Initiation of Sevelamer and Mortality among Hemodialysis Patients Treated with Calcium-Based Phosphate Binders

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Abstract

Background and objectives Prior studies have shown that sevelamer attenuates progression of arterial calcification and may reduce the risk of death compared with calcium-based phosphate binders. In clinical practice, however, sevelamer is used not only as an alternative but also as an add-on therapy in patients already being treated with calcium-based phosphate binders. We analyzed the Dialysis Outcomes and Practice Patterns Study (DOPPS) data to test the hypothesis that the initiation of sevelamer is associated with improved survival in patients on hemodialysis treated with calcium-based phosphate binders.

Design, setting, participants, & measurements We included 12,564 patients from DOPPS phase 3 and phase 4 (2005–2011) who were prescribed calcium-based phosphate binders at baseline or before sevelamer treatment. Mortality risk was assessed using a sequential stratification method to identify as-yet-untreated patients who were appropriately matched to the newly treated patients on the basis of their risk of death.

Results Of 12,564 patients, 2606 were subsequently treated with sevelamer hydrochloride or sevelamer carbonate. After beginning sevelamer therapy, mean serum phosphorus levels decreased by 0.3 mg/dl in the first 4 months and gradually decreased thereafter. We matched 2501 treated patients with at least one as-yet-untreated patient. Patients treated with sevelamer had a 14% lower risk for mortality compared with as-yet-untreated patients (hazard ratio, 0.86; 95% confidence interval, 0.76 to 0.97). Similar results were observed in the sensitivity analyses when changing the matching calipers or the treated and as-yet-untreated ratios, and by using propensity score matching.

Conclusions The use of sevelamer as an add-on or alternative therapy to calcium-based phosphate binders is associated with improved survival in patients on maintenance hemodialysis.

Clin J Am Soc Nephrol 12: 1489–1497, 2017. doi: https://doi.org/10.2215/CJN.13091216

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Introduction

Hyperphosphatemia is an almost inevitable consequence of ESRD. Observational studies have identified hyperphosphatemia as an independent risk factor for cardiovascular disease and mortality in patients receiving dialysis (1–3), and controlling serum phosphorus has been a key focus for clinicians in order to affect clinical outcomes. For many years, the predominant pharmacologic therapy for hyperphosphatemia was a calcium-based phosphate binder, such as calcium carbonate or calcium acetate. However, these binders have been linked to arterial calcification (4), which poses additional challenges for clinicians treating patients with elevated phosphorus levels and increased risk of cardiovascular events. Indeed, approximately half of the participants in phase 1 (1996–2001) of the Dialysis Outcomes and Practice Patterns Study (DOPPS) who were prescribed calcium-based phosphate binders had serum phosphorus levels >5.5 mg/dl. The same proportion of patients had serum calcium levels >9.5 mg/dl (5), suggesting that the efficacy of these binders may be limited at doses that do not have a profound effect on serum calcium.

Sevelamer hydrochloride is a calcium-free, resin-based phosphate binder that has been available since 1998 and has recently been replaced by sevelamer carbonate in several countries. Because excessive calcium loading may exacerbate vascular calcification, previous randomized controlled trials have focused on whether the calcium-free binder, sevelamer, might attenuate the progression of coronary artery calcification, and whether it reduces the risk of mortality in a head-to-head comparison with calcium-based phosphate binders (6–9). However, although some studies reported potential benefits, results of three separate meta-analyses assessing the comparative superiority of noncalcium-based versus calcium-based binders were discordant (10–12), thus indicating ongoing uncertainty. Further, unlike the circumstances of these prior clinical trials, sevelamer is used not only as an

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alternative but also as an adjunct to calcium-based phosphate binders, particularly when further increases in calcium-based binder doses are not possible due to the risk of hypercalcemia or calcium overload, according to the current international guideline (13). Thus, the use of sevelamer has the potential to contribute to both the prevention of calcium overload and improvements in hyperphosphatemia, both of which may lead to improved clinical outcomes. However, whether the initiation of sevelamer therapy improves the survival of patients receiving dialysis has not yet been investigated.

Therefore, the aim of this study was to test the hypothesis that either add-on or switch therapy with sevelamer is associated with improved survival in patients who are already being treated with calcium-based phosphate binders, using data from the worldwide DOPPS. To better estimate the survival effect of sevelamer treatment, we applied a sequential stratification method that was developed to compare post-treatment survival rates with survival rates observed theoretically in the absence of treatment (14,15).

Materials and Methods

Data Source

The DOPPS was a prospective cohort study of in-center hemodialysis patients ≥18 years old in 12 countries (Australia, Belgium, Canada, France, Germany, Italy, Japan, New Zealand, Sweden, Spain, the United Kingdom, and the United States). The DOPPS study design has been described previously (16,17). Briefly, the study population was composed of randomly selected patients from a random sample of dialysis facilities within each country. Demographics and information on comorbid conditions were obtained at study entry. Data on monthly laboratory values and prescription medications were abstracted from patient records at baseline and again every month (DOPPS phase 4) or every 4 months (DOPPS phase 3). Study approval was obtained by a central institutional review board and local ethics committees as required. Informed patient consent was obtained in accordance with local requirements.

Study Population

The current analysis included study participants in DOPPS phase 3 (2005–2008) and phase 4 (2009–2011) who were prescribed a calcium-based phosphate binder at study enrollment or who began calcium-based phosphate binder treatment after enrollment. Patients who were prescribed sevelamer at study enrollment or who began taking sevelamer before initiating a calcium-based phosphate binder were excluded. Patient-months before the initiation of a calcium-based phosphate binder were also excluded from the analysis.

Statistical Analyses

Our exposure of interest was the initiation of sevelamer hydrochloride or sevelamer carbonate treatment during the DOPPS follow-up. The objective of this analysis was to compare post-treatment survival in sevelamer-treated patients with survival in the absence of sevelamer treatment in similar as-yet-untreated patients. Standard methods treating sevelamer as time-invariant would fail whether we begin follow-up at study entry or at sevelamer initiation because they would erroneously use future information on sevelamer prescription to determine what exposure should be assigned or when to begin follow-up. A standard time-dependent approach would likely fail to account for confounding by indication, *i.e.*, sevelamer prescription is often driven by mortality risk factors. To avoid these biases and obtain the most accurate effect estimate, we thus implemented a sequential stratification method (14,15) to identify as-yet-untreated patients who were appropriately matched to the newly sevelamer-treated patients on the basis of their risk of death.

For each patient's survival time, we computed a prognostic score (18) on the basis of the pretreatment hazard of mortality as a function of the following variables: age, sex, time on dialysis, body mass index, single-pool Kt/V, 13 comorbid conditions (listed in Table 1), albumin, hemoglobin, predialysis BUN, creatinine, calcium, phosphorus, intact parathyroid hormone (PTH), total cholesterol, erythropoiesis-stimulating agent use, intravenous vitamin D use, oral vitamin D use, calcium carbonate use, lanthanum carbonate use, calcium channel blocker use, and angiotensin converting enzyme inhibitor/angiotensin II receptor blocker use. When calculating prognostic score at each time point, we used only preceding variables so that they could not be influenced by subsequent changes in therapy (*e.g.*, sevelamer initiation). We then matched each sevelamer-treated patient with as-yet-untreated patients. Each patient was matched to controls within the same DOPPS phase and country with similar prognostic scores, constituting a stratum; "similar" was defined as a hazard ratio (HR) of mortality between $1/\alpha$ and α. Different calipers were tested in sensitivity analyses, but α=1.05 was used in the primary analysis. One-to-many matching was implemented, using all matched controls with an HR within the caliper. Sevelamer-treated patients who could not be matched to any as-yet-untreated patients were excluded. Figure 1 provides an illustration of how patients were matched, using hypothetic scenarios. For additional details regarding the sequential stratification method, see Li *et al.* (14) and Schaubel *et al.* (15).

In the prognostic score-matched analysis, the association with mortality for treated patients and as-yet-untreated patients was assessed using Cox regression stratified by each matched set of patients and controlling for the differential prognostic score between treated patients and matched as-yet-untreated patients. Follow-up started at sevelamer initiation (for treated patients) or the time-matched point (for as-yet-untreated controls), and continued until death, study phase end, or 7 days after leaving the facility due to loss to follow-up, transplantation, or modality switch (whichever occurred first). For as-yet-untreated controls, follow-up was also censored at sevelamer initiation. Patients initiating sevelamer were considered "always on" regardless of subsequent discontinuation. The proportional hazards assumption for all model covariates was confirmed by plotting log-log survival curves. To account for the effect of dependent censoring because of sevelamer initiation, each patient was weighted using the inverse probability of censoring weighting method. Nonindependence of patients who were included in the final analysis multiple times was accounted for using sandwich-type SEM estimates.

We performed several sensitivity analyses to test the robustness of our findings. We separately estimated the effect of sevelamer "add-on" and "switch." We also varied the methodology regarding how patients were matched by

Table 1. Patient characteristics of the overall cohort and the prognostic score-matched cohort

Characteristic	Overall Cohort, n=12,564[a]	Prognostic Score-Matched Cohort[b]	
		Control Strata, N Strata=2501[c]	Sevelamer-Treated Patients, N Patients=2501
Demographics			
Age, yr	64±14	64±10	61±14
Men, %	60	59	58
Time on dialysis, mo	24 (7–64)	44 (30–71)	25 (6–65)
BMI, kg/m^2	25.7±6.2	25.5±3.5	26.1±6.3
Single-pool Kt/V	1.45±0.32	1.46±0.15	1.43±0.32
Comorbidities, %			
Coronary heart disease	45	43	44
Cancer	14	13	12
Other cardiovascular disease	32	30	31
Cerebrovascular disease	16	16	14
Congest heart failure	33	31	34
Diabetes	45	43	45
GI bleeding	5	4	4
Hypertension	84	84	85
Lung disease	13	11	12
Neurologic disease	11	10	9
Psychiatric disorder	14	13	13
Peripheral vascular disease	27	24	24
Recurrent cellulitis/gangrene	9	7	8
Laboratory tests			
Albumin, g/dl	3.7±0.5	3.8±0.3	3.8±0.4
Hemoglobin, g/dl	11.3±1.5	11.4±0.9	11.3±1.4
BUN (predialysis), mg/dl	61±18	61±9	63±18
Creatinine, mg/dl	8.4±3.0	8.8±2.2	9.3±2.9
Calcium, mg/dl	8.9±0.9	9.0±0.3	9.2±0.9
Phosphorus, mg/dl	5.2±1.6	5.1±0.8	5.8±1.7
Intact PTH, pg/ml	193 (98–336)	243 (172–324)	217 (105–380)
Total cholesterol, mg/dl	160±42	159±19	159±41
Medication, %			
ESA	87	88	88
Active vitamin D derivatives[d]			
Oral	33	37	34
IV	24	22	24
Calcium carbonate[e]	69	63	60
Lanthanum carbonate	5	6	6
Calcium channel blocker	39	38	40
ACEI/ARB	42	41	43

Data are shown as mean±SD, median (interquartile range), or percentage. BMI, body mass index; GI, gastrointestinal; PTH, parathyroid hormone; ESA, erythropoiesis-stimulating agent; IV, intravenous; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

[a]All values were obtained at the time of first prescription of calcium-based phosphate binders in the Dialysis Outcomes and Practice Patterns Study.

[b]All values were obtained at the time point of prognostic score calculation for matching (*i.e.*, preceding the starting point for survival analysis).

[c]N control patients per stratum ranged from 1 to 91 for a total of 9594 distinct patients; note that patients could contribute to more than one stratum. Each stratum was assigned equal weight for calculating means.

[d]Includes calcitriol, doxercalciferol, paricalcitol, maxacalcitol, alphacalcidol, and falecalcitriol.

[e]Because the study population was restricted to those who had been prescribed calcium-based phosphate binders, all patients not prescribed calcium carbonate were prescribed calcium acetate.

prognostic score: (*1*) prognostic score matching at 1:5 ratios rather than using all possible matches; (2) matching at 1:9 ratios rather than using all possible matches; (3) matching with a narrower caliper of 1.01 instead of 1.05; and (*4*) matching with a wider caliper of 1.10 instead of 1.05. We also performed a separate analysis using propensity score matching (19) instead of prognostic score matching.

In addition to mortality analyses, changes in serum phosphorus, calcium, and intact PTH from 8 months before to 16 months after treatment with sevelamer were summarized every 4 months using mean (SEM) or median (interquartile range [IQR]).

Baseline missing data were imputed using IVEware (20) on the basis of the sequential regression imputation

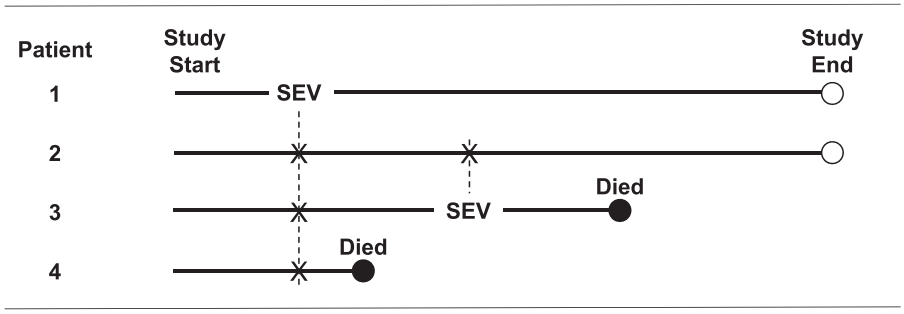

Figure 1. | **Illustration of sequential stratification method for 4 hypothetical patients.** Finding controls for each sevelamer initiator using the example illustrated. Patient 1 could be matched to patient 2, 3, or 4 (if similar mortality risk at sevelamer initiation), with mortality follow-up beginning at time of sevelamer initiation for patient 1. All were alive and as-yet-untreated at the time patient 1 initiated sevelamer. Follow-up for patient 3 would be censored at time of sevelamer initiation. Patient 3 could be matched to patient 2 only (if similar mortality risk at sevelamer initiation), with mortality follow-up beginning at time of sevelamer initiation for patient 3. Patient 4 had already died at the time patient 3 initiated sevelamer. Patient 1 had already initiated sevelamer and thus is not an eligible control after this point. SEV, sevelamer.

method. Follow-up missing data were predicted using linear regression within each patient. All analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, NC).

Results

Study Sample

Figure 2 illustrate the inclusion criteria of the study. A total of 27,847 patients participated in phase 3 or phase 4 of the DOPPS, and our primary analysis included 12,564 DOPPS patients who were prescribed calcium-based phosphate binders at baseline or before sevelamer prescription. Demographic and clinical characteristics of the study cohort at study baseline are shown in Table 1. Among these patients, 2606 were subsequently treated with sevelamer hydrochloride or sevelamer carbonate. In the DOPPS, the median time between the first prescription of calcium-based phosphate binders and the first prescription of sevelamer was 8 months (IQR, 4–15 months).

Sevelamer Use and Changes in Mineral Metabolism

Biochemical parameters after the initiation of sevelamer are shown in Figure 3. Mean serum phosphorus levels decreased by 0.3 mg/dl during the first 4 months of treatment and continued to decrease gradually thereafter. There were no clinically meaningful changes in serum levels of calcium and PTH during the study.

Prognostic Score–Matched Analysis

During a median follow-up of 19 months (IQR, 9–30), 2408 patients died (12.0/100 person-years) in the study cohort. After matching with prognostic scores, 2501 sevelamer-treated patients remained in the analysis with at least one matched as-yet-untreated patient. The 105 sevelamer initiators who were not matched to any controls were much younger (mean age, 53.8 versus 61.4 years), healthier (mean albumin, 4.0 versus 3.8 g/dl), and had lower prevalence of comorbidities (diabetes, 21% versus 45%; coronary heart disease, 31% versus 44%) compared with the sevelamer initiators who were matched to controls; see Supplemental Table 1 for complete comparison. Among the 2501 matched treated patients, 1560 (62%) were also prescribed a calcium-based phosphate binder at the time of sevelamer initiation ("add-on" therapy) and 941 (38%) were not prescribed a calcium-based phosphate binder at the time of sevelamer initiation ("switchers"). The number of matched as-yet-untreated patients ranged from 1 to 91 across matched sets, with a median of 12 (IQR, 5–27). The right side of Table 1 shows the demographic and clinical characteristics collected at the time of prognostic score matching (*i.e.*, at the starting point of the survival analysis), comparing patients who were subsequently treated with sevelamer with those as yet untreated. Because patients were matched by prognostic scores (outcome) rather than by propensity scores (treatment), some patient characteristics will not appear to be "balanced" across treatment groups, although on average our method properly accounts for differences in all measured confounders (14,15).

Our primary result showed that patients treated with sevelamer had a lower risk of mortality compared with as-yet-untreated patients (HR, 0.86; 95% confidence interval [95% CI], 0.76 to 0.97). Figure 4 shows the HRs for mortality associated with sevelamer prescription according to baseline clinical characteristics. The survival benefit of sevelamer treatment was more pronounced in both younger patients (P=0.04 for interaction) and those with lower serum albumin (P=0.03 for interaction). We found no evidence for effect modification by serum phosphorus levels.

Sensitivity Analyses

We performed several sensitivity analyses to test the robustness of our findings. First, we separately estimated the effect of "add-on" and "switching"; the HR (95% CI) of mortality was 0.80 (0.69 to 0.94) for add-on therapy (versus matched controls) and 0.94 (0.78 to 1.14) for switchers (versus matched controls). We also varied the methodology regarding how patients were matched by prognostic score, and observed qualitatively similar results under the following alternatives: (*1*) at 1:5 ratios rather than using all possible matches (HR, 0.81; 95% CI, 0.71 to 0.93); (*2*) at 1:9 ratios rather than using all possible matches (HR, 0.90; 95% CI, 0.78 to 1.05); (*3*) with a narrower caliper of 0.01 instead of 0.05 (HR, 0.91; 95% CI, 0.79 to 1.05); and (*4*) with a wider caliper of 0.10 instead of 0.05 (HR, 0.85; 95% CI, 0.75 to 0.95).

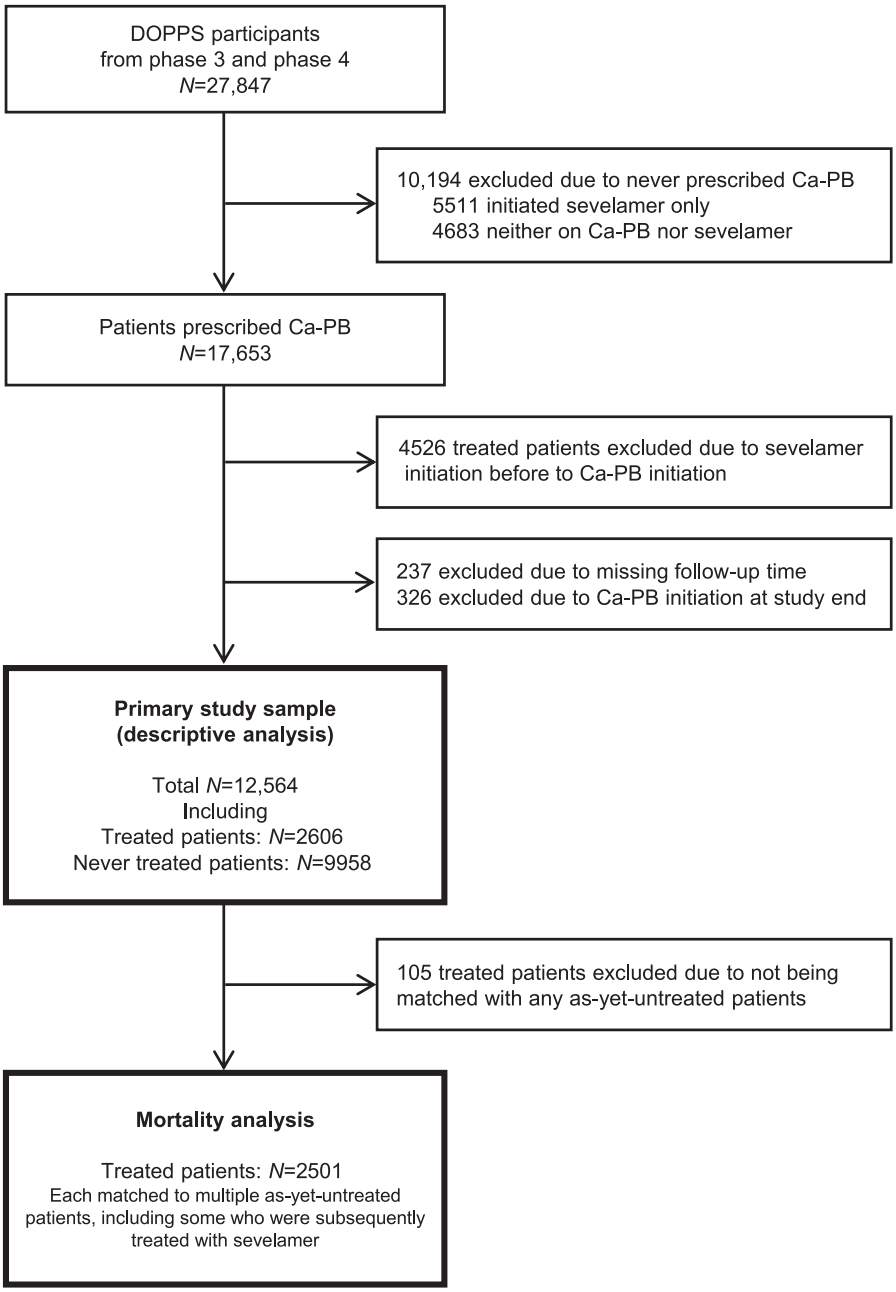

Figure 2. | **Flow chart illustrating study inclusion and exclusion criteria.** Ca-PB, calcium-based phosphate binder; DOPPS, Dialysis Outcomes and Practice Patterns Study.

Finally, we performed a propensity score–matched analysis and found similar results (HR, 0.90; 95% CI, 0.79 to 1.01).

Discussion

In this international DOPPS cohort, we found that sevelamer was frequently prescribed for controlling hyperphosphatemia, with approximately 20% of patients on calcium-based phosphate binders being subsequently treated with sevelamer either as a switch or as an add-on therapy. Among patients who were treated with calcium-based phosphate binders, the initiation of sevelamer led to reductions in serum phosphorus levels and was associated with a survival advantage compared with treatment without sevelamer. These data suggest a potential benefit of prescribing sevelamer in patients on maintenance hemodialysis currently receiving calcium-based phosphate binder treatment.

Sevelamer is the first noncalcium-based phosphate binder to become available after the widespread introduction of calcium-based phosphate binders. The efficacy of sevelamer as compared with calcium-based phosphate binders has been extensively evaluated in several clinical studies, with particular focus on its effect on vascular calcification and mortality (6–12). However, in real-world clinical practice, sevelamer is used not only as an alternative

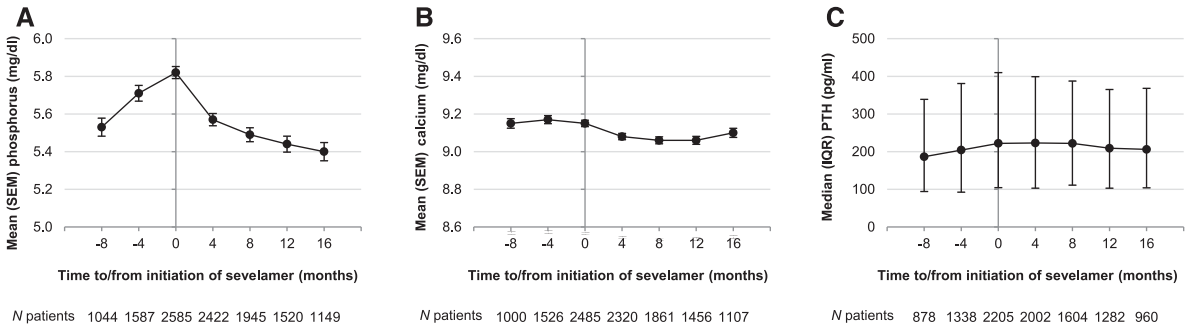

Figure 3. | Levels of biochemical parameters before and after sevelamer initiation. (A) Serum phosphorus. (B) Serum calcium. (C) Intact PTH. PTH, parathyroid hormone.

but also as an adjunct to calcium-based phosphate binder therapy. To date, no studies have specifically addressed the question of whether the use of sevelamer in that context is associated with improved clinical outcomes. To the best of our knowledge, this study is the first to demonstrate the potential benefit of add-on or switch therapy with sevelamer as compared with conventional monotherapy with calcium-based binders. Our results extend the findings from recent observational studies showing the survival benefit of phosphate-lowering therapy (21–24) and provide a new rationale for using sevelamer as a switch or add-on therapy in patients on hemodialysis being treated with calcium-based phosphate binders.

Because reasons for switching to sevelamer (*e.g.*, side effects or intolerance of calcium-based phosphate binders) may sometimes differ from reasons for add-on (*e.g.*, monotherapy failure), we performed sensitivity analyses to estimate separate effects. We observed a relatively stronger association for add-on therapy (HR, 0.80 versus matched controls; 95% CI, 0.69 to 0.94) than switching (HR, 0.94 versus matched controls; 95% CI, 0.78 to 1.14), which might suggest that the overall survival benefit associated with sevelamer could be explained by improved phosphorus control rather than reduction in calcium load. However, we caution against overinterpreting these findings because an indicator for whether patients were prescribed a calcium-based binder at the time of sevelamer initiation may not be representative of total calcium load experienced by the patient. Data on total calcium load are not available for most DOPPS patients who were sampled months or years after dialysis initiation. Furthermore, precise definitions of switch or add-on are limited in DOPPS data, because we only have indicators of use—prescriber intentions behind sevelamer initiation are not collected and reasons for initiation may overlap between switches and add-on therapy. Therefore, primary analyses combined switches with add-on therapy.

Hyperphosphatemia commonly results from excess phosphate intake, which is closely associated with overall nutrient intake (25). Thus, patients who are prescribed sevelamer for controlling hyperphosphatemia are expected to have better nutritional status, which is associated with better overall survival (26). Therefore, it is important to select nonsevelamer controls from those subjects with similar mortality risks to those in treatment with sevelamer. A sequential stratification method is one of the best approaches to avoid such sources of bias (14,15), and it enabled us to yield an accurate estimate of the survival benefit of sevelamer therapy. The treatment benefit of sevelamer remained robust throughout different analytic strategies, including a propensity score analysis that was developed to minimize selection bias by calculating the probability of receiving treatment.

There are several possible mechanisms through which sevelamer was associated with improved survival. The most plausible mechanism is that the improved control of serum phosphorus, along with decreases in the calcium load, was associated with attenuation of vascular calcification and thereby led to improved cardiovascular outcomes. Recent investigations have also revealed the toxic effects of phosphate on the aging process (27,28), which may further explain the potential benefit of prescribing sevelamer. It is, however, noteworthy that the benefit associated with sevelamer prescription was independent of pretreatment serum phosphorus levels. Furthermore, given the previous finding from the DOPPS that serum phosphorus levels of 6.1–7.0 mg/dl were associated with an 18% greater risk of mortality compared with the reference range of 3.6–5.0 mg/dl (2), the observed 0.3 mg/dl reduction in serum phosphorus alone may not completely explain the 14% risk reduction in mortality associated with sevelamer use, which suggests that additional mechanisms may be involved. One possible explanation is that the amelioration of hyperphosphatemia using sevelamer might have allowed for a more relaxed dietary phosphate restriction, which may have led to better nutritional status and consequently improved survival (29). Supporting this possibility, the survival benefit of a sevelamer prescription was pronounced in patients with lower serum albumin, a population with a typically high likelihood of poor nutritional status. Another interesting possibility pertains to the effect of sevelamer on fibroblast growth factor 23 (FGF23). Recent studies have shown that FGF23 plays a causal role in the pathogenesis of left ventricular hypertrophy (30) and immune dysfunction (31). Because sevelamer lowers FGF23 levels (32), the improved survival associated with sevelamer might be partly mediated by the attenuation of these toxic effects of FGF23. Furthermore, sevelamer has been shown to decrease circulating levels of uric acid (33), LDL cholesterol (34), and advanced glycation end products (8), which may also explain the improved survival associated with sevelamer.

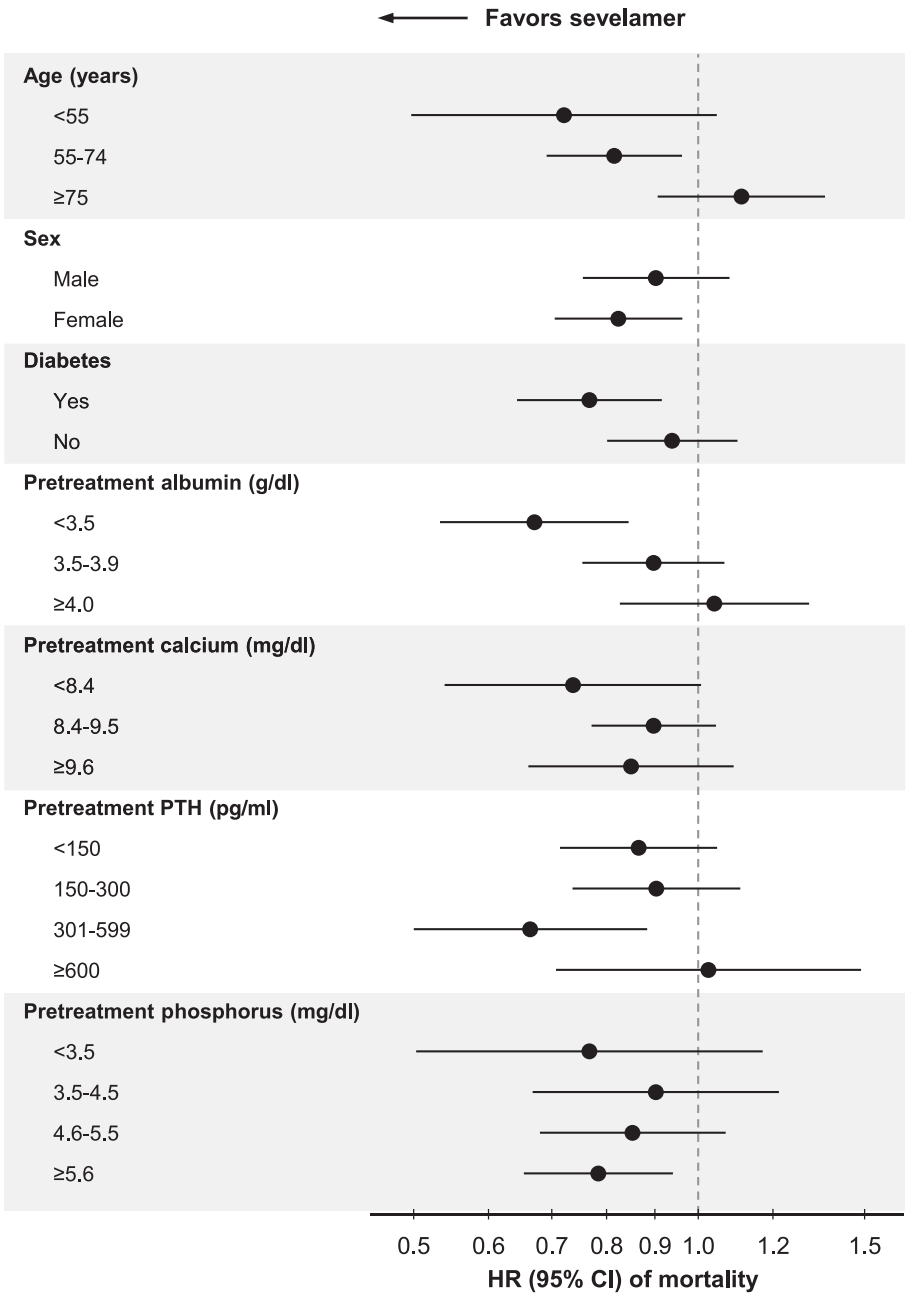

Figure 4. | **Stratified HRs (and 95% CIs) for mortality comparing sevelamer initiators with patients as yet untreated.** To take into account the potential different categories for the control patients and their paired treated patients, differences between each control patient and their paired treated patient were also adjusted for in the model. 95% CI, 95% confidence interval; HR, hazard ratio; PTH, parathyroid hormone.

In the stratified analysis, the survival benefit of sevelamer treatment was pronounced in younger patients. This finding is seemingly at odds with a previous observation from the Dialysis Clinical Outcomes Revisited (DCOR) trial showing that sevelamer decreased mortality risk in patients over 65 years of age only (9). However, it should be noted that the DCOR trial compared sevelamer with calcium-based binders, whereas our study compared the use of sevelamer as an alternative or adjunctive treatment with conventional calcium-based phosphate binder monotherapy. In other words, the DCOR trial focused almost exclusively on the adverse effect of calcium load during treatment with phosphate binders, whereas our study focused additionally on the benefit of improved control of serum phosphorus. Therefore, these apparently contradictory results may indicate that the adverse effect of calcium load is more crucial in older patients who tend to have greater calcification burden, whereas the benefit of improved control of serum phosphorus is more pronounced in younger patients who tend to have a higher dietary intake of phosphate. Future research should attempt to identify patients who would most likely benefit from alternative or combination therapy with sevelamer or other noncalcium-based phosphate binders.

This study has several potential limitations. First, the possibility that unmeasured confounders contributed to the survival benefit of sevelamer cannot be completely excluded. Although the extensive DOPPS database and detailed longitudinal data collection allowed us to perform a comprehensive analysis using a sequential stratification method, we cannot exclude residual confounding by unmeasured confounders that might affect both sevelamer prescription patterns and patient outcomes. Second, we combined data on the use of sevelamer hydrochloride and sevelamer carbonate into a single variable, due to the inconsistent availability of sevelamer carbonate across participating countries and DOPPS phases. The two types of sevelamer have different profiles in terms of the effect on metabolic acidosis (35), which might affect the potential survival benefit of sevelamer because acidosis plays a role in bone metabolism (36) and nutritional status (37). Third, our data collection methods focused on medication prescriptions on the basis of medical records, and thus we could not account for any over-the-counter calcium carbonate; only patients with a prescription for calcium carbonate were included in the study. Fourth, we did not have information as to dietary intake of phosphate or protein. It is likely that patients who were prescribed sevelamer had higher intake of both phosphate and protein than those not treated with sevelamer. Assuming that the benefit of increased protein intake outweighed the potential toxicity of a high phosphate burden, this lack of information might have caused an overestimation of the survival benefit of sevelamer, although we did adjust for multiple nutritional indicators including body mass index, albumin, creatinine, and total cholesterol. Fifth, we did not have enough information on phosphate binder dosage (sevelamer or calcium-based) to incorporate into our analysis, and thus used a Yes/No indicator of sevelamer use as the primary treatment of interest. Finally, we were unable to directly assess adherence to phosphate binder prescriptions (*e.g.*, pill counts). Data on self-reported adherence was available in DOPPS phase 4 but not phase 3 ("During the last month, how often did you skip taking your phosphate binders?") and was studied by Fissell *et al.* (38). Because timing of this survey question corresponds with either pre- or postsevelamer initiation (not both), we could not explore potential changes in adherence after initiation of sevelamer.

In conclusion, using the worldwide DOPPS cohort, we found that treatment with sevelamer was associated with a survival benefit in patients receiving hemodialysis treated with calcium-based phosphate binders. Our results provide an additional rationale for controlling serum phosphorus levels and reassert the value of sevelamer in this context. Future studies should focus on determining whether better or more intensive management of hyperphosphatemia might reduce mortality risk in patients on hemodialysis.

Acknowledgments

The Dialysis Outcomes and Practice Patterns Study (DOPPS) Program is supported by Amgen, Kyowa Hakko Kirin, and Baxter Healthcare. Additional support for specific projects and countries is provided by Amgen, AstraZeneca, the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA), the German Society of Nephrology, Hexal AG, Janssen, the Japanese Society for Peritoneal Dialysis, Keryx, Proteon, Relypsa, Roche, Società Italiana di Nefrologia, the Spanish Society of Nephrology, and Vifor Fresenius Medical Care Renal Pharma. Public funding and support is provided for specific DOPPS projects, ancillary studies, or affiliated research projects by, Australia: National Health and Medical Research Council; Canada: Canadian Institutes of Health Research and Ontario Renal Network; France: Agence Nationale de la Recherche; Thailand: Thailand Research Foundation, Chulalongkorn University Matching Fund, King Chulalongkorn Memorial Hospital Matching Fund, and the National Research Council of Thailand; United Kingdom: National Institute for Health Research *via* the Comprehensive Clinical Research Network; and United States: National Institutes of Health and Patient-Centered Outcomes Research Institute. All support is provided without restrictions on publications.

Disclosures

H.K. has received honoraria, consulting fees, and/or grant/research support from Bayer Yakuhin and Kyowa Hakko Kirin. M.T. has received consulting fees from Kyowa Hakko Kirin. S.Y. has received honoraria from Kyowa Hakko Kirin. T.N. is an employee of Kyowa Hakko Kirin. M.F. has received honoraria, consulting fees, and/or grant/research support from Astellas Pharma, Bayer Yakuhin, Kyowa Hakko Kirin, Ono Pharmaceutical, and Torii Pharmaceutical. F.T. has received consulting fees from MedScape. The remaining authors have no conflicts to report.

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Received: December 22, 2016 **Accepted:** May 30, 2017

Published online ahead of print. Publication date available at www.cjasn.org.

This article contains supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.13091216/-/DCSupplemental.