that are produced by erythropoietin therapy [23]. In uremic animals with hypertension, CCBs increase stable nitric oxide (NOS) metabolites and enhance vascular NOS activity [24]. Among the general population, CCBs reduce the pathologic changes associated with LVH [25, 26]. In one study of chronic dialysis patients, diltiazem treatment improved the hemodynamics of LVH, as measured by echocardiography [27].

Alternatively, CCBs may be producing beneficial effects via their specific actions on intracellular calcium (iCa) in the setting of renal failure. Pathologic iCa levels in renal failure have been documented in a variety of cell types, including neutrophils, pancreatic islets, platelets, endothelial cells, and cardiac myocytes [10, 28–30]. Accompanying these changes in iCa are significant abnormalities in cell function, including an inability to respond to signals that use calcium as an intracellular messenger.

For example, in myocytes, a rise in intracellular calcium is associated with impaired response to IGF-1, and decreased protein synthesis [29]. The derangement of iCa produced by renal failure has been linked to elevated levels of circulating parathyroid hormone, and is normalized by parathyroidectomy, and by calcium channel blockers [11, 31]. CCBs prevent an increase of intracellular calcium by directly antagonizing PTH at the cellular level, blocking the influx of calcium stimulated by this hormone [28, 31–33]. It is possible that CCBs confer a survival advantage among patients with ESRD by restoring levels of iCa.

Our study has several limitations. First, since CCB use was assessed at a single point in time, we could not determine the length of CCB treatment prior to data collection or whether CCBs were in use at the time of death. However, if users and non-users of CCBs were equally likely to change medications without respect to their subsequent mortality status, then non-selective misclassification of CCB use would occur. This type of misclassification would dilute the association between CCB use and mortality leading to an underestimation of the true relative risk. Non-selective misclassification may have been a particular problem with aspirin use because patients may not have considered aspirin to be a prescription medication. The result would be an underestimation of the effect of aspirin use.

Although we controlled for many known factors that influence mortality in ESRD patients, it is quite plausible that other important factors were not measured. In order to bias our results, these factors would have to disproportionately affect the users or non-users of CCBs and be associated with mortality. It is possible that the indication for a CCB per se identifies patients with inherent characteristics that influence their long-term mortality (confounding by indication). For example, some dialysis patients may experience low blood pressure or poor general health, which could preclude them from being prescribed a CCB. If a higher proportion of these patients were to die compared to patients prescribed a CCB, we could falsely conclude that CCBs have protective effects. However, in this case it is more likely that the intention to prescribe a CCB identifies patients at a higher baseline risk of death, because the common indications to prescribe a CCB are hypertension and atrial fibrillation, which increase the risk of mortality. To further address this problem, we included estimations of the relative risks of death for other cardiovascular medications that would be prescribed for similar reasons as CCBs within our cohort. Furthermore, sensitivity analyses were performed and no significant change was found in our results after adjustment for markers of pre-ESRD care, such as erythropoietin use, the number of visits, and number of months in which patients saw their nephrologist prior to starting dialysis.

Finally, it is possible that there was misclassification of cause of death. A previous study by Perneger, Klag and Whelton suggested that there is a poor correlation between cause of death identified on the Death Notification Form and death certificates [34]. However, 40% of deaths among patients with ESRD were classified as due to "renal failure" on their death certificate. Since most ESRD patients do not die of renal failure per se, the results of Perneger's study suggests that the Death Notification Form may be more accurate than a death certificate. While our study has limitations, it is the first, to our knowledge, to assess outcomes associated with CCB use in the ESRD population. In addition, as a population based study, the results are not a reflection of physician- or region-specific characteristics and therefore can be generalized to the entire ESRD population.

In conclusion, the use of a calcium channel blocker is associated with lower total and cardiovascular specific mortality among a cohort of ESRD patients in the USRDS DMMS II. This finding is particularly notable for patients with a prior history of cardiovascular disease. Further investigations are needed to confirm these results and help guide optimal therapy for this patient population.

ACKNOWLEDGMENTS

This study was supported by a Department of Veterans Affairs Career Development Award and a PHS grant (DK07721-6) from the National Institutes of Health (Bethesda, MD, USA). The data reported here have been supplied by the USRDS. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the U.S. Government.

Reprint requests to Bryan Kestenbaum, M.D., Veterans Affairs Puget Sound Health Care System, 1660 South Columbian Way, Mailstop 111A, Seattle, Washington 98108, USA.
E-mail: epware@earthlink.net

REFERENCES

1. Foley RN, Parfrey PS, Sarnak MJ: Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 32 (Suppl):S112–S119, 1998
2. Brown MJ, Palmer CR, Castaigne A, *et al*: Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet* 356:366–372, 2000
3. Psaty BM, Heckbert SR, Koepsell TD, *et al*: The risk of myocardial infarction associated with antihypertensive drug therapies. *JAMA* 274:620–625, 1995
4. Hansson L, Hedner T, Lund-Johansen P, *et al*: Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: The Nordic Diltiazem (NORDIL) study. *Lancet* 356:359–365, 2000
5. Hansson L, Zanchetti A, Carruthers SG, *et al*: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: Principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 351: 1755–1762, 1998
6. Estacio RO, Jeffers BW, Hiatt WR, *et al*: The effect of nisoldipine

as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med* 338:645–652, 1998
7. Tuomilehto J, Rastenyte D, Birkenhager WH, *et al*: Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *N Engl J Med* 340:677–684, 1999
8. Borhani NO, Mercuri M, Borhani PA, *et al*: Final outcome results of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS). A randomized controlled trial. *JAMA* 276:785–791, 1996
9. Zhang YB, Smogorzewski M, Ni Z, *et al*: Altered cytosolic calcium homeostasis in rat cardiac myocytes in CRF. *Kidney Int* 45:1113–1119, 1994
10. Alexiewicz JM, Smogorzewski M, Akmal M, *et al*: Nifedipine reverses the abnormalities in $[Ca^{2+}]_i$ and proliferation of B cells from dialysis patients. *Kidney Int* 50:1249–1254, 1996
11. Horl WH, Haag-Weber M, Mai B, *et al*: Verapamil reverses abnormal $[Ca^{2+}]_i$ and carbohydrate metabolism of PMNL of dialysis patients. *Kidney Int* 47:1741–1745, 1995
12. System USRDS: *Researcher's Guide to the USRDS Database.* Bethesda, The National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1999
13. The Multicenter Diltiazem Postinfarction Trial Research Group: The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med* 319:385–392, 1988
14. Effect of verapamil on mortality and major events after acute myocardial infarction: The Danish Verapamil Infarction Trial II—DAVIT II. *Am J Cardiol* 66:779–785, 1990
15. Gibson RS, Hansen JF, Messerli F, *et al*: Long-term effects of diltiazem and verapamil on mortality and cardiac events in non-Q-wave acute myocardial infarction without pulmonary congestion: Post hoc subset analysis of the multicenter diltiazem postinfarction trial and the second Danish Verapamil Infarction Trial studies. *Am J Cardiol* 86:275–279, 2000
16. Jollis JG, Simpson RJ, Chowdhury MK, *et al*: Calcium channel blockers and mortality in elderly patients with myocardial infarction. *Arch Intern Med* 159:2341–2348, 1999
17. Reicher-Reiss H, Behar S, Boyko V, *et al*: Long-term mortality follow-up of hospital survivors of a myocardial infarction randomized to nifedipine in the SPRINT study. Secondary Prevention Reinfarction Israeli Nifedipine Trial. *Cardiovasc Drugs Ther* 12: 171–176, 1998
18. Moss AJ, Oakes D, Rubison M, *et al*: Effects of diltiazem on long-term outcome after acute myocardial infarction in patients with and without a history of systemic hypertension. The Multicenter Diltiazem Postinfarction Trial Research Group. *Am J Cardiol* 68: 429–433, 1991
19. Agodoa LY, Appel L, Bakris GL, *et al*: Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: A randomized controlled trial. *JAMA* 285:2719–2728, 2001
20. Goldbourt U, Behar S, Reicher-Reiss H, *et al*: Early administration of nifedipine in suspected acute myocardial infarction. The Secondary Prevention Reinfarction Israel Nifedipine Trial 2 Study. *Arch Intern Med* 153:345–353, 1993
21. Ha SK, Park HS, Kim SJ, *et al*: Prevalence and patterns of left ventricular hypertrophy in patients with predialysis chronic renal failure. *J Korean Med Sci* 13:488–494, 1998
22. Harnett JD, Parfrey PS, Griffiths SM, *et al*: Left ventricular hypertrophy in end-stage renal disease. *Nephron* 48:107–115, 1988
23. Ni Z, Wang XQ, Vaziri ND: Nitric oxide metabolism in erythropoietin-induced hypertension: Effect of calcium channel blockade. *Hypertens* 32:724–729, 1998
24. Vaziri ND, Ni Z, Wang XQ, *et al*: Downregulation of nitric oxide synthase in chronic renal insufficiency: Role of excess PTH. *Am J Physiol* 274:F642–F649, 1998
25. De Rosa ML, Giordano A, Della Guardia D, *et al*: Reversal of left ventricular hypertrophy following once daily administration of felodipine for two years to elderly subjects with isolated systolic hypertension. *Cardiology* 92:39–44, 1999
26. Schmieder RE, Martus P, Klingbeil A: Reversal of left ventricular hypertrophy in essential hypertension. A meta-analysis of randomized double-blind studies. *JAMA* 275:1507–1513, 1996
27. Cice G, Tagliamonte E, Ferrara L, *et al*: Efficacy of diltiazem in uremic hemodialyzed patients with isolated diastolic dysfunction and dialysis hypotensive crisis. *Cardiologia* 44:289–294, 1999
28. Thanakitcharu P, Fadda GZ, Hajjar SM, *et al*: Verapamil prevents the metabolic and functional derangements in pancreatic islets of chronic renal failure rats. *Endocrinology* 129:1749–1754, 1991
29. Qing DP, Ding H, Vadgama J, *et al*: Elevated myocardial cytosolic calcium impairs insulin-like growth factor-1-stimulated protein synthesis in chronic renal failure. *J Am Soc Nephrol* 10:84–92, 1999
30. Raine AE, Bedford L, Simpson AW, *et al*: Hyperparathyroidism, platelet intracellular free calcium and hypertension in chronic renal failure. *Kidney Int* 43:700–705, 1993
31. Smogorzewski M, Tian J, Massry SG: Down-regulation of PTH-PTHrP receptor of heart in CRF: Role of $[Ca^{2+}]_i$. *Kidney Int* 47: 1182–1186, 1995
32. Picotto G, Massheimer V, Boland R: Parathyroid hormone stimulates calcium influx and the cAMP messenger system in rat enterocytes. *Am J Physiol* 273:C1349–C1353, 1997
33. Skouteris GG: Parathyroid hormone co-stimulation of hepatocyte proliferation is sensitive to protein kinase A and calcium channel inhibitors. *Biosci Rep* 16:343–350, 1996
34. Perneger TV, Klag MJ, Whelton PK: Cause of death in patients with end-stage renal disease: death certificates vs. registry reports. *Am J Public Health* 83:1735–1738, 1993