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Cinacalcet hydrochloride treatment significantly improves all-cause and cardiovascular survival in a large cohort of hemodialysis patients

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Secondary hyperparathyroidism (SHPT) affects a significant number of hemodialysis patients, and metabolic disturbances associated with it may contribute to their high mortality rate. As patients with lower serum calcium, phosphorus, and parathyroid hormone are reported to have improved survival, we tested whether prescription of the calcimimetic cinacalcet to hemodialysis patients with SHPT improved their survival. We prospectively collected data on hemodialysis patients from a large provider beginning in 2004, a time coincident with the commercial availability of cinacalcet hydrochloride. This information was merged with data in the United States Renal Data System to determine all-cause and cardiovascular mortality. Patients included in the study received intravenous (i.v.) vitamin D therapy (a surrogate for the diagnosis of SHPT). Of 19,186 patients, 5976 received cinacalcet and all were followed from November 2004 for up to 26 months. Unadjusted and adjusted time-dependent Cox proportional hazards modeling found that all-cause and cardiovascular mortality rates were significantly lower for those treated with cinacalcet than for those without calcimimetic. Hence, this observational study found a significant survival benefit associated with cinacalcet prescription in patients receiving i.v. vitamin D. Definitive proof, however, of a survival advantage awaits the performance of randomized clinical trials.

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Despite recent modest improvements in adjusted mortality rates among hemodialysis patients, mortality rates remain above 225 per 1000 patient-years, nearly six times the rates in the general age-matched population.[1] Overall 5-year survival of hemodialysis patients remains only 31% and the mortality rate for patients on dialysis for longer than 5 years is above 250 per 1000 patient-years.[1] In the last decade, considerable emphasis has been placed on the role of abnormalities in mineral metabolism (elevated levels of calcium, phosphorus, and parathyroid hormone (PTH)) in this high rate of mortality.[2] Secondary hyperparathyroidism (SHPT) is present in a substantial percentage of hemodialysis patients and prevalence increases with increasing dialysis duration. For much of the past two decades, the primary SHPT treatments have been phosphate binders to control serum phosphorus, and intravenous (i.v.) vitamin D to suppress PTH. As i.v. vitamin D commonly increases serum calcium and phosphorus, efforts to control PTH often resulted in elevated serum calcium and phosphorus values.

Elevations in serum calcium, phosphorus, and PTH have all been associated with increased morbidity and mortality in observational studies.[3–6] Observational data suggest that optimal outcomes are associated with serum calcium values in the low-normal range of 7.5–9.5 mg/dl and serum phosphorus values in the range of 3–5 mg/dl.[5] Serum PTH levels associated with optimal outcomes are less well defined and vary by specific study; however, it is difficult to show an independent effect of PTH on outcomes until PTH values are above 600 pg/ml.[6]

The strength of observational data has led to many national and international patient care guidelines that recommend control of serum calcium, phosphorus, and PTH within specific ranges. The most well recognized of these sets of guidelines is the US-based National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI). The KDOQI guideline for bone and mineral disease recommends target calcium of 8.4–9.5 mg/dl, target phosphorus of 3.5–5.5 mg/dl, and target PTH of 150–300 pg/ml.[7]

Calcimimetics increase the sensitivity of the calcium-sensing receptor to extracellular calcium and represent an

alternative therapy for SHPT. The first calcimimetic, cinacalcet hydrochloride (Sensipar; Amgen, Thousand Oaks, CA, USA), was approved for clinical use in April 2004 and became commercially available in May 2004. Pivotal clinical trials were conducted in patients with persistent SHPT despite use of a standard therapy (phosphate binders and vitamin D). These trials consistently showed that adding cinacalcet reduced PTH, calcium, and phosphorus levels.[8] Extension studies and *post-hoc* analyses suggested that adding cinacalcet produced long-term favorable effects on these biomarkers and that patients given cinacalcet were more likely to reach target values than patients given standard therapy.[9,10]

Compelled by the observations that patients with lower serum values of calcium, phosphorus, and PTH had improved survival, we prospectively tested the hypothesis that prescribing cinacalcet to a large hemodialysis population with SHPT would be associated with improved survival.

RESULTS

Baseline characteristics

The final study population consisted of 5976 patients with cinacalcet prescriptions and 13,210 without. Detailed descriptions of patient characteristics at baseline and at first cinacalcet prescription are shown in Tables 1 and 2. Patients with cinacalcet prescriptions were younger with longer dialysis duration, more likely to be African American, and less likely to have diabetes. In the baseline period, a higher percentage of patients with cinacalcet prescriptions had 0 hospital days and a lower percentage had >5 hospital days. Consistent with these demographic differences suggesting that patients with cinacalcet prescriptions were generally healthier, baseline cardiovascular comorbidity was also lower. Cardiovascular medication use was generally similar between patients with and without cinacalcet prescriptions; however, cinacalcet patients were less likely to receive prescriptions for calcium-containing phosphate binders and more likely to receive prescriptions for sevelamer. Baseline serum calcium, phosphorus, and PTH values were higher for cinacalcet than for non-cinacalcet patients. In particular, proportions of cinacalcet patients with severe hyperparathyroidism (PTH >600 pg/ml), hypercalcemia (calcium >10.2 mg/dl), and hyperphosphatemia (phosphorus >8.0 mg/dl) in the baseline period were higher than proportions of non-cinacalcet patients.

Outcomes analyses: mortality

The unadjusted all-cause mortality rate for patients with cinacalcet prescriptions was significantly lower than for non-cinacalcet patients (17.6 vs 23.0 deaths per 100 patient-years, respectively, hazard ratio (HR) 0.73, 95% confidence interval (CI) 0.68–0.78, $P<0.001$; Table 3). Fully adjusted models showed an almost identical HR of 0.74 (95% CI 0.67–0.83), suggesting that demographic characteristics favoring cinacalcet patients were balanced by laboratory characteristics favoring non-cinacalcet patients (Table 4). Unadjusted cardiovascular mortality rates were 8.1 deaths per 100 patient-years for cinacalcet patients and 10.0 for non-cinacalcet patients. Models adjusted for all variables showed an HR of 0.76 (95% CI 0.66–0.86, $P<0.001$) for cardiovascular mortality (Table 5).

Concomitant medication use (cardiovascular, lipid lowering) and phosphate binder use were investigated as covariates. However, there was no statistically significant association between use of these medications during the baseline period and mortality. Removing these medications from the model did not affect the parameter estimate for all-cause mortality or cardiovascular-specific mortality.

Stratified analysis

Although we detected no interactions between treatment and any factor of interest (age, sex, race, dialysis duration, diabetes, access type, body mass index (BMI), phosphorus, and PTH), and despite adjustment for multiple baseline covariates, slight differences in treatment effect between strata of covariates could occur. Thus, fully adjusted time-dependent stratified analyses were conducted for all-cause mortality. The upper end of the 95% CI was <1.0 in 46 of the 59 strata presented (Figure 1). Stratification by severity of SHPT revealed no survival benefit for patients with PTH <150 pg/ml (HR 0.97, CI 0.74–1.26) and the largest survival benefit (HR 0.66, CI 0.53–0.83) for patients with the most severe disease (PTH >600 pg/ml). We also conducted stratified analyses for associations with cardiovascular mortality. Trends were similar, except that CI were even wider and overlapped 1.0 more often, reflecting smaller numbers of events.

Sensitivity analyses using dialysis duration and propensity matched cohorts revealed a HR of 0.81 (CI 0.75–0.88).

DISCUSSION

This prospectively designed observational study, initiated in 2004, shows a significant survival benefit associated with prescribing cinacalcet for hemodialysis patients with evidence of SHPT and receiving i.v. vitamin D. This survival benefit was maintained after adjustment for baseline and time-dependent characteristics. Sensitivity analyses designed to address the difference in dialysis duration between groups (and possible lead-time bias) modified the HR towards 1; however, significant survival benefit was maintained. In stratified analysis, the upper end of the 95% CI was <1 in most strata, supporting a consistent benefit among subgroups. Improved survival was also shown for cardiovascular mortality, consistent with the hypothesis that intervention in mineral metabolism is directly related to cardiovascular health in hemodialysis patients. That stratified analyses failed to show a survival effect in patients with PTH <150 pg/ml and the strongest effect was observed in patients with the most severe SHPT (PTH >600 pg/ml) strongly support this hypothesis.

Because cinacalcet use has been shown to result in decrements in serum levels of calcium, phosphorus, and PTH, it is tempting to speculate that these reductions may be

Table 1 | Patient demographic and health information at baseline (1 November 2004) and at first cinacalcet use

	All patients,[a] 1 November		Cinacalcet patients[a]				Non-cinacalcet patients,[a] 1 November	
			1 November		At first cinacalcet use[b]			
Characteristics	*n*	Percent	*n*	Percent	*n*	Percent	*n*	Percent
Mean age (year)	62.9		58.3		59.2		65.0	
Age groups, %	19,186		5976		5976		13,210	
0–44	2418	12.6	1119	18.7	1030	17.2	1299	9.8
45–64	6976	36.4	2602	43.5	2578	43.1	4374	33.1
65–74	5108	26.6	1405	23.5	1424	23.8	3703	28.0
⩾75	4684	24.4	850	14.2	944	15.8	3834	29.0
Mean dialysis duration (year)	3.8		4.4		5.3		3.5	
Dialysis duration, %	19,179		5975		5976		13,204	
<1	3189	16.6	704	11.8	133	2.2	2485	18.8
1–3	6485	33.8	1755	29.4	1521	25.5	4730	35.8
3–5	4719	24.6	1599	26.8	1769	29.6	3120	23.6
>5 years	4786	25.0	1917	32.1	2553	42.7	2869	21.7
Mean body mass index (kg/m^2)	18,861	26.9	5861	27.7	5866	27.6	12,820	26.5
Body mass index, %								
0–<18.5	906	4.9	216	3.7	215	3.7	690	5.4
⩾18.5 to <25.0	7569	40.5	2168	37.0	2210	37.7	5401	42.1
⩾25.0 to <30.0	5439	29.1	1712	29.2	1723	29.4	3727	29.1
⩾30.0 to <35.0	2722	14.6	935	16.0	910	15.5	1787	14.0
⩾35.0 to <40.0	1220	6.5	496	8.5	480	8.2	724	5.7
⩾40.0	825	4.4	334	5.7	328	5.6	491	3.8
Sex								
Men	10,310	53.7	3096	51.8	3096	51.8	7214	54.6
Women	8876	46.3	2880	48.2	2880	48.2	5996	45.4
Race								
African American	7821	40.8	3018	50.5	3018	50.5	4803	36.4
White	6309	32.9	1592	26.6	1592	26.6	4717	35.7
Other	5056	26.4	1366	22.9	1366	22.9	3690	27.9
Primary cause of renal failure								
Diabetes	8760	45.7	2401	40.2	2401	40.2	6359	48.1
Hypertension	5853	30.5	1957	32.8	1957	32.8	3896	29.5
Glomerulonephritis	1851	9.7	730	12.2	730	12.2	1121	8.5
Other	2722	14.2	888	14.9	888	14.9	1834	13.9
Hospital days								
0	10,566	55.1	3541	59.3	3579	59.9	7025	53.2
1–3	2307	12.0	744	12.5	773	12.9	1563	11.8
4–5	1181	6.2	353	5.9	360	6.0	828	6.3
>5	5132	26.8	1338	22.4	1264	21.2	3794	28.7

[a]Demographic information defined on 1 November 2004; baseline hospital days determined from 1 May to 31 October 2004.
[b]Characteristics collected immediately before first cinacalcet prescription or, for hospital days, in the 6 months before first cinacalcet prescription.

the proximate cause of a survival benefit. Indeed, the strength of the observational data suggesting that high levels of these minerals are associated with mortality led to the development of national and international guidelines that adopt narrow target values.[11] The KDOQI guidelines for bone and mineral disease recommend target levels of 8.4–9.5 mg/dl for calcium, 3.5–5.5 mg/dl for phosphorus, and 150–300 pg/ml for PTH. A recent report using data from a large dialysis provider (Fresenius Medical Care North America, Waltham, MA, USA) found that consistent control of mineral metabolism was associated with improved survival for hemodialysis patients, and that as patients met increasing numbers of KDOQI targets, HR of mortality were reduced.[12] In addition, sustaining each target level over time was associated with improved survival. The authors estimated that maintaining KDOQI targets for calcium, phosphorus, and PTH could reduce mortality by as much as 20%. Using data from DaVita (Denver, CO, USA), we recently reported that serum calcium, phosphorus, and PTH were significantly reduced for patients given cinacalcet prescriptions from mid 2004 to 2006, and these patients were more likely to reach KDOQI target values and less likely to experience biochemical adverse events.[13]

Table 2 | Comorbid conditions, medication use, and laboratory values at baseline (1 November 2004) and at first cinacalcet use

			Cinacalcet patients[a]					
	All patients,[a] 1 November		1 November		At first cinacalcet use[b]		Non-cinacalcet patients,[a] 1 November	
Characteristics	*n*	Percent	*n*	Percent	*n*	Percent	*n*	Percent
Diabetes	11,672	60.8	3241	54.2	3284	55.0	8431	63.8
CVD								
CHF	8886	46.3	2427	40.6	2483	41.5	6459	48.9
ASHD	6866	35.8	1716	28.7	1807	30.2	5150	39.0
PVD	6859	35.8	1783	29.8	1892	31.7	5076	38.4
CVA/TIA	3284	17.1	796	13.3	813	13.6	2488	18.8
Dysrhythmia	4730	24.7	1093	18.3	1234	20.6	3637	27.5
Other CVD[c]	5879	30.6	1594	26.7	1607	26.9	4285	32.4
Cancer	1579	8.2	424	7.1	420	7.0	1155	8.7
COPD	3118	16.3	795	13.3	873	14.6	2323	17.6
Beta blockers[d]	10,442	54.4	3370	56.4	3601	60.3	7072	53.5
Calcium channel blockers[e]								
Dihydropyridine	9012	47.0	2997	50.2	3023	50.6	6015	45.5
Nondihydropyridine	1554	8.1	519	8.7	512	8.6	1035	7.8
Statins[f]	6036	31.5	1774	29.7	1900	31.8	4262	32.3
ACEIs/ARBs[g]	11,030	57.5	3590	60.1	3628	60.7	7440	56.3
Phosphate binders								
Calcium-based	9980	52.0	2850	47.7	2511	42.0	7130	54.0
Lanthanum	—	0.0	—	0.0	939	15.7	0	0.0
Sevelamer	10,134	52.8	4004	67.0	4444	74.4	6130	46.4
Albumin, g/dl, mean (s.d.)	18,985	3.9 (0.4)	5935	3.9 (0.4)	5904	3.9 (0.4)	13,050	3.8 (0.4)
Albumin, %								
<3.6	3807	20.1	830	14.0	942	16.0	2977	22.8
$\geqslant 3.6$ to <4.0	6815	35.9	2060	34.7	2074	35.1	4755	36.4
$\geqslant 4.0$	8363	44.1	3045	51.3	2888	48.9	5318	40.8
Corrected calcium, mg/dl, mean (s.d.)	18,918	9.6 (0.7)	5923	9.8 (0.7)	5895	9.7 (0.7)	12,995	9.5 (0.7)
Corrected calcium, %								
<9.0	2586	13.7	527	8.9	781	13.2	2059	15.8
$\geqslant 9.0$ to $\leqslant 10.2$	13,198	69.8	3898	65.8	3658	62.1	9300	71.6
>10.2	3134	16.6	1498	25.3	1456	24.7	1636	12.6
Phosphorus, mg/dl, mean (s.d.)	18,990	5.4 (1.6)	5936	5.7 (1.6)	5906	6.1 (1.7)	13,054	5.2 (1.5)
Phosphorus, %								
<3.5	1467	7.7	265	4.5	203	3.4	1202	9.2
$\geqslant 3.5$ to <5.0	6595	34.7	1714	28.9	1386	23.5	4881	37.4
$\geqslant 5.0$ to <6.0	5118	27.0	1683	28.4	1514	25.6	3435	26.3
$\geqslant 6.0$ to <7.0	3073	16.2	1136	19.1	1233	20.9	1937	14.8
$\geqslant 7.0$ to <8.0	1527	8.0	623	10.5	797	13.5	904	6.9
$\geqslant 8.0$	1210	6.4	515	8.7	773	13.1	695	5.3
Intact PTH, pg/ml, median (IQR)	18,830	251.9 (225.0)	5902	323.1 (317.3)	5890	548.1 (465.5)	12,928	230.8 (186.5)
Intact PTH, %								
<150	3696	19.6	730	12.4	219	3.7	2966	22.9
$\geqslant 150$ to $\leqslant 300$	7844	41.7	2010	34.1	683	11.6	5834	45.1
$>300 \leqslant 600$	5248	27.9	2005	34.0	2408	40.9	3243	25.1
>600	2042	10.8	1157	19.6	2580	43.8	885	6.8
Hemoglobin, g/dl, mean (s.d.)	18,959	12.4 (1.4)	5929	12.4 (1.3)	5899	12.4 (1.3)	13,030	12.3 (1.4)
Hemoglobin, %								
<10	84	4.4	218	3.7	215	3.6	625	4.8
$\geqslant 10$ to $\leqslant 12$	6566	34.6	1950	32.9	2058	34.9	4616	35.4

Table 2 Continued on the following page

Table 2 | Continued

Characteristics	All patients,[a] 1 November		Cinacalcet patients[a] 1 November		Cinacalcet patients[a] At first cinacalcet use[b]		Non-cinacalcet patients,[a] 1 November	
	n	Percent	*n*	Percent	*n*	Percent	*n*	Percent
>12 to ⩽13	5398	31.3	1954	33.0	1919	32.5	3984	30.6
>13	5612	29.6	1807	30.5	1707	28.9	3805	29.2
Bicarbonate, mEq/l, mean (s.d.)	18,925	21.2 (4.0)	5922	21.0 (3.9)	5894	23.2 (3.7)	13,003	21.3 (4.0)
Bicarbonate, %								
<22	10,204	53.9	3303	55.8	1893	32.1	6901	53.1
⩾22 to ⩽30	8503	44.9	2555	43.1	3832	65.0	5948	45.7
>30	218	1.2	64	1.1	169	2.9	154	1.2
Kt/V UKM, mean (s.d.)	18,832	1.7 (0.3)	5908	1.6 (0.3)	5882	1.6 (0.3)	12,924	1.7 (0.3)
Kt/V UKM, %								
<1.2	1032	5.5	308	5.2	312	5.3	724	5.6
⩾1.2 to ⩽1.4	2264	12.0	721	12.2	716	12.2	1543	11.9
>1.4	15,536	82.5	4879	82.6	4854	82.5	10,657	82.5
URR, mean (s.d.)	18,936	73.9 (6.7)	5924	73.8 (6.6)	5889	74.0 (6.6)	13,012	74.0 (6.8)
URR, %								
<65	1416	7.5	434	7.3	394	6.7	982	7.5
⩾65	17,520	92.5	5490	92.7	5495	93.3	12,030	92.5

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASHD, atherosclerotic heart disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; CVD, cardiovascular disease; IQR, inter-quartile range; Kt/V, dialysis adequacy; PTH, parathyroid hormone; PVD, peripheral vascular disease; s.d., standard deviation; TIA, transient ischemic attack; UKM, urea kinetic modeling; URR, urea reduction ratio.
[a]Baseline comorbidity determined 1 May to 31 October 2004; at least one record of medication prescription in the medication class required in the 3 baseline months (August–October 2004) to be counted as medication exposure; baseline laboratory data determined 1 August to 31 October 2004, using values closest to 31 October 2004.
[b]Baseline comorbidity determined in the 6 months before first cinacalcet prescription; at least one record of medication prescription in the medication class required in the 3 months before first cinacalcet prescription to be counted as a medication exposure; baseline laboratory data determined in the 3 months before first cinacalcet prescription.
[c]Includes ill-defined complication of heart disease, tachycardia, palpitations, murmurs, acute pericarditis, acute and subacute endocarditis, other diseases of pericardium, and other diseases of the endocardium.
[d]Acebutolol, atenolol, betaxolol, bisoprolol, carteolol, carvedilol, esmolol, labetalol, metoprolol, nadolol, penbutolol, pindolol, propranolol, and timolol.
[e]Dihydropyridine-based: amlodipine, bepridil, felodipine, isradipine, nicardipine, nifedipine, and nisoldipine; non-dihydropyridine-based: diltiazem and verapamil.
[f]Atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, and simvastatin.
[g]ACEIs: benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril; ARBs: candesartan, eprosartan, irbesartan, losartan, telmisartan, and valsartan.

Table 3 | Unadjusted all-cause and cardiovascular mortality

Variable	Cinacalcet patients	Non-cinacalcet patients	*P*
n	5976	19,174	
All-cause mortality			
Follow-up			
Mean, patient-years	1.1	1.3	
Minimum–maximum, years	0.0–2.2	0.0–2.2	
Total deaths, *n* (%)	1148 (19.2)	5882 (30.7)	
Mortality incidence rate, per 100 patient-years (95% CI)	17.6 (16.58–18.61)	23.0 (22.38–23.55)	
Raw hazard ratio[a] (95% CI)	0.73 (0.68–0.78)		<0.0001
Time to event, months[b]			<0.0001
1-year survival (s.e.)	0.85 (0.01)	0.80 (0.00)	
2-year survival (s.e.)	0.70 (0.01)	0.63 (0.00)	
Cardiovascular mortality			
Follow-up			
Mean, patient-years	1.1	1.3	
Minimum–maximum, years	0.0–2.2	0.0–2.2	
Cardiovascular deaths, *n* (%)	525 (8.8)	2571 (13.4)	
Cardiovascular mortality incidence rate, per 100 patient-years (95% CI)	8.1 (7.36–8.73)	10.0 (9.65–10.43)	
Raw hazard ratio[a] (95% CI)	0.78 (0.71–0.86)		<0.0001
Time to event, months[b]			<0.0001
1-year survival (s.e.)	0.92 (0.00)	0.91 (0.00)	
2-year survival (s.e.)	0.85 (0.01)	0.82 (0.00)	

Abbreviations: CI, confidence interval; s.e., standard error.
[a]Time-dependent Cox-proportional hazard regression model.
[b]Log-rank test.

Table 4 | Adjusted hazard ratios for all-cause mortality[a]

Parameter	Parameter estimate	s.e.	Hazard ratio (95% CI)	*P*
Treatment (referent: non-cinacalcet patients)	−0.298	0.054	0.74 (0.67–0.83)	<0.0001
Age, year (referent: 18–44)				
45–64	0.508	0.106	1.66 (1.35–2.04)	<0.0001
65–74	0.847	0.119	2.33 (1.85–2.95)	<0.0001
⩾75	1.147	0.121	3.15 (2.48–3.99)	<0.0001
Sex (referent: men)	−0.073	0.040	0.93 (0.86–1.01)	0.0669
Race (referent: white)				
African American	−0.365	0.048	0.69 (0.63-0.76)	<0.0001
Other	−0.286	0.049	0.75 (0.68-0.83)	<0.0001
Dialysis duration, year (referent: 1–3)				
<1	−0.212	0.061	0.81 (0.72-0.91)	0.0005
3–5	0.119	0.060	1.13 (1.00–1.27)	0.0466
>5	0.214	0.074	1.24 (1.07–1.43)	0.0036
BMI, kg/m^2 (referent: ⩾18–<25)				
<18.5	0.366	0.074	1.44 (1.25–1.67)	<0.0001
⩾25 to <30	−0.282	0.043	0.75 (0.69-0.82)	<0.0001
⩾30 to <35	−0.416	0.054	0.66 (0.59-0.73)	<0.0001
⩾35 to <40	−0.604	0.081	0.55 (0.47-0.64)	<0.0001
⩾40	−0.461	0.091	0.63 (0.53-0.75)	<0.0001
Primary cause of renal failure (referent: glomerulonephritis)				
Diabetes	0.210	0.084	1.23 (1.05–1.46)	0.0124
Hypertension	0.131	0.077	1.14 (0.98–1.33)	0.0873
Other	0.174	0.085	1.19 (1.01–1.41)	0.0402
Hospital days (referent: 0)				
1–3	0.038	0.065	1.04 (0.91–1.18)	0.5565
4–5	0.065	0.078	1.07 (0.92–1.24)	0.4058
>5	0.126	0.056	1.14 (1.02–1.27)	0.0242
Diabetes (referent: no)	0.187	0.058	1.21 (1.08–1.35)	0.0013
Congestive heart failure (referent: no)	0.250	0.042	1.28 (1.18–1.39)	<0.0001
Atherosclerotic heart disease (referent: no)	0.004	0.045	1.00 (0.92–1.10)	0.932
Peripheral vascular disease (referent: no)	0.093	0.040	1.10 (1.01–1.19)	0.0206
CVA/TIA (referent: no)	0.142	0.046	1.15 (1.05–1.26)	0.002
Dysrhythmia (referent: no)	0.169	0.044	1.18 (1.09–1.29)	0.0001
Other CVD[b] (referent: no)	0.098	0.043	1.10 (1.01–1.20)	0.0245
Cancer (referent: no)	0.163	0.068	1.18 (1.03–1.34)	0.016
GI bleeding (referent: no)	0.086	0.070	1.09 (0.95–1.25)	0.2223
COPD (referent: no)	0.173	0.047	1.19 (1.08, 1.30)	0.0002
Liver disease (referent: no)	0.080	0.116	1.08 (0.86, 1.36)	0.4892
Albumin, g/dl (referent: ⩾4.0)				
<3.6	1.014	0.034	2.76 (2.58–2.95)	<0.0001
⩾3.6 to <4.0	0.373	0.030	1.45 (1.37–1.54)	<0.0001
Corrected calcium, mg/dl (referent: ⩾9.0–⩽10.2)				
<9.0	−0.063	0.082	0.94 (0.80–1.10)	0.4448
>10.2	0.127	0.046	1.14 (1.04–1.24)	0.0059
Phosphorus, mg/dl (referent: ⩾3.5–<5.0)				
<3.5	0.060	0.116	1.06 (0.85–1.33)	0.6028
⩾5.0 to <6.0	0.065	0.043	1.07 (0.98–1.16)	0.1279
⩾6.0 to <7.0	0.141	0.050	1.15 (1.04–1.27)	0.0048
⩾7.0 to <8.0	0.207	0.069	1.23 (1.07–1.41)	0.0028
⩾8.0	0.365	0.073	1.44 (1.25–1.66)	<0.0001
Intact PTH, pg/ml (referent: >150–⩽300)				
<150	−0.0002	0.065	1.00 (0.88–1.14)	0.9968
>300 to ⩽600	0.025	0.044	1.03 (0.94–1.12)	0.5748
>600	0.171	0.063	1.19 (1.05–1.34)	0.0065

Table 4 Continued on the following page

Table 4 | Continued

Parameter	Parameter estimate	s.e.	Hazard ratio (95% CI)	P
Bicarbonate, mEq/l (referent: ⩾22–⩽30)				
<22	0.043	0.041	1.04 (0.96–1.13)	0.2979
>30	0.296	0.072	1.34 (1.17–1.55)	<0.0001
Hemoglobin, g/dl (referent: ⩾10–⩽12)				
<10	0.177	0.139	1.19 (0.91–1.57)	0.2034
>12 to ⩽13	−0.107	0.027	0.90 (0.85–0.95)	<0.0001
>13	−0.079	0.029	0.92 (0.87–0.98)	0.0065
Kt/V UKM per treatment (referent: ⩾1.2–⩽1.4)				
<1.2	0.086	0.165	1.09 (0.79–1.51)	0.5997
>1.4	−0.231	0.039	0.79 (0.74–0.86)	<0.0001
TSAT, % (referent: ⩾20–<50)				
<20	0.164	0.047	1.18 (1.07–1.29)	0.0005
⩾50	−0.035	0.041	0.97 (0.89–1.05)	0.3941
Ferritin, ng/ml (referent: ⩾200–<500)				
<200	−0.067	0.086	0.94 (0.79–1.11)	0.4303
⩾500 to <800	0.019	0.030	1.02 (0.96–1.08)	0.5205
⩾800 to <1000	0.006	0.039	1.01 (0.93–1.09)	0.8847
⩾1000	0.180	0.038	1.20 (1.11–1.29)	<0.0001
WBC, mm^3 (referent: ⩾1000–⩽10,000)				
<1000	3.105	0.705	22.31 (5.60–88.83)	<0.0001
>10,000	0.298	0.047	1.35 (1.23–1.48)	<0.0001
Vascular access (referent: fistula)				
Catheter	0.365	0.043	1.44 (1.32–1.57)	<0.0001
Graft	0.188	0.032	1.21 (1.13–1.29)	<0.0001
Other	0.932	0.648	2.54 (0.71–9.04)	0.1503

Abbreviations: BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; CVD, cardiovascular disease; GI, gastrointestinal; PTH, parathyroid hormone; s.e., standard error; TIA, transient ischemic attack; TSAT, transferrin saturation; UKM, urea kinetic modeling; WBC, white blood cell count.
[a]Time-dependent Cox proportional hazards regression model, adjusted for demographic characteristics, comorbidity, hospital days, vascular access, and laboratory information.
[b]Includes ill-defined complication of heart disease, tachycardia, palpitations, murmurs, acute pericarditis, acute and subacute endocarditis, other disease of pericardium, and other diseases of the endocardium.

However, it is imperative to note that no randomized clinical trial has shown that reduced serum levels of these minerals are associated with improved clinical outcome. Despite the compelling nature of our results, these data most strongly support the ongoing EVOLVE trial (Evaluation of cinacalcet HCL therapy to lower cardiovascular events; clinicaltrials.gov identifier NCT 00345839). Nephrology is currently mired in an unfortunate situation, in which observational data are used to generate clinical treatment guidelines rather than hypotheses to be tested with randomized controlled clinical trials. Such an approach has often proved to be erroneous when ultimately tested in properly conducted clinical trials. Remarkably, some members of the community go so far as to suggest that, on the basis of observational data alone, conducting randomized controlled trials is precluded on ethical grounds. We must resist adopting this approach.

As with all observational reports, the current study has several limitations. Chief among these is the possibility that residual confounding by indication might be responsible for our findings. However, this analysis has several strengths that distinguish it from previous observational reports on outcome in this clinical arena. Merging data from DaVita with data from the United States Renal Data System (USRDS) allowed us to characterize and adjust for comorbidity and hospitalization at study entry and to update these factors at cinacalcet initiation. Furthermore, use of USRDS data allowed us to more fully identify mortality events. Previous reports using only large dialysis chain data are limited in this regard because of individual patients leaving a particular provider or changing health insurance. Using USRDS data, we identified approximately 3600 more deaths than we would have identified using only DaVita-provided mortality information. Our analysis mimicked an intent-to-treat trial design by forcing patients who received cinacalcet prescriptions to stay in the exposed arm. Any misclassification bias that might have occurred with this approach would serve only to minimize the likelihood of finding an independent effect. Uniquely, compared with previous work, our analyses included only patients who had received i.v. vitamin D, the main treatment for SHPT, before cinacalcet availability. Previous reports comparing outcomes among exposed and unexposed patient populations have all been susceptible to confounding by indication, in that patients

Table 5 | Adjusted hazard ratios for cardiovascular mortality[a]

Parameter	Parameter estimate	s.e.	Hazard ratio (95% CI)	P
Treatment (referent: non-cinacalcet patients)	–0.281	0.0692	0.76 (0.66–0.86)	<0.0001
Age, year (referent: 18–44)				
45–64	0.520	0.119	1.68 (1.33–2.12)	<0.0001
65–74	0.841	0.125	2.32 (1.81–2.96)	<0.0001
⩾75	1.085	0.127	2.96 (2.31–3.80)	<0.0001
Sex (referent: men)	–0.084	0.047	0.92 (0.84–1.01)	0.0777
Race (referent: white)				
African American	–0.296	0.057	0.74 (0.67–0.83)	<0.0001
Other	–0.196	0.060	0.82 (0.73–0.92)	0.0010
Dialysis duration, year (referent: 1–3)				
<1	–0.263	0.073	0.77 (0.67–0.89)	0.0003
3–5	0.123	0.063	1.13 (1.00–1.28)	0.0507
>5	0.224	0.070	1.25 (1.09–1.43)	0.0013
BMI, kg/m^2 (referent: ⩾18–<25)				
<18.5	0.483	0.088	1.62 (1.36–1.93)	<0.0001
⩾25 to <30	–0.246	0.053	0.78 (0.70–0.87)	<0.0001
⩾30 to <35	–0.389	0.071	0.68 (0.59–0.78)	<0.0001
⩾35 to <40	–0.662	0.108	0.52 (0.42–0.64)	<0.0001
⩾40	–0.623	0.130	0.54 (0.42–0.69)	<0.0001
Primary cause of renal failure (referent: glomerulonephritis)				
Diabetes	0.355	0.106	1.43 (1.16–1.75)	0.0008
Hypertension	0.249	0.098	1.28 (1.06–1.55)	0.0111
Other	0.179	0.108	1.20 (0.97–1.48)	0.0973
Hospital days (referent: 0)				
1–3	0.006	0.074	1.01 (0.87–1.16)	0.9353
4–5	–0.030	0.095	0.97 (0.81–1.17)	0.7546
>5	0.121	0.062	1.13 (1.00–1.28)	0.0510
Diabetes (referent: no)	0.144	0.069	1.15 (1.01–1.32)	0.0372
Congestive heart failure (referent: no)	0.318	0.051	1.37 (1.24–1.52)	<0.0001
Atherosclerotic heart disease (referent: no)	0.088	0.052	1.09 (0.99–1.21)	0.0923
Peripheral vascular disease (referent: no)	0.157	0.048	1.17 (1.06–1.29)	0.0012
CVA/TIA (referent: no)	0.105	0.055	1.11 (1.00–1.24)	0.0583
Dysrhythmia (referent: no)	0.257	0.052	1.29 (1.17–1.43)	<0.0001
Other CVD[b] (referent: no)	0.082	0.052	1.09 (0.98–1.20)	0.1194
Cancer (referent: no)	–0.055	0.081	0.95 (0.81–1.11)	0.4995
GI bleeding (referent: no)	0.058	0.081	1.06 (0.91–1.24)	0.4692
COPD (referent: no)	0.168	0.056	1.18 (1.06–1.32)	0.0027
Liver disease (referent: no)	–0.050	0.122	0.95 (0.75–1.21)	0.6806
Albumin, g/dl (referent: ⩾4.0)				
<3.6	0.850	0.049	2.34 (2.13–2.58)	<0.0001
⩾3.6 to <4.0	0.340	0.043	1.41 (1.29–1.53)	<0.0001
Corrected calcium, mg/dl (referent: ⩾9.0–⩽10.2)				
<9.0	–0.065	0.077	0.94 (0.81–1.09)	0.3998
>10.2	0.161	0.059	1.17 (1.05–1.32)	0.0065
Phosphorus, mg/dl (referent: ⩾3.5–<5.0)				
<3.5	0.056	0.109	1.06 (0.85–1.31)	0.6045
⩾5.0 to <6.0	0.101	0.056	1.11 (0.99–1.24)	0.0711
⩾6.0 to <7.0	0.183	0.066	1.20 (1.05–1.37)	0.0056
⩾7.0 to <8.0	0.175	0.088	1.19 (1.00–1.42)	0.0467
⩾8.0	0.345	0.096	1.41 (1.17–1.70)	0.0003
Intact PTH, pg/ml (referent: >150–⩽300)				
<150	–0.022	0.070	0.98 (0.85–1.12)	0.7526
>300 to ⩽600	0.053	0.056	1.06 (0.94–1.18)	0.3456
>600	0.256	0.079	1.29 (1.11–1.51)	0.0012

Table 5 Continued on the following page

Table 5 | Continued

Parameter	Parameter estimate	s.e.	Hazard ratio (95% CI)	P
Bicarbonate, mEq/l (referent: ⩾22–⩽30)				
<22	0.117	0.041	1.13 (1.04–1.22)	0.0042
>30	0.180	0.101	1.20 (0.98–1.46)	0.0754
Hemoglobin, g/dl (referent: ⩾10–⩽12)				
<10	0.054	0.131	1.06 (0.82–1.36)	0.6809
>12 to ⩽13	–0.109	0.039	0.90 (0.83–0.97)	0.0047
>13	–0.083	0.041	0.92 (0.85–1.00)	0.0443
Kt/V UKM per treatment (referent: ⩾1.2–⩽1.4)				
<1.2	0.011	0.140	1.01 (0.77–1.33)	0.9383
>1.4	–0.239	0.053	0.79 (0.71–0.87)	<0.0001
TSAT, % (referent: ⩾20–<50)				
<20	0.148	0.053	1.16 (1.05–1.28)	0.0051
⩾50	–0.166	0.062	0.85 (0.75–0.96)	0.0075
Ferritin, ng/ml (referent: ⩾200–<500)				
<200	–0.054	0.076	0.95 (0.82–1.10)	0.4760
⩾500 to <800	0.030	0.042	1.03 (0.95–1.12)	0.4691
⩾800 to <1000	–0.008	0.057	0.99 (0.89–1.11)	0.8861
⩾1000	0.101	0.055	1.11 (0.99–1.23)	0.0661
WBC, mm^3 (referent: ⩾1000–⩽10,000)				
<1000	–5.181	0.525	0.01 (0.00–0.02)	<0.0001
>10,000	0.212	0.060	1.24 (1.10–1.39)	0.0004
Vascular access (referent: fistula)				
Catheter	0.305	0.057	1.36 (1.21–1.52)	<0.0001
Graft	0.228	0.047	1.26 (1.14–1.38)	<0.0001
Other	0.796	0.524	2.22 (0.79–6.18)	0.1287

Abbreviations: BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; CVD, cardiovascular disease; GI, gastrointestinal; PTH, parathyroid hormone; s.e., standard error; TIA, transient ischemic attack; TSAT, transferrin saturation; UKM, urea kinetic modeling; WBC, white blood cell count.
[a]Time-dependent Cox proportional hazards regression model, adjusted for demographic characteristics, comorbidity, hospital days, vascular access, and laboratory information.
[b]Includes ill-defined complication of heart disease, tachycardia, palpitations, murmurs, acute pericarditis, acute and subacute endocarditis, other disease of pericardium, and other diseases of the endocardium.

who never received the medication of interest were different from those who did, in ways that cannot be adjusted for in routine analyses. Because of previous observational reports of survival benefit for patients exposed to i.v. vitamin D, we believed that eliminating this feature as a potential confounder was important. Vitamin D use may have differed modestly after exposure to cinacalcet; however, because this event would be in the causal pathway of potential clinical benefit, we did not find it reasonable to adjust for vitamin D use in our model. In addition, we previously reported that changes in vitamin D dose are very modest for patients in this population with cinacalcet prescriptions.[13] It is noteworthy that we did not investigate potential mechanisms of action as to the reason cinacalcet prescription was associated with survival benefit, and any hypotheses in this regard must be considered speculative.

In this prospectively designed observational cohort study, we found that prescription of cinacalcet to hemodialysis patients with SHPT, who have received i.v. vitamin D, was associated with significant reductions in all-cause and cardiovascular mortality. We must emphasize, however, that these results are observational and cannot establish a cause-and-effect relationship. These data do not definitively establish a survival effect of cinacalcet, and we caution against interpreting these data in any way other than supporting the hypothesis that intervention with cinacalcet and the resultant favorable effect on parameters of mineral metabolism may be in the clinical pathway for cardiovascular outcomes. Definitive evidence of actual clinical benefit will be ascertained in the ongoing EVOLVE clinical trial. However, our results provide compelling data, indicating that interventions to reduce calcium, phosphorus, and PTH levels are associated with meaningful patient outcomes.

MATERIALS AND METHODS

Patients and data sources

Patient data from DaVita were obtained through a data-licensing agreement. DaVita is a large dialysis provider in the United States, serving approximately one-third of the US dialysis population. All prevalent hemodialysis patients as of 1 August 2004 were selected, and data were collected prospectively through 31 December 2006. Using unique patient identifiers, data were linked to the Centers for Medicare & Medicaid Services (CMS) end-stage renal disease (ESRD) database by the USRDS through a data use agreement with the National Institute of Diabetes and Digestive and Kidney Diseases. Study approval was obtained from the Hennepin County Medical Center Human Subjects Research Committee (Minneapolis,

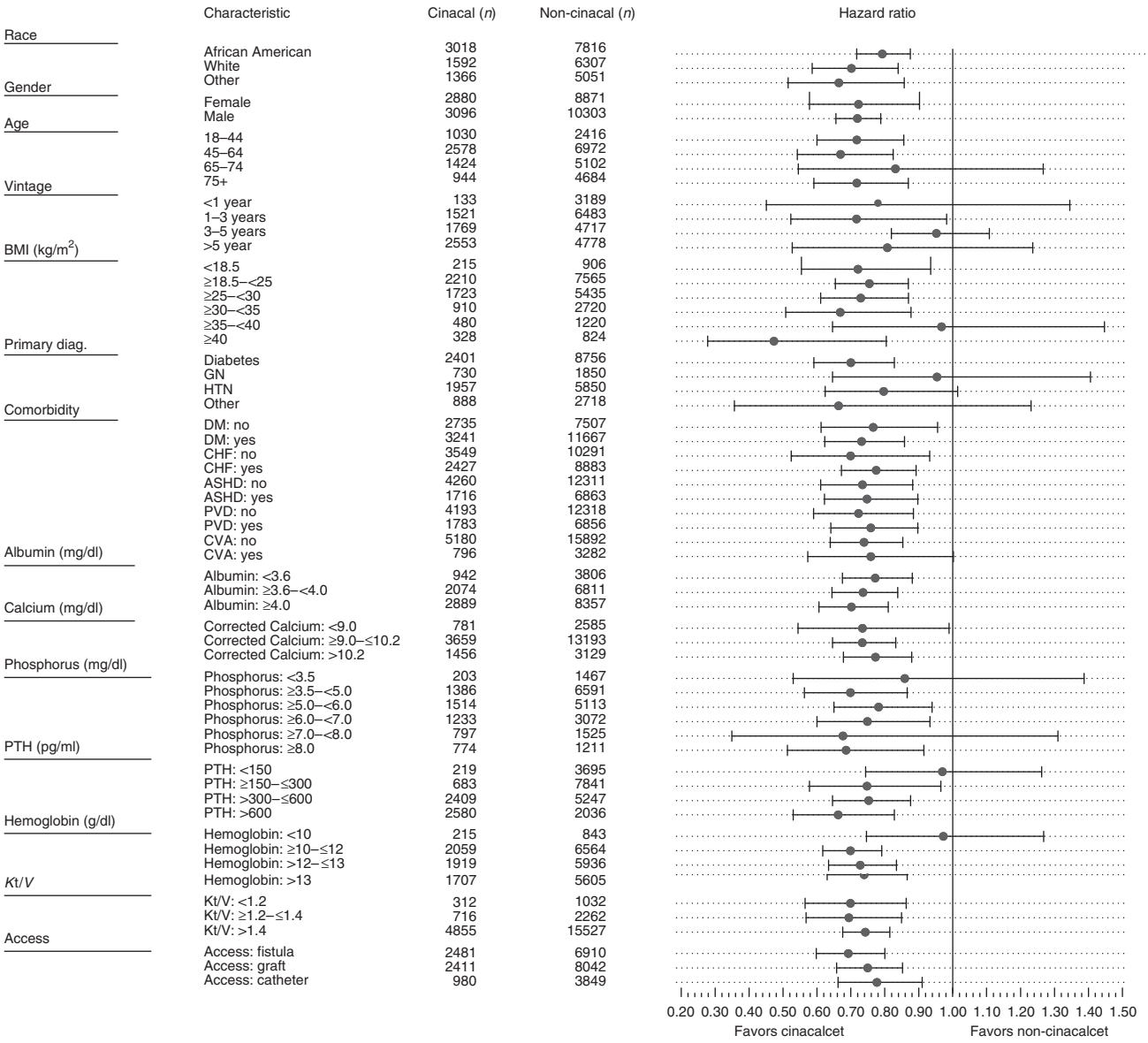

Figure 1 | Hazard ratios and 95% confidence intervals (CI) for mortality associated with cinacalcet prescription stratified by patient characteristics. Each row reflects a multivariable adjusted model including the covariates in our final model (see Table 4). The number of patients in each group (patients with and without cinacalcet prescriptions) within each stratum is represented by *n*. Circles represent point estimates and horizontal lines 95% CI. The referent group for each analysis is the group without cinacalcet prescriptions. ASHD, atherosclerotic heart disease; BMI, body mass index; CHF, congestive heart failure; CVA, cerebrovascular accident/transient ischemic attack; DM, diabetes; GN, glomerulonephritis; HTN, hypertension; PTH, parathyroid hormone; PVD, peripheral vascular disease.

Minnesota, USA) and the Exempla Healthcare Institutional Review Board (Denver, Colorado, USA).

The DaVita database provided information on demographics, weight and height, laboratory values, dialysis treatment, vascular access, i.v. vitamin D use, home medications, censoring (mortality, outside transfer, modality change), and insurance coverage. The CMS ESRD data provided information on ESRD initiation date, comorbid conditions, ESRD cause, medical claims (which include hospitalization information), and mortality date and cause.

Patient selection criteria

All hemodialysis patients as of August 2004 ($n = 45{,}589$) were eligible for consideration for inclusion. Included patients were required to be aged at least 18 years on 1 August 2004 and to have survived 90 days ($n = 43{,}848$). To allow full identification of comorbidity and clinical outcomes, included patients were required to have Medicare Centers for Medicare & Medicaid Services, 7500 Security Blvd., Baltimore, MD as primary payer and to have dialysis claims of $\geqslant$\$675 in August, September, and October 2004 ($n = 29{,}202$). Patients with cinacalcet prescriptions before 31 October 2004 were excluded (remaining $n = 25{,}292$) because of lack of adequate time to assess baseline characteristics. Because this analysis was specifically designed to test the *a priori* hypothesis that cinacalcet prescription independently improved clinical outcomes, and because cinacalcet is specifically indicated for patients with evidence of SHPT, all analyses were restricted to patients with evidence of i.v. vitamin D use during the

baseline period, August through October 2004. A total of 1044 patients (273 with cinacalcet prescriptions and 771 without) were censored due to renal transplant, transferring out of DaVita, or loss to follow-up. Applying these criteria left 19,186 patients in the cohort. Cinacalcet use was defined as first cinacalcet prescription between 1 November 2004 and 31 December 2006. The final study population included 5976 cinacalcet patients and 13,210 non-cinacalcet patients.

Demographic information, comorbidity, hospitalization, and vascular access

Demographic information was defined on 31 October 2004 for all patients and included age, sex, race, dialysis duration, primary cause of renal failure, and BMI. Comorbidity information was collected from the medical evidence report (form CMS-2728) at dialysis initiation. CMS claims data were used to collect additional comorbidity information and hospital days before study start, from 1 May to 31 October 2004, for all patients. A standard methodology was applied to collect this information.[1] Comorbid conditions included: diabetes, congestive heart failure, atherosclerotic heart disease, peripheral vascular disease, cerebrovascular accident/transient ischemic attack, dysrhythmia, other cardiovascular diseases, cancer, gastrointestinal bleeding, chronic obstructive pulmonary disease, and liver disease. The most recent vascular access type (catheter, graft, and arteriovenous fistula) in use before 1 November 2004 was characterized.

Laboratory data

Baseline laboratory data were determined from 1 August to 31 October 2004 and values closest to 31 October 2004 were used for all patients. Laboratory values included albumin, corrected calcium, phosphorus, PTH, bicarbonate, hemoglobin, Kt/V (dialysis adequacy: dialyzer clearance multiplied by time divided by volume of water in patient's body), transferrin saturation, ferritin, and white blood cell count.

Home medication determinations

The DaVita home medication files contain detailed medication information. Drug-specific files were created for cinacalcet by searching for its generic and trade name. Each file was reviewed by study personnel to verify the drug name, dose, and administration frequency. Final drug-specific sequence files contained unique dates for each prescription start, stop, and dosage change. Validity of actual cinacalcet use was confirmed by biochemical evidence of reductions in serum calcium, phosphorus, and PTH in the month immediately following cinacalcet initiation.

The study cohort was examined for additional concomitant medications often prescribed for hemodialysis patients (e.g., phosphate binders). At least one record of medication prescription within the medication class was required during the 3-month baseline period (August–October 2004) to count as a medication exposure (Table 2).

Cinacalcet exposure

Cinacalcet exposure was defined as a dichotomous variable on the basis of the presence (1, yes) or absence (0, no) of a cinacalcet prescription during the study period, and was used as a time-dependent variable on the basis of first cinacalcet prescription date. Follow-up time for all patients started on 1 November 2004. Time before first cinacalcet prescription was attributed to the non-cinacalcet treatment group. Treatment status changed with first cinacalcet prescription. Once designated as cinacalcet patients, patients were considered to be cinacalcet patients until the end of the study period.

Statistical methods

A time-dependent Cox proportional hazards regression model was used to assess all-cause and cardiovascular mortality. Baseline demographic, comorbidity, hospital days, vascular access, and laboratory information, and phosphate binder and cardiovascular medication use were used as covariates.

Cinacalcet prescription was treated as a time-dependent variable. Age, dialysis duration, BMI, most recent vascular access type, hospital days in the previous 6 months, and most recent laboratory values within 3 months of cinacalcet start were updated on cinacalcet initiation. Vascular access type and laboratory values were also updated quarterly in the follow-up period for both patient groups, except that calcium, phosphorus, and PTH were not updated quarterly as these biochemical markers may be in the causal pathway for any effect that cinacalcet may have on mortality.

Unadjusted and adjusted analyses were performed. Models for adjusted analyses were adjusted for the factors noted above. Homogeneity of treatment effect across levels of these factors was assessed through additional models, including an interaction term of treatment with one of the factors of interest (age, sex, race, dialysis duration, diabetes, access type, BMI, phosphorus, and PTH), and main effects of all variables. The final model included significant ($P<0.05$) interaction terms and all main effects. As no interactions were detected, no interaction terms were included in the final model. Patients were followed from 1 November 2004 to death. Censoring was applied for modality change (including kidney transplant), withdrawal from dialysis, loss to follow-up (lack of CMS ESRD dialysis claims), or end of 2006.

To address the possibility of lead-time bias that might be created by difference in the dialysis duration between groups, a sensitivity analysis was conducted. Groups based on dialysis duration (monthly through month 120, yearly from months 121 to 168, and a single cohort after month 168) were created. A propensity score was developed to predict factors associated with cinacalcet prescription. Factors important in this model included BMI, age, diabetes, duration of SHPT, dialysis duration, sex, race, hospital days in the preceding 6 months, albumin, calcium, phosphorus, and PTH. This propensity score was divided by intervals that corresponded to approximately 0.25 of an s.d. of the score. Cross-classifying the 24 propensity levels and the 126 dialysis duration categories yielded 2435 cohorts of cinacalcet and non-cinacalcet patients. Cinacalcet patients were matched with non-cinacalcet patients by baseline dialysis duration and propensity score. We subsequently performed the same Cox regression model with Anderson–Gill approach stratifying by matching groups.

DISCLOSURE

This study was partially supported by a research contract with Amgen. The contract provides for the authors to have final determination of the manuscript content, and the authors had sole responsibility for all data collection, analysis, reporting, and publication. GAB, MP, and SB are employed by Denver Nephrology; GS consults for Denver Nephrology. DZ, KN, and JL are employed by the Chronic Disease Research Group; WLStP is employed by the University of Minnesota and affiliated with the Chronic Disease Research Group. The Chronic Disease Research Group receives research funding from Amgen, and has received funding from Abbott. GAB, a consultant and advisor for Amgen and Genzyme, has received grant funding and speaking fees from Genzyme and has received grant funding from Shire. WLStP has received honoraria from Abbott and has served on its Advisory Board. The findings and discussion do not represent the USRDS or the National Institutes of Health.

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