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ORIGINAL ARTICLE

Survival in end stage renal disease: calcium carbonate vs. sevelamer

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ABSTRACT

Background and objective: **There is concern regarding long-term excess calcium intake in end-stage renal disease populations. Because calcium carbonate is an over-the-counter (OTC) medication, few studies have been able to track its use. The Veterans Health Administration (VA) tracks national pharmacy data for both OTC and prescription drugs. We thus compared survival in incident dialysis patients on sevelamer and calcium carbonate phosphate binders.**

Methods: **This was a retrospective cohort study of veterans initiating haemodialysis using existing VA databases. Patients were divided into calcium only (n = 769) and sevelamer only (n = 608) groups, then followed for up to 2 years until FY03 end. Survival was modelled using Cox regression adjusting for age, gender, race, marital status, service-connected disability, region, diabetes, hypertension and Charlson index. Stability of findings was examined using propensity score analysis.**

Results: **Sevelamer only vs. calcium only subjects were younger (respective mean ages 59·6 and 63·0, $P < 0{\cdot}001$) with fewer comorbidities (Charlson index 3·8 and 4·5, $P < 0{\cdot}001$). By study end, 24% of sevelamer and 30% of calcium subjects had died. Comparing sevelamer to calcium, the unadjusted hazard ratio for death was 0·62 (95% CI 0·50–0·76); the adjusted hazard ratio was 0·67 (CI 0·54–0·84). Propensity score analysis revealed similar results, with a hazard ratio of 0·65 (CI 0·54–0·80).**

Conclusions: **In a national incident dialysis cohort, sevelamer treatment was associated with improved survival compared with calcium carbonate. Further research should investigate whether the worse survival with calcium is a long-term consequence of increased calcium accumulation.**

***Keywords*: chronic, phosphate binders, renal dialysis, renal failure, survival**

BACKGROUND

End-stage renal disease (ESRD) populations are at high risk of death because of cardiovascular complications (1). This increased risk is because of a number of pathophysiologic changes that promote athero or ateriosclerosis including dyslipidaemia, hypertension and hyperhomocysteinemia (1). Recently other metabolic complications such as failure to maintain calcium and phosphorus balance have also been thought to contribute (2).

Although impaired phosphate excretion leads to secondary hyperparathyroidism and osteodystrophy, elevation of the calcium–phosphorus product also results in metastatic calcification of soft tissues, joints, blood vessels and internal viscera (2). Hyperphosphatemia and high calcium–phosphorus product have been associated with increased mortality independent of cholesterol or blood pressure levels (2). This is presumed because of an

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excess of cardiovascular complications resulting from increased cardiovascular arterial calcification.

Phosphate binders are routinely used in these patients to control phosphate levels and to lower the calcium–phosphorus product. They act by binding phosphates in the gastrointestinal (GI) tract, thus limiting systemic absorption of phosphates. They include aluminium or calcium-based agents and more recently agents such as sevelamer. Aluminium-based agents have fallen out of use because of skeletal and neurotoxicity. Calcium-based agents are commonly used and include calcium acetate and calcium carbonate. There is concern that use of calcium-based agents may be associated with hypercalcaemia and elevation of the calcium–phosphorus product despite lowering of phosphorus levels. Calcium acetate has a theoretical advantage over calcium carbonate, in that it is less pH dependent and binds phosphates more efficiently in the GI tract with less systemic calcium absorption. Despite this theoretical advantage, studies have shown no difference in serum calcium levels (3). Sevelamer, a non-absorbed, calcium and aluminium free polymer offers a potential advantage over calcium-based agents in that is has been shown to decrease serum phosphorus without raising calcium levels and thus may reduce vascular calcification and mortality (4, 5). Although sevelamer has been shown to attenuate arterial calcification compared with calcium-based phosphate binders, there is relatively little data regarding its effect on mortality (5, 6). The purpose of this study was to compare survival in new dialysis patients on sevelamer to those on calcium containing phosphate binders.

METHODS

Study subjects and sites

We identified a cohort of veterans with ESRD who were enrolled in the Veterans Health Administration (VA) healthcare system and who had initiated chronic haemodialysis during fiscal years (FY) 2002 through 2003 and followed them through to the end of FY03.

Using FY 2001–2003 VA databases, eligible subjects had: (i) ≥15 haemodialysis procedure codes in the Fee Basis Files over a 60-day period (CPT-4 90935 or 90937), or ≥15 haemodialysis clinic codes in the outpatient files (clinic codes 601–604) also over a 60-day period (7), during FY02 or 03 and (ii) 6 months of preceding utilization data without a dialysis code or dialysis clinic visit in VA administrative databases (CPT 90935–90947, or 90999) and (iii) a sevelamer or calcium containing prescription in the VA pharmacy database. The start of the study was defined based on the first eligible dialysis code or dialysis clinic code in FY02 or 03; study end was date of death or the end of FY03. Patients were divided into those prescribed calcium only (n = 769) and sevelamer only (n = 608) groups; a third group, concurrent calcium and sevelamer (n = 388) was included as part of a sensitivity analysis (see Fig. 1). All calcium prescriptions were for calcium carbonate; there were no calcium acetate prescriptions. The study protocol was approved by the Bedford VA Medical Center's institutional review board.

Data collection and sources

We used existing national databases. Demographics and comorbidities were obtained from the VA's National Patient Care Database (NPCD; FY01 through FY03 inclusive). Information on dialysis procedures and dialysis clinic visits was obtained from the NPCD and the VA's Fee Basis File. The NPCD contains information on all outpatient encounters and inpatient stays, organized into separate files. Both files include demographics (age, sex, race, marital status), up to 10 diagnostic codes per discharge or encounter (ICD-9-CM coded) and procedural codes (CPT coded in the outpatient file; ICD-9-CM coded in the inpatient file). The inpatient file also includes date of death if the patient died in hospital (8). The outpatient file includes type of clinic (e.g. dialysis clinic) and per cent service-connected disability – a measure of military disability, and access to VA healthcare; patients with ≥50% service connected disability are exempt from co-pays for medications or healthcare services (9). The Fee Basis file includes episodes of non-VA care performed under VA contract such as dialysis (CPT-coded) (10).

Medication data were obtained from the Pharmacy Benefits Management database, which contains information on all prescriptions dispensed within the VA. Vital status was obtained from the NCPD inpatient file supplemented by the

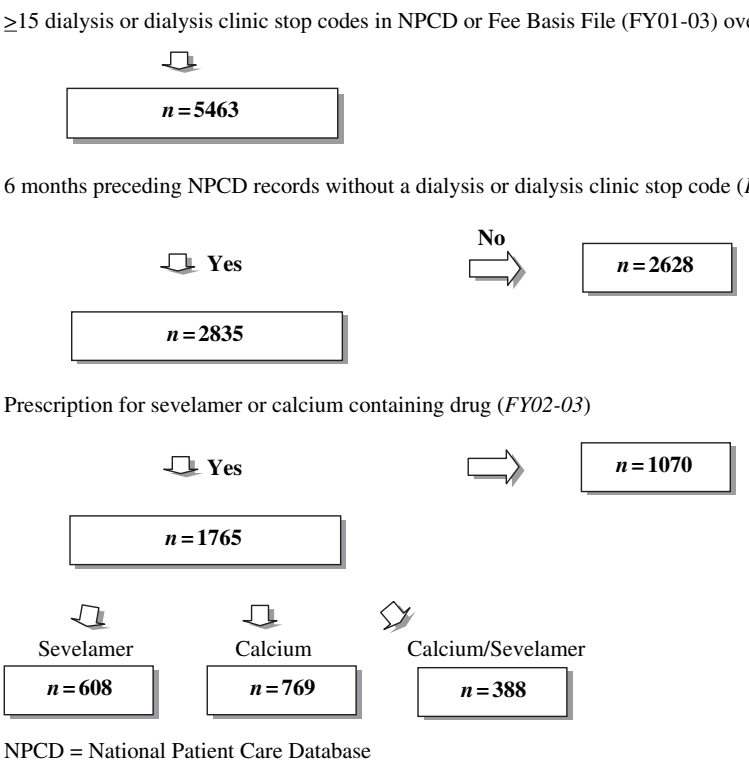

Fig. 1. Study sample – sampling strategy.

Beneficiary Identification and Records Locator Subsystem Death File (a registry of all veterans whose families have applied for VA death benefits) and the Social Security Administration Death Master File (which contains records of individuals with assigned social security numbers whose death was reported to the SSA). Limited laboratory information was obtained from the VA Decision Support System Laboratory Results Data Extract File.

Statistical analyses

Our outcome was time from study entry to death. Descriptive characteristics by drug group were compared using chi-squared analysis or analysis of variance (ANOVA) as appropriate. Survival was modelled using Cox regression (Cox proportional hazards model) adjusting for age, gender, race, marital status, service-connected disability (<50, ≥50%), geographical region (north-east, mid-atlantic, south, mid-west, west), diabetes, hypertension, and additional baseline comorbidities in the form of the modified Charlson index (11). Baseline comorbidities were identified by the presence of specified ICD-9-CM codes in the 12 months preceding and including the visit representing the start of the study. (We first tested for violation of the hazards assumption of proportionality and found the assumption was valid.)

Given the non-random assignment of patients to drug groups and the differences in several baseline characteristics between groups, we then used a propensity-score approach (12). The propensity score is the probability of assignment to a particular treatment, given the distribution of known covariates, and is used to balance the distribution of covariates across treatment groups. We used logistic regression to calculate the probability of receiving sevelamer (propensity score) for each patient in the sample adjusting for the demographics and comorbidities noted above. Subjects were next divided into tertiles based on their score. We then modelled survival by drug group within each tertile using Cox proportional hazards models. We also derived an overall hazard ratio using the propensity score approach.

Additionally we performed further models to test the robustness of our findings. We repeated the previous propensity analysis adjusting for the presence of coronary artery disease,

cerebrovascular disease, congestive heart failure and peripheral vascular disease at baseline using ICD-9-CM codes as specified in our previous work (13). We also repeated our initial propensity analysis with inclusion of baseline haemoglobin, albumin and low-density lipoprotein (LDL). Laboratory values were identified as close as possible to study entry examining the period of 6 months after and 6 months before study entry. Missing values were imputed using the sample mean.

Finally, although we lacked data on over-the-counter (OTC) calcium use, we examined the effect of known concurrent sevelamer and calcium use as identified in the pharmacy database by repeating models with inclusion of these subjects. For those with concomitant use, we considered them first as part of the sevelamer group and then as a separate group in order to test the robustness of our findings. All analyses were performed using SAS software, version 8·02 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Table 1 shows the baseline characteristics for the two groups and variables measured during the follow-up period. (Mean follow-up was 452 ± 244 days.) Sevelamer only subjects were younger than calcium only subjects (respective mean ages, 59·6 and 63·0 years, $P < 0·001$). Sevelamer subjects were more likely to be white (43%) than the calcium group (34%). Of the non-whites,

Table 1. Baseline characteristics

Variable	Sevelamer only (n = 608)	Calcium only (n = 769)	P-value
Age, years (mean ± SD)	59·6 ± 12·5	63·0 ± 12·3	<0·001
Male (%)	96·7	98·1	0·12
Race (%)			
White	43·1	34·4	<0·001
Black	45·0	45·8	
Hispanic	2·7	11·1	
Other	9·2	8·7	
Married (%)	49·0	43·6	0·04
Region (%)			
North-east	25·8	28·0	<0·001
Mid-Atlantic	35·9	17·6	
South	18·9	22·1	
Mid-west	8·7	19·5	
West	10·7	12·9	
Service connected disability, ≥50% (%)	36·5	25·6	<0·001
Comorbidities			
Hypertension (%)	66·3	72·2	0·02
Diabetes (%)	43·9	52·3	0·002
Coronary artery disease (%)	38·3	38·9	0·83
Congestive heart failure (%)	25·3	31·3	0·01
Cerebrovascular disease (%)	14·5	14·6	0·96
Peripheral vascular disease (%)	25·2	27·2	0·40
Charlson index (mean ± SD)	3·8 ± 2·6	4·5 ± 2·8	<0·001
Any hospitalization during study (%)	83·7	89·3	0·002
Deaths (%)	24·3	29·7	0·03
Follow-up, days (mean ± SD)	516·5 ± 229·1	417·4 ± 230·1	<0·001
Days on Drug (mean ± SD)	324·5 ± 190·9	224·6 ± 157·4	<0·001
Haemoglobin, g/dL (mean ± SD)	11·1 ± 2·1	10·9 ± 1·9	NS
LDL, mg/dL (mean ± SD)	85·2 ± 35·9	89·3 ± 40·7	NS
Albumin, g/dl (mean ± SD)	3·4 ± 0·6	3·2 ± 0·6	<0·004

SD, standard deviation; LDL, low-density lipoprotein; NS, not significant.

the percentage of blacks were similar in both groups, but the calcium group had a higher percentage of hispanic subjects (11% vs. 3%). Sevelamer subjects were also more likely to have ≥50% service connected disability (37% vs. 26%) and to be from the mid-Atlantic than calcium subjects. In addition, sevelamer subjects had fewer comorbidities as measured by those with diabetes, hypertension and congestive heart failure. Sevelamer subjects also had lower Charlson index scores than subjects on calcium (respective scores were 3·8 for sevelamer only and 4·5 for calcium only). However, there was no difference in baseline prevalence of other cardiovascular conditions such as coronary artery disease, cerebrovascular or peripheral vascular disease. Over 80% of subjects in both groups had a hospitalization during the study period. By study end, 24% of the sevelamer and 30% of the calcium group had died. Mean haemoglobin and LDL was similar between groups; subjects in the calcium group had lower albumins. Of note, laboratory values were missing in 50% of the calcium group and 70% of the sevelamer group. Subjects with available laboratory values were more likely to have more comorbidities but were similar in age to those with missing values. We also found a strong negative correlation between Charlson index score and albumin.

Comparing sevelamer only to calcium only, the unadjusted hazard ratio for death was 0·62 (95% CI 0·50–0·76). Adjusting for age, gender, race, marital status, service-connected disability (<50, ≥50%), geographical region, diabetes, hypertension and Charlson index, the hazard ratio was 0·67 (CI 0·54–0·84) indicating better survival in the group on sevelamer (Table 3).

Our logistic model to derive propensity scores had a *c*-statistic of 0·69 indicating moderate fit. Although the propensity score is an aggregate risk score, when comparing drug groups by tertile (Table 2), we can see that within each tertile subjects were similar with respect to age, race and comorbidities. Using the propensity score in our survival analysis, patients on sevelamer similarly had better survival than those on calcium; this difference was statistically significant in all but the highest tertile (see Table 3). Repeating analyses, adjusting for cardiovascular comorbidities instead of the Charlson index or including laboratory values had little impact on results (respective propensity model *c*-statistics were 0·68 and 0·75; results not shown, available upon request).

Table 2. Baseline characteristics by tertile of propensity score

	Tertile 1		Tertile 2		Tertile 3	
Variable	Sevelamer, n = 94	Calcium, n = 285	Sevelamer, n = 406	Calcium, n = 433	Sevelamer, n = 96	Calcium, n = 38
Age (mean ± SD)	65·5 ± 10·2	67·9 ± 10·8	60·3 ± 12·2	60·5 ± 12·2	51·6 ± 11·4	54·9 ± 12·2
White (%)	19·1	19·3	45·6	41·8	56·3	63·2
North-east (%)	25·5	18·6	32·0	37·0**	7·3	5·3
Mid-Atlantic (%)	0·0	0·0	32·0	22·4	86·5	94·7
South (%)	21·3	23·9	20·9	22·9	6·3	0·0
Midwest (%)	36·2	42·1	4·4	5·5	0·0	0·0
West (%)	17·0	15·4	10·6	12·2	4·2	0·0
Service connected disability ≥50% (%)	10·6	12·6	35·0	30·5	67·7	65·8
Hypertension (%)	77·7	83·9	69·7	67·2	49·0	63·2
Diabetes (%)	60·6	67·7	47·0	46·9	18·8	15·8
Charlson index (mean ± SD)	5·3 ± 2·6	5·6 ± 2·6	3·8 ± 2·5	3·9 ± 2·6	2·4 ± 2·1	2·5 ± 1·8
Deaths (%)	21·3	25·6	25·1	32·8*	25·0	28·9

*P < 0·05, **P < 0·001.

Table 3. Survival model

Sample	Time to death sevelamer vs. calcium hazard ratio (95% CI)
Overall; using baseline multivariate Cox model	0·67 (0·54, 0·84)**
Overall; using propensity score model	0·65 (0·52, 0·80)**
Tertile 1	0·60 (0·36, 0·99)*
Tertile 2	0·66 (0·51, 0·85)**
Tertile 3	0·54 (0·26, 1·14)

Using baseline cardiovascular comorbidities – coronary artery disease, cerebrovascular disease, congestive heart failure and peripheral vascular disease – instead of Charlson index or adding haemoglobin, low-density lipoprotein and albumin in the logistic model for the propensity score, did not appreciably change results.
*$P < 0·05$, **$P < 0·001$.

In addition, models that included those who were known to be taking both sevelamer and calcium containing binders continued to show a survival advantage for the sevelamer group when these subjects were added to the sevelamer group. When analysed as a separate group, the group taking both sevelamer and calcium also had a survival advantage compared with the calcium only group (data not shown; available from authors).

DISCUSSION

Among veterans with ESRD newly started on haemodialysis, use of sevelamer was associated with improved survival compared with subjects taking only calcium-carbonate as a phosphate binder after 2 years of follow-up.

There are surprisingly few comparable studies (6, 14, 15). A follow-up study of a small trial of new dialysis patients ($n = 127$) initially randomized to sevelamer vs. calcium containing phosphate binders designed to examine coronary artery calcification scores at 18 months, found a significant survival benefit in favour of sevelamer at a median follow-up of 44 months, with an adjusted hazard ratio of 0·32 (6). The Dialysis Clinical Outcomes Revisited study, an as of yet unpublished randomized trial, compared survival between sevelamer and calcium-based phosphate binders (14). Investigators enrolled approximately 2000 prevalent haemodialysis patients and followed them over a 3-year period. They found a non-significant benefit in terms of reduced all-cause mortality in the sevelamer arm. Statistical significance was only achieved in terms of mortality benefit in those over 65, and this association was strengthened if they had used sevelamer for more than 2 years.

An observational study, a case–control study of Medicare patients on dialysis, examined mortality risk and risk of all-cause first hospitalization during a 17-month follow-up period among 152 sevelamer-treated patients compared with those not on sevelamer (15). Although, subjects were not new dialysis patients, prior time on dialysis was adjusted for in the models. There were more deaths among control subjects (101/1000 patients at risk vs. 67/1000, hazard ratio 0·56 for death among cases compared with controls). However, the study was underpowered to show a significant mortality difference.

This is one of the largest observational studies examining outcomes in haemodialysis patients and one of the first to analyse a cohort of incident dialysis subjects. This study is unique in that national pharmacy data are used that include calcium carbonate phosphate binders, a medication that is often not tracked in other healthcare systems because it is usually prescribed OTC. The VA, one of the nation's largest integrated healthcare systems has a system of medication distribution that keeps records of prescription and OTC medications. Our results are robust as evidenced by the consistency of our findings when we repeated models including the more rigorous propensity approach or adjusted for individual cardiovascular comorbidities or laboratory values.

This study is limited by a lack of laboratory data on calcium and phosphate, variables that have been shown to be associated with increased mortality in dialysis patients (2). However, we were able to incorporate albumin and haemoglobin, two variables that are associated with mortality in other studies, without any change in our results (16, 17). Our sample also consists of veterans who are predominantly male and thus our results may not be generalizable to other populations. However, the advanced age and multiple comorbidities found in our VA sample is typical of other chronic dialysis

populations such as those receiving Medicare (18). Additionally, we were unable to reliably identify and thus did not include subjects on peritoneal dialysis or those who obtained their calcium carbonate OTC. Although exclusion of peritoneal dialysis patients may have limited our sample size, we would not expect this to appreciably bias our results in any particular direction. When we repeated our analysis including subjects who were on calcium concomitant with sevelamer during the study period, we found persistence of the survival advantage for sevelamer. Finally, we did not have information on cause of death and thus, cannot confirm that the increased death risk in the calcium group was because of an excess of cardiovascular events.

In a national incident haemodialysis cohort, sevelamer treatment was associated with improved survival compared with calcium carbonate phosphate binders. This finding is significant because to date no major interventions including treatment with erythropoietin or atorvastatin have been shown to have an impact on survival in chronic dialysis patients (19, 20). Further large controlled clinical trials in incident dialysis populations are necessary to confirm our findings. Further research may also confirm whether the worse survival observed in the calcium group is a long-term consequence of increased calcium accumulation.

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