Sevelamer revisited: pleiotropic effects on endothelial and cardiovascular risk factors in chronic kidney disease and end-stage renal disease

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Abstract: Endothelial dysfunction underlies multiple cardiovascular consequences of chronic kidney disease (CKD) and antecedent diabetes or hypertension. Endothelial insults in CKD or end-stage renal disease (ESRD) patients include uremic toxins, serum uric acid, hyperphosphatemia, reactive oxygen species, and advanced glycation endproducts (AGEs). Sevelamer carbonate, a calcium-free intestinally nonabsorbed polymer, is approved for hyperphosphatemic dialysis patients in the US and hyperphosphatemic stage 3–5 CKD patients in many other countries. Sevelamer has been observed investigentially to reduce absorption of AGEs, bacterial toxins, and bile acids, suggesting that it may reduce inflammatory, oxidative, and atherogenic stimuli in addition to its on-label action of lowering serum phosphate. Some studies also suggest that noncalcium binders may contribute less to vascular calcification than calcium-based binders. Exploratory sevelamer carbonate use in patients with stages 2–4 diabetic CKD significantly reduced HbA1c, AGEs, fibroblast growth factor (FGF)-23, and total and low-density lipoprotein (LDL) cholesterol versus calcium carbonate; inflammatory markers decreased and defenses against AGEs increased. Sevelamer has also been observed to reduce circulating FGF-23, potentially reducing risk of left ventricular hypertrophy. Sevelamer but not calcium-based binders in exploratory studies increases flow-mediated vasodilation, a marker of improved endothelial function, in patients with CKD. In contrast, lanthanum carbonate and calcium carbonate effects on FMV did not differ in hemodialysis recipients. The recent INDEPENDENT-CKD randomized trial compared sevelamer versus calcium carbonate in predialysis CKD patients (investigational in the US, on-label in European participants); sevelamer reduced 36-month mortality and the composite endpoint of mortality or dialysis inception. Similarly, INDEPENDENT-HD in incident dialysis patients showed improved survival with 24 months of sevelamer versus calcium-based binders. This review discusses recent exploratory evidence for pleiotropic effects of sevelamer on endothelial function in CKD or ESRD. Endothelial effects of sevelamer may contribute mechanistically to the improved survival observed in some studies of CKD and ESRD patients.

Keywords: advanced glycation endproducts, atherosclerosis, fetuin-A, fibroblast growth factor-23, sevelamer, vascular dysfunction

Introduction

Chronic kidney disease (CKD) multiplies cardiovascular risk for affected patients even beyond the risk conferred by antecedent diabetes and/or hypertension. Patients with CKD stage 5 have 10–20 times the general public’s risk of cardiovascular death after stratification for age, gender, and ethnicity (Figure 1a) [Foley et al. 1998] and are more likely to die of cardiovascular disease than to progress to dialysis. In fact, cardiovascular
disease is the most common cause of death for patients with CKD or end-stage renal disease (ESRD). This risk stems from multiple pathogenic processes affecting the heart and vessels, e.g. atherogenic [Stenvinkel et al. 2003], inflammatory, and thrombogenic states; endothelial dysfunction; and disrupted blood pressure regulatory molecules [Kovesdy and Kalantar-Zadeh, 2008]. In addition, reduced vitamin D receptor activation, which occurs in CKD mineral and bone disorder (MBD), is associated with hypertension, left ventricular hypertrophy, vascular stiffening, and/or accelerated atherosclerosis and arteriosclerosis, all of which contribute to cardiovascular mortality [Kovesdy and Kalantar-Zadeh, 2008].

Vascular calcification is a major source of ESRD-related cardiovascular risk. It results from metabolic, inflammatory, and developmental effects of CKD (especially CKD-MBD) upon vascular cells and structures [Sage et al. 2010]. While classic CKD-related vascular calcification affects the smooth muscle layer (tunica media), hyperphosphatemia and calcium loading may also worsen calcification of atherosclerotic plaques in the endothelium (intima or neointima). Vascular calcification prevalent at dialysis initiation can progress rapidly, contributing to the high mortality risk of the first 90 days on dialysis [Block et al. 2007]. Vascular calcification also predicts mortality risk in prevalent dialysis patients. In a maintenance hemodialysis patient cohort, high overall and vessel-specific coronary artery calcification scores (101–400 or >400) predicted significantly higher 6-year mortality risk versus patients with zero calcification scores at baseline [Shantouf et al. 2010].

Phosphate binder treatment (approved for hyperphosphatemic dialysis patients in the US and hyperphosphatemic stage 3–5 CKD patients in many other countries) reduces cardiovascular risk in renal disease. Phosphate loading has deleterious effects on vascular smooth muscle (tunica media) and endothelium; it contributes to cardiovascular calcification and atherogenesis both in patients with CKD-MBD and the general population [Ellam and Chico, 2012]. In incident dialysis patients, use of phosphate binders within the first 90 days of dialysis has been observed in the following study to reduce early dialytic mortality versus patients not receiving binders [Isakova et al. 2009]. In the extension of the Renagel in New Dialysis (RIND) randomized open-label study of 129 incident hemodialysis patients, baseline vascular calcification (e.g. coronary artery calcification score) and selected phosphate binders independently predicted mortality on 44-month follow up [Block et al. 2007]. Post hoc analysis of the Cholesterol and Recurrent Events (CARE) study [Tonelli et al. 2005] of patients with prior myocardial infarctions and hyperlipidemia, including those with normal glomerular filtration rate (GFR), suggested that increasing serum phosphate even within the normal range may also be associated with cardiovascular events in renally normal persons. The CARE authors state that

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Figure 1. Increased cardiovascular mortality risk associated with Stage 5 CKD versus the general population. Reproduced with kind permission from Elsevier (Foley et al. 1998).
to 3.4, 3.5 to 3.9, and ≥4 mg/dL), a graded relation between phosphate and death was observed after adjustment for age, race, and sex \((p \text{ for trend } = 0.01)\)” [Tonelli et al. 2005]. Finally, the INDEPENDENT-HD study [Di Iorio et al. 2013] of 466 incident dialysis patients receiving sevelamer or calcium-based binders for 24 months showed that sevelamer recipients had significantly lower arrhythmic, all-cardiovascular, and all-cause mortality by month 36 than calcium-binder recipients.

Sevelamer (Figure 2) is a metal-free, nonabsorbed polymeric anion exchange resin phosphate binder. In addition to phosphate, it binds other substances in the gut (e.g., bile acids, bacterial endotoxins, and advanced glycation endproducts [AGEs]), leading to pleiotropic effects specific to a polymeric phosphate binder [Charmot, 2012]. Two formulations exist: sevelamer hydrochloride and sevelamer carbonate. Sevelamer carbonate has been shown to lower serum phosphate to the same extent as sevelamer hydrochloride; however, whereas sevelamer hydrochloride has been reported to decrease serum bicarbonate levels and contribute to metabolic acidosis in dialysis recipients, sevelamer carbonate is associated with higher bicarbonate levels and less acidosis [Fan et al. 2009; Pai and Shepler, 2009; Savica et al. 2008]. The polymeric nature of sevelamer and its ability to bind not only phosphate but also other molecules in the intestine drive its pleiotropic effects. Observed reduction of early dialytic cardiovascular mortality with sevelamer hydrochloride may have several possible mechanisms: not only lowering of serum phosphate, lipids, and reduced vascular calcification but potentially also anti-inflammatory and anti-uremic effects [Evenepoel, 2007]. Phosphate-reducing and possible phosphate-independent biochemical interactions of sevelamer are summarized in Figure 3.

Several studies (Table 1) suggest that sevelamer may be associated with less progression of coronary artery and aortic calcifications than calcium-based binders in dialysis patients, for whom it is indicated in the US [Asmus et al. 2005; Block et al. 2005; Braun et al. 2004; Chertow et al. 2002, 2003; Kakuta et al. 2011; Shantouf et al. 2010] and hyperphosphatemic patients with CKD not requiring dialysis, for whom it is also indicated under European Medicines Agency approval [Block et al. 2012; Caglar et al. 2008; Di Iorio et al. 2012; Russo et al. 2007; Yilmaz et al. 2010]. Incident dialysis patients assigned to calcium-based binder use in the 18-month parent RIND study showed progression of vascular calcification [Block et al. 2005] and increased 44-month mortality in the RIND extension [Block et al. 2007], whereas assignment to sevelamer hydrochloride use was associated with attenuated 18-month progression of vascular calcification [Block et al. 2005] and decreased 44-month mortality (Figure 4) [Block et al. 2007]. The metallic non-calcium phosphate binder lanthanum carbonate similarly was associated with less progression of coronary calcification than calcium carbonate in a pilot study of hemodialysis patients [Kalil et al. 2012]. Authors of another pilot randomized controlled trial in 45 dialysis patients concluded that ‘Lanthanum carbonate was associated with reduced progression of aortic calcification compared with CC [calcium carbonate] in HD patients over 18 months’ [Toussaint et al. 2011].

The vascular endothelium is a key mediator of vascular homeostasis [Santoro et al. 2010]. It responds to mechanical stimuli from blood flow and to blood-borne metabolic and endocrine signals; in turn it sends chemical signals to regulate vascular tone, permeability, proliferation, coagulation, and inflammation [Santoro et al. 2010]. Endothelial inflammation is one of the initiating events of atherosclerosis [Ross, 1999]. Endothelial...
Effects of Sevelamer in CKD/ESRD

**Figure 3.** Summary of proposed phosphate-reducing and phosphate-independent effects of sevelamer.

- **Phosphate-dependent**
  - In normophosphatemic CKD:
    - Reduced urinary phosphate, FE(P), and FGF-23
    - Reduced stimulus for cardiovascular calcification
  - In hyperphosphatemic CKD/ESRD
    - Lowered serum phosphate
    - Reduced sequence of hyperphosphatemia
      - Reduced stimulus for cardiovascular calcification
      - Reduced osteoclastic changes in smooth muscle
      - Reduced phosphate-mediated endothelial dysfunction

- **Phosphate-independent**
  - Avoidance of calcium load
  - Prevention, amelioration, or regression of cardiovascular calcification
  - Lowering of serum cholesterol & thus atherogenesis
  - Reduction of endothelial damage through:
    - Reduced endotoxemia & Inflammation
    - Reduced advanced glycation endproducts
    - Increased fetuin A

**Objective**
This review will discuss recent evidence for effects of sevelamer on parameters affecting vascular endothelial function.

**Normal endothelial function**
The vascular endothelium, a monolayer of endothelial cells weighing 1.5 kg with surface area equivalent to four tennis courts, acts as the main integrator of vascular homeostasis [Santoro et al. 2010]. It senses mechanical stimuli (pressure and shear stress) related to blood flow dynamics and hormonal stimuli related to vasomotor regulation [Santoro et al. 2010]. In turn, it releases biochemical mediators to regulate vascular tone, coagulation, vascular permeability, and inflammation [Santoro et al. 2010].

**Endothelial dysfunction in CKD, hypertension, and diabetes**
Endothelial dysfunction is an important common link among hypertension, diabetes, hypertensive or diabetic CKD, and their cardiovascular sequelae. Cardiovascular disorders such as atherosclerosis [Ross, 1999], peripheral and coronary artery disease, and chronic heart failure both contribute to and are worsened by endothelial dysfunction. Vascular consequences of endothelial dysfunction include impaired response to shear stress (e.g. reduced flow-mediated vasodilation [FMV]), reduced vascular compliance, inflammation, prothrombic state, increased cellular permeability,......
Table 1. Effects of sevelamer on vascular calcification in patients with CKD requiring or not requiring dialysis.

| Stage of CKD       | Studies and references                  | Populations and regimens                                                                 | Key results                                                                                                                                 |
|-------------------|----------------------------------------|----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| Dialysis recipients | Treat to Goal Study [Chertow et al. 2002] | Hemodialysis patients, N = 200, receiving sevelamer hydrochloride or calcium (acetate or carbonate) for 52 weeks | Significantly less median % changes from baseline with sevelamer than calcium in CACS (6% versus 25%, $p = 0.02$) and aortic calcification score (5% versus 28%, $p = 0.02$) |
|                   | Subanalysis of Treat to Goal Study [Chertow et al. 2003] | Hemodialysis patients, N = 108, receiving sevelamer hydrochloride or calcium acetate for 1 year | No significant changes from baseline in EBCT calcification with sevelamer; calcium acetate significantly increased calcification scores at coronary arteries (mean $+182 \pm 350$, median $+20$, $p = 0.002$) and aorta (mean $+181 \pm 855$, median $+73$, $p < 0.0001$). |
|                   | [Braun et al. 2004] | Adults on hemodialysis, N = 114, receiving open-label sevelamer hydrochloride or CaCO$_3$ for 52 weeks | Sevelamer patients did not experience increases in EBCT calcification. CaCO$_3$ patients had significant median increases from baseline in aortic (+32%, $p < 0.01$) and coronary artery (+34%, $p < 0.01$) calcification. |
|                   | [Asmus et al. 2005] | Adults on hemodialysis, N = 72, randomized to sevelamer hydrochloride or CaCO$_3$ for 2 years | CaCO$_3$ patients had significantly worse median increases in EBCT calcification scores than sevelamer patients at the coronary artery (CaCO$_3$ 484, $p < 0.0001$, sevelamer 37, $p = 0.3118$, between-group $p = 0.0178$) and aorta (CaCO$_3$ 610, $p = 0.0003$, sevelamer 0, $p = 0.5966$, between-group $p = 0.0039$). |
|                   | [Block et al. 2005] | New adult hemodialysis patients, N = 129, randomized to open-label sevelamer hydrochloride or calcium binders for 18 months | Calcium recipients had more rapid and severe increases in EBCT CACS than sevelamer recipients ($p = 0.056$ at 12 months, $p = 0.01$ at 18 months). |
|                   | [Shantouf et al. 2010] | Cross-sectional study of maintenance hemodialysis patients (N = 117 who had received either sevelamer hydrochloride alone or calcium binders alone) | CACS was significantly lower with sevelamer than calcium (283 ± 83 versus 494 ± 94, $p = 0.02$). Odds ratio of a CACS ≥ 400 versus CACS ≤ 10 with calcium use was 4.35 (95% CI 1.5–9.9, $p = 0.008$), adjusted for case mix variables, diabetes, inflammatory factors, and lipid-lowering agent use. |
|                   | [Kakuta et al. 2011] | Adults on hemodialysis, N = 183, receiving sevelamer hydrochloride or calcium carbonate for 12 months | Sevelamer recipients had 112.3 points less CACS increase from baseline than calcium recipients ($p < 0.001$). |
| Patients with CKD stages 3–5 not requiring dialysis | [Russo et al. 2007] | Predialysis CKD patients (N = 90) consuming low-phosphate diet with or without sevelamer or calcium carbonate for an average of 2 years | Sevelamer left TCS unchanged from baseline to final visit (415 ± 153 versus 453 ± 127; $p = $NS) whereas calcium (340 ± 38 versus 473 ± 69; $p < 0.001$) and diet only (369 ± 115 versus 547 ± 175; $p < 0.001$) increased TCS. Annual rate of TCS progression was 36 ± 32 with sevelamer, 178 ± 40 with calcium, and 205 ± 82 with diet only. |

(Continued)
Table 1. (Continued)

| Stage of CKD | Studies and references | Populations and regimens | Key results |
|--------------|------------------------|--------------------------|-------------|
| INDEPENDENT-CKD study [Di Iorio et al. 2012] | Consecutive CKD stage 3–4 outpatients (N = 212) randomized to receive sevelamer or calcium carbonate and followed for ≥36 months | Among patients with baseline CACS > 0, 24 sevelamer patients and 2 calcium patients had significant CAC regression. New-onset CAC affected 12.8% of sevelamer patients but 81.8% of calcium patients; calcium recipients also had more severe CAC scores. |
| PNT study [Block et al. 2012] | Adults with CKD (MDRD eGFR 20–45 ml/min/1.73 m²), randomized to receive placebo, sevelamer carbonate, lanthanum carbonate, or calcium acetate for median follow up of 249 days; n = 98 scanned for coronary and abdominal-aortic calcification. | No patients with zero baseline calcium scores experienced increased calcification during treatment. Among the 81 patients with nonzero baseline calcification scores, binder recipients experienced significant increases in median annualized percent change of coronary and abdominal-aortic calcification versus placebo recipients. Calcium acetate had the most pronounced effects on calcification. |

CACS, coronary artery calcium score; CI, confidence interval; CKD, chronic kidney disease; EBCT, electron beam computed tomography; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease equation; PNT, Phosphate to Normal Treatment; TCS, total calcium score.

Pleiotropic effects of sevelamer affecting endothelial function and cardiovascular risk

In addition to lowering serum phosphate and reducing calcium burden, sevelamer hydrochloride or carbonate exerts diverse pleiotropic effects on parameters associated with cardiovascular risk in CKD patients. Specifically, improvements in endothelial and/or vascular function [Brandenburg et al., 2009; Nikolov et al., 2006; Caglar et al., 2008; Takenaka and Suzuki, 2005; Yilmaz et al., 2012] have been shown in exploratory studies to increase FMV, a marker of improved endothelial function in patients with CKD [Caglar et al., 2008; Yilmaz et al., 2012]. In contrast, lanthanum carbonate and calcium carbonate did not differ in their effect on FMV in hemodialysis recipients [Kalliomaki et al., 2012].

In Patients with CKD, endothelial dysfunction probably contributes to both progression of renal disease and cardiovascular sequelae. Treatments intended to protect the endothelium, improve endothelial function, and prevent atherosclerosis are commonly prescribed [Turner et al., 2012], such as inhibitors of the renin-angiotensin system, other antihypertensives, insulin-sensitizing agents, lipid-lowering agents to reduce LDL-cholesterol, antiplatelet agents, and antithrombotic agents. Potential sources of endothelial dysfunction in Patients with CKD include uremic toxins, serum phosphate, serum uric acid, oxidative stress, and AGEs; thus, therapies with CKD are likely to experience additive effects. [Pool and Taylor, 2007].
calcification in patients with dialysis-dependent ESRD [Asmus et al. 2005; Block et al. 2005; Braun et al. 2004; Chertow et al. 2002, 2003; Kakuta et al. 2011; Shantouf et al. 2010] or predialysis CKD [Caglar et al. 2008; Di Iorio et al. 2012; Russo et al. 2007]; reduced absorption of bile acids from the gut [Braunlin et al. 2002], leading to lower serum total and LDL cholesterol [Bleyer et al. 1999; Di Iorio et al. 2012; Evenepoel et al. 2009; Ferramosca et al. 2005; Gulati et al. 2010; Hervas et al. 2003; Lin et al. 2011], reduced absorption of endotoxin from gut bacteria [Stinghen et al. 2010; Sun et al. 2009], lower levels of inflammatory mediators and biomarkers [Caglar et al. 2008; Ferramosca et al. 2005; Shantouf et al. 2008, 2010; Stinghen et al. 2010; Sun et al. 2009; Yamada et al. 2009], reduced absorption of dietary AGEs [Vlassara et al. 2012a], and decreased carotid intima-media thickness (CIMT), a surrogate marker of atherosclerosis [Boaz et al. 2011]. CKD fosters proatherogenic conditions through multiple pathways, including oxidative stress, increased infection and inflammation, decreased clearance of inflammatory mediators, increased formation and decreased clearance of AGEs, LDL oxidation, and adverse changes in endothelial and vascular smooth muscle cells [Stenvinkel et al. 2003]. Atherogenesis and inflammation, not only phosphate–calcium metabolism, in turn contribute to vascular calcification [Sage et al. 2010]. Sevelamer thus may ameliorate multiple processes that contribute to calcification and other sources of cardiovascular disease risk in CKD (Figure 5).

Endothelium-dependent vasodilation and its determinants. Hyperphosphatemia may directly induce endothelial dysfunction and damage, as indicated by in vitro, animal, and human studies [Ellam and Chico, 2012]. In healthy human volunteers, acute postprandial increases in serum phosphate after a breakfast containing 1200 mg phosphate decreased nitric oxide synthase activity and FMV [Shuto et al. 2009]. Circulating fetuin-A, the main inhibitor of soft-tissue calcification, decreases as GFR declines, parallel to an increase in the vasoconstrictive protein endothelin-1 [Cottone et al. 2010]. Decreased fetuin-A is correlated not only with vascular calcification itself [Sage et al. 2010] but also with endothelial vasomotor dysfunction shown by decreased FMV [Caglar et al. 2008]. A short-term study showed FMV and circulating fetuin-A to decrease significantly in patients with stage 4 nondiabetic CKD compared with healthy controls; 8 weeks of sevelamer treatment significantly increased fetuin-A and FMV in this study’s CKD participants [Caglar et al. 2008]. FMV and fetuin-A levels had independent multivariate association both at baseline and after treatment. In another 8-week randomized investigation of 100 nondiabetic patients with stage 4 CKD [Yilmaz et al. 2012], sevelamer significantly increased brachial artery endothelium-dependent FMV. Changes in FMV were significantly associated with changes in fibroblast growth factor-23 (FGF-23), phosphate, parathyroid hormone (PTH), fetuin-A, and C-reactive protein (CRP); phosphate and PTH lost their predictive power on multivariate analysis. Fetuin-A increases also have been associated with significant reductions of all-cause and cardiovascular mortality in dialysis patients [Hermans et al. 2007].

Figure 4. Effects of sevelamer versus calcium on mortality in patients new to hemodialysis. Adapted with kind permission from Macmillan Publishers Ltd. (Block et al. 2007).
| Parameter                                  | Studies and references            | Populations and regimens                                                                 | Key results                                                                                                                                                                                                 |
|-------------------------------------------|-----------------------------------|-----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Increased bone formation and improved architecture | [Mathew et al. 2007]               | Mouse model of diabetic CKD with vascular calcification and metabolic syndrome, treated with sevelamer carbonate | Sevelamer reduced CKD-induced trabecular osteopenia, increased tibial and femoral osteoblast surfaces, osteoid volumes and bone formation rates.                                                                 |
|                                           | [Asmus et al. 2005]                | Adults on hemodialysis, N = 72, randomized to sevelamer hydrochloride or CaCO₃ for 2 years | Sevelamer patients had a significant increase in median trabecular bone density by CT whereas CaCO₃ patients had a significant decrease [sevelamer +3%, $p = 0.0296$, CaCO₃ −6%, $p = 0.0049$, between-group $p = 0.0025$]. |
|                                           | [Ferreira et al. 2008]             | Adults on hemodialysis, N = 119, who provided iliac bone biopsies and were randomized to open-label sevelamer hydrochloride or CaCO₃ for 1 year | Sevelamer but not CaCO₃ patients had significantly increased bone formation rates from baseline ($p = 0.019$). Trabecular architecture improved in 7 of 10 sevelamer pts but 0 of 3 CaCO₃ patients. |
|                                           | [Lin et al. 2010]                  | Taiwanese adults on hemodialysis, N = 52, randomized to open-label sevelamer hydrochloride or calcium acetate for 8 weeks, dosed according to starting serum PO₄ | Alkaline phosphatase (AP) was significantly increased from baseline to week 8 with sevelamer but not calcium ($p = 0.014$ for treatment difference). AP increase showed dose-response to sevelamer. |
| Subanalysis of Treat to Goal study [Raggi et al. 2005] |                                   | Hemodialysis patients, N = 200, receiving sevelamer hydrochloride or calcium (acetate or carbonate) for 52 weeks | Calcium patients experienced unexpected significant decreases in vertebral trabecular QCT BMD [30% of calcium recipients experienced a ≥10% trabecular and cortical decrease]. Sevelamer patients had significantly higher total and bone-specific alkaline phosphatase, osteocalcin, and PTH ($p < 0.001$). |
| Improved vascular or endothelial function  | [Takenaka and Suzuki, 2005]        | Dialysis patients (N = 15) who switched from 6 months of CaCO₃ to 6 months of sevelamer hydrochloride | PWV increased by 45 ± 16 cm/s per month during CaCO₃ use; the 6 months of sevelamer use arrested PWV increase, showing PWV decrease of −20 cm/s per month.                                                                 |
|                                           | [Caglar et al. 2008]               | Nondiabetic hyperphosphatemic stage 4 CKD patients (N = 50) and 36 matched healthy volunteers randomized to receive sevelamer hydrochloride or calcium acetate for 8 weeks | CKD patients had significantly lower baseline serum fetuin-A and FMD and higher hsCRP than controls. Sevelamer significantly increased median fetuin-A (0.27 to 0.35 g/l, $p < 0.001$) and improved FMD (5.7 ± 0.8% to 6.7 ± 0.8%, $p < 0.001$) from baseline; calcium had no effect (0.27 to 0.28 g/l; 5.7 ± 0.4% to 5.7 ± 0.6%). Serum fetuin-A significantly increased by 21% during sevelamer use, and remained elevated during the subsequent calcium period |
|                                           | [Brandenburg et al. 2010]          | 57 dialysis patients receiving 3 successive 8-week treatments: calcium acetate-sevelamer hydrochloride-calcium acetate | Sevelamer increased FMV from 6.1% to 7.1% ($p < 0.001$); calcium did not change FMV [6.0% versus 6.0%]. Treatment-induced FMV changes were significantly ($p < 0.001$) associated with changes in FGF-23 levels [−27.1% [−33.2% to −8.8%] on sevelamer; 3.5% [−8.4% to 12.1%] on calcium acetate], as well as with CRP and fetuin A levels. |
|                                           | [Yilmaz et al. 2012]               | Hyperphosphatemic stage 4 CKD patients (N = 100) randomized to sevelamer hydrochloride or calcium acetate for 8 weeks |                                                                                                                                                |

(Continued)
| Parameter                                                                 | Studies and references                                                                 | Populations and regimens                                                                 | Key results                                                                                                                                                                                                 |
|--------------------------------------------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Anti-inflammatory, anti-endotoxin, or anti-dyslipidemic effects           | [Ferramosca et al. 2005]                                                               | 108 hemodialysis patients randomized to sevelamer hydrochloride or calcium acetate for 1 year | Sevelamer significantly decreased beta2-microglobulin ($p = 0.018$), and hsCRP ($p < 0.002$) from baseline; hsCRP change was significantly different from calcium group (between-group $p < 0.01$). Sevelamer decreased total and LDL cholesterol and apolipoprotein B significantly more than calcium (all between-group $p < 0.01$). |
|                                                                          | [Yamada et al. 2005]                                                                   | 36 hyperphosphatemic hemodialysis patients receiving sevelamer for 24 weeks            | Sevelamer lowered hsCRP significantly from baseline to 12 and 24 weeks (1.03 versus 0.57 and 0.38 mg/dl, respectively, $p = 0.0259$).                                                                       |
|                                                                          | [Caglar et al. 2008]                                                                  | 50 nondiabetic hyperphosphatemic stage 4 CKD patients and 36 matched healthy volunteers randomized to receive sevelamer hydrochloride or calcium acetate for 8 weeks | Sevelamer significantly decreased LDL cholesterol from baseline ($113.5 \pm 16.0$ mg/dl to $103.7 \pm 17.0$, $p < 0.05$); calcium had no effect ($117.8 \pm 19.2$ mg/dl to $123.2 \pm 15.8$ mg/dl, $p = \text{NS}$). Sevelamer significantly decreased hsCRP from baseline (15 to 10 mg/l, $p < 0.001$); calcium had no effect (14 mg/l remained constant). |
|                                                                          | [Shantouf et al. 2008]                                                                | Cross-sectional Nutritional and Inflammatory Evaluation of Dialysis (NIED) study of 787 adults on hemodialysis receiving sevelamer hydrochloride, calcium, or both | Sevelamer patients were more likely to have CRP <10 mg/dl than calcium patients (OR 1.06, 95% CI 1.02–1.11), independent of age, dialysis vintage, body mass index or statin use. |
|                                                                          | [Sun et al. 2009]                                                                    | Pilot cross-sectional study in 46 hemodialysis patients (65% sevelamer hydrochloride users) | Sevelamer users had lower mean plasma endotoxin than nonusers ($0.23 \pm 0.01$ versus $0.30 \pm 0.01$ EU/ml, $p = 0.001$) but serum IL-6 and CRP were not significantly different. Sevelamer use predicted lower endotoxin after multivariate adjustment for race, gender, age, dialysis vintage, total cholesterol, and white blood count. |
|                                                                          | [Stinghen et al. 2010]                                                               | Hemodialysis patients who switched from calcium to 6 months of sevelamer hydrochloride | Plasma endotoxin and hsCRP significantly decreased from baseline to 6 months on sevelamer.                                                                                                                   |
|                                                                          | INDEPEN-DENT-CKD study [Di Iorio et al. 2012]                                         | Nonblinded pilot study in 239 predialysis CKD patients randomized to sevelamer or calcium for 3 years | Sevelamer significantly lowered mean total cholesterol (from 165 to 146 mg/dl, $p < 0.01$) and LDL cholesterol (from 95 to 86 mg/dl, $p < 0.01$), whereas calcium changes were insignificant (respectively 169 to 166 and 106 to 112 mg/dl). Sevelamer significantly lowered CRP from baseline while calcium raised CRP. |
|                                                                          | [Bleyer et al. 1999]                                                                 | Open-label crossover study in 84 hemodialysis patients randomized to sevelamer hydrochloride or calcium acetate for 8 weeks, 2-week washout, then 8 weeks on the other agent | Sevelamer use decreased LDL cholesterol by 24%. Calcium use did not affect lipids.                                                                                                                   |
Table 2. (Continued)

| Parameter | Studies and references | Populations and regimens | Key results |
|-----------|------------------------|--------------------------|-------------|
| Reduced glycoxidative stress (Suppression of advanced glycation end product accumulation or reduction of oxidative stress biomarkers) | [Kakuta et al. 2011] | Adults on hemodialysis, \( N = 183 \), receiving sevelamer hydrochloride or calcium carbonate for 12 months | Plasma pentosidine increased from baseline with calcium but not with sevelamer \((p < 0.001)\) |
| | [Vlassara et al. 2012b] | Crossover study of adults with stage 2–4 diabetic CKD receiving sevelamer carbonate or calcium carbonate (crossover, 2 months on each with 1-week washout between) | Sevelamer significantly lowered serum Hb1Ac and glucose, serum and intracellular carboxymethyllysine and methylglyoxal, increased AGE receptor and sirtuin 1 mRNA, and decreased TNF-\( \alpha \) and 8-isoprostanes. \( In vitro \) testing showed that sevelamer carbonate bound AGE-BSA at intestinal but not stomach pH. |
| | [Vlassara et al. 2012a] | Adults on hemodialysis, \( N = 132 \), receiving sevelamer carbonate 2.4, 4.8, or 7.2 g/day or placebo for 3 weeks | Serum AGEs (methylglyoxal and carboxymethyllysine) were reduced from baseline with 4.6 or 7.2 g/day sevelamer carbonate but remained similar to baseline on 2.4 g/day sevelamer carbonate. Serum phosphate decreased dose-dependently \((p < 0.001\) for trend). |

In vitro chemical study with sevelamer hydrochloride

Sevelamer reduced total cholesterol by 16.5\%, LDL cholesterol by 29.9\%, and increased HDL cholesterol by 19.5\% \((p < 0.05\) for all). Calcium did not affect lipids.

Sevelamer significantly decreased total and LDL cholesterol and uric acid and increased bone-specific alkaline phosphatase from baseline \((p < 0.001\) for all).

Sevelamer significantly lowered total and LDL cholesterol by week 12 \((p = 0.02)\)

Sevelamer-exposed patients had significantly less carotid intima-media thickness and lower LDL cholesterol than unexposed patients.

Total and LDL cholesterol decreased significantly from baseline in the sevelamer group; changes were correlated with decreases of serum \( \text{PO}_4 \) on treatment \((r = 0.266\) and 0.386, respectively).
Table 2. (Continued)

| Parameter                         | Studies and references | Populations and regimens                                                                 | Key results                                                                                                                                                                                                 |
|-----------------------------------|------------------------|------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antihyperuricemic                 | Subanalysis of Treat to Goal study [Garg et al. 2005]                                  | Adults on hemodialysis, N = 200, randomized to sevelamer hydrochloride or calcium for 52 weeks                                              | Mean serum uric acid decreased more from baseline with sevelamer than calcium (−0.64 versus −0.26 mg/dl, p = 0.03)                                                                                           |
|                                   | [Evenepoel et al. 2009]                                                | Adults on peritoneal dialysis, N = 143, randomized to sevelamer hydrochloride or calcium acetate for 12 weeks                              | Sevelamer significantly decreased serum uric acid from baseline (−0.53 ± 0.79, p < 0.001) whereas calcium did not statistically change uric acid (−0.11 ± 0.83, p > 0.05); between-group (p = 0.010) |
|                                   | [Ohno et al. 2009]                                                     | Japanese adults on hemodialysis, N = 127, receiving sevelamer hydrochloride on top of previous care for 6 months                             | Sevelamer lowered serum uric acid only in patients with baseline hyperuricemia. Rates of uric acid change were correlated with rates of phosphate reduction.                                                  |
|                                   | [Lin et al. 2011]                                                     | Taiwanese adults on hemodialysis, N = 52, randomized to open-label sevelamer hydrochloride or calcium acetate for 8 weeks, dosed according to starting serum PO₄  |
|                                   |                                                                      |                                                                                         | Sevelamer significantly decreased serum uric acid; (p = 0.020); changes were correlated with decrease of serum phosphate (r = 0.458).                                                                 |
| Reduced circulating FGF-23        | [Cancela et al. 2011]                                                 | Brazilian adults on hemodialysis, N = 72, randomized to receive sevelamer hydrochloride or calcium acetate for 1 year                      | Serum FGF-23 decreased significantly from baseline in sevelamer recipients (p < 0.001) but did not change significantly in calcium recipients (p = 0.062).                                                   |
|                                   | [Oliveira et al. 2010]                                                | Adults with CKD stages 3–4, N = 40, randomized to receive sevelamer hydrochloride or calcium for 6 weeks                                          | Sevelamer decreased serum FGF-23 from baseline significantly more than calcium did (changes: −53.6 ± 64.7 versus −16 ± 49.1; between-group p < 0.05).                                                        |
|                                   | [Block et al. 2012]                                                   | Adults with CKD (MDRD eGFR 20–45 ml/min/1.73 m²), N = 148, randomized to receive placebo, sevelamer carbonate, lanthanum carbonate, or calcium acetate for median follow up of 249 days | Serum intact FGF-23 decreased significantly with sevelamer versus placebo (median change −24 pg/ml, p = 0.002 versus placebo), increased significantly with calcium versus placebo (median change +28 pg/ml, p = 0.03 versus placebo), and did not differ between lanthanum and placebo (p = 0.38). C-terminal FGF-23 changes from baseline did not differ significantly between binder and placebo groups (p = 0.42). |

AGE, advanced glycation endproduct; BSA, bovine serum albumin; CAC(S), coronary artery calcification (score); CI, confidence interval; CKD, chronic kidney disease; CT, computed tomography; EBCT, electron beam computed tomography; eGFR, estimated glomerular filtration rate; FGF-23, fibroblast growth factor-23; FMW, flow-mediated vasodilation; HDL, high-density lipoprotein; hCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; MDRD, Modification of Diet in Renal Disease equation; OR, odds ratio; PTH, parathyroid hormone; PWV, pulse wave velocity; QCT, quantitative computed tomography; TCS, total calcium score.
A possible challenge to the postulated interrelationship of endothelial dysfunction (e.g. impaired FMV) and vascular calcification or atherosclerosis comes from a 6-month pilot randomized study of lanthanum carbonate in hemodialysis patients [Kalil et al. 2012]. Lanthanum carbonate recipients experienced significantly less progression of coronary artery calcification than did patients receiving other binders (mostly combinations of sevelamer and calcium binders); however, FMV and inflammatory markers did not differ between treatments. The study authors stated that this was the first study to dissociate FMV changes from progression of coronary artery calcification [Kalil et al. 2012].

Advanced glycation endproducts. AGEs are highly reactive, oxidative [Kakuta et al. 2011; Vlassara et al. 2012b], inflammatory, and atherogenic [Prasad et al. 2012] molecules formed from oxidation of carbohydrates, lipids, and amino acids [Uribarri and Tuttle, 2006]. AGEs are produced during normal glucose oxidation and immune-cell function [Uribarri and Tuttle, 2006], in nonenzymatic sugar–protein reactions [Prasad et al. 2012], and during dry-heat cooking of foods [Uribarri and Tuttle, 2006]. In the body AGEs form adducts with structural proteins, stiffening cardiovascular structures and altering their mechanics [Falcao-Pires et al. 2012; Prasad et al. 2012]. AGEs accumulate with declining eGFR in patients with CKD, induce expression of the inflammatory Receptor for AGEs (RAGE) on neutrophils, and impair endothelial vasomotor function [Linden et al. 2008]. Plasma levels of the AGE pentosidine are correlated with cardiovascular calcification in patients with diabetic CKD [Kakuta et al. 2011] and with CIMT, a direct measure of atherosclerosis, in first-year dialysis patients [Suliman et al. 2006]. A low-AGE diet

Figure 5. Potential pleiotropic effects of sevelamer affecting parameters involved in the inflammatory, metabolic, or developmental modulation of vascular calcification. Factors that have been shown to respond to sevelamer are shown in yellow ovals. Adapted with kind permission from Macmillan Publishers Ltd. [Sage et al. 2010]. ALP, alkaline phosphatase; BMP, bone morphogenetic protein; FGF-23, fibroblast growth factor-23; HDL, high-density lipoprotein; IFN-γ, interferon gamma; IGF-1, insulin-like growth factor-1; IL-6, interleukin-6; MGP, matrix GLA protein; MMP, matrix metalloproteinase; Pi, inorganic phosphate; PTH, parathyroid hormone; TNF, tumor necrosis factor.
reduced circulating AGEs significantly in a study of healthy subjects and predialysis CKD patients, showing that intestinal AGE absorption determines plasma AGE concentrations [Vlassara et al. 2009]. Sevelamer reduced serum and intracellular AGEs (likely through intestinal absorption of dietary AGEs) in patients with predialysis diabetic nephropathy [Vlassara et al. 2012b] and in diabetic dialysis patients [Vlassara et al. 2012a], and reduced circulating pentosidine in dialysis patients, whereas pentosidine was increased by calcium-based binders [Kakuta et al. 2011].

Vlassara and colleagues [Vlassara et al. 2012b] enrolled 20 patients with proteinuric diabetic CKD into a 2-month, open-label, crossover study comparing effects of sevelamer carbonate (1600 mg thrice daily with meals) versus calcium carbonate (1200 mg thrice daily with meals) on AGEs. Binder order was randomly assigned; patients received each binder for 8 weeks separated by a 1-week washout. Serum phosphate and calcium did not change from baseline on either binder in this brief study; 24-hour urinary phosphate excretion was decreased similarly by sevelamer and calcium. Blood glucose, dietary AGE intake, adipokines, and CRP remained similar between groups. Sevelamer (in comparison with calcium) reduced HbA1c, total cholesterol, triglycerides, 8-isoprostanes, and proteins modified with carboxymethyllysine (CML) or methylglyoxal. Calcium carbonate significantly increased 8-isoprostanes. In polymorphonuclear neutrophils, sevelamer carbonate but not calcium carbonate decreased tumor necrosis factor-α levels and increased messenger RNAs for AGE receptor 1 and sirtuin 1 (thus demonstrating reduced inflammatory responses and enhanced defenses against AGE-induced damage).

In 132 diabetic hemodialysis patients, sevelamer at 4.8 or 7.2 g/day for 3 weeks significantly reduced serum MG and CML from baseline and versus placebo, while sevelamer at 2.4 g/day did not change MG and CML from baseline. Vlassara and colleagues state that ‘An important therapeutic issue pointed out by this study was that sevelamer carbonate at a dosage of 2.4 g/day did not significantly reduce cytopathic AGEs. Because cytopathic AGEs are inducers of ROS and/or inflammation, assuring that patients reach and maintain the 4.8 g/day dosage level may represent an important therapeutic goal.’ [Vlassara et al. 2012a]

**Fibroblast growth factor-23.** Circulating FGF-23 increases progressively with declining renal function in CKD and ESRD in an effort to increase per-nephron phosphorus excretion [Slatopolsky, 2011]. Elevation of FGF-23 directly induces left ventricular hypertrophy [Faul et al. 2011] and is linked to endothelial/vascular dysfunction (impairment of FMV) in patients with CKD [Yilmaz et al. 2010, 2012] and community-dwelling elders in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) [Mirza et al. 2009b]. High serum FGF-23 also predicted total body atherosclerosis scores in PIVUS [Mirza et al. 2009a] and carotid atherosclerosis scores in ESRD patients [Balci et al. 2010]. Circulating FGF-23 is negatively associated with circulating fetuin-A [Coen et al. 2011]; thus, increased FGF-23 may also contribute to endothelial dysfunction and vascular calcification by lowering fetuin-A levels. Calcium-based phosphate binders elevate serum FGF-23 in patients with CKD or ESRD, while noncalcium binders (sevelamer or lanthanum) reduce it [Cancela et al. 2011; Oliveira et al. 2010; Yilmaz et al. 2012]. In the Vlassara and colleagues diabetic nephropathy study [Vlassara et al. 2012b], sevelamer significantly decreased FGF-23 versus calcium in the subset of patients with baseline FGF-23 >70 pg/ml; overall, FGF-23 numerically decreased with sevelamer and numerically increased with calcium; although within-treatment changes from baseline were not statistically significant, the difference between treatments was significant (p = 0.04).

**Inflammation.** Endothelial and vascular inflammation are implicated in multiple cardiovascular disorders in the general population and patients with CKD/ESRD [Cottone et al. 2007, 2008; Nikolov et al. 2006; Ross, 1999; Santoro et al. 2010]. Sources of inflammation include oxidized LDL cholesterol, bacterial endotoxins (from gut absorption or infections of dialysis accesses or peripheral tissues [Hauser et al. 2011]), AGEs, and uremic toxins. Reactive oxygen species in turn are increased by inflammatory cell activity, leading to oxidative damage. Sevelamer has been shown to reduce circulating high-sensitivity C-reactive protein (hsCRP) in patients with CKD [Yilmaz et al. 2012] and on dialysis [Shantouf et al. 2008; Yamada et al. 2005], whereas calcium-based binders do not [Shantouf et al. 2008; Yilmaz et al. 2012]. In a short-term comparison of lanthanum carbonate and calcium carbonate in hemodialysis patients, inflammatory markers did not change in either group [Kalil et al. 2012].
Reduced levels of plasma endotoxins (reflecting reduced absorption from gut bacteria) were associated with sevelamer use in a pilot study of hemodialysis patients [Sun et al. 2009] and a prospective study of dialysis patients switched from calcium carbonate to sevelamer for 6 months of follow up [Stinghen et al. 2010]; in the latter cohort, hsCRP decreased in parallel to reduced endotoxemia. Animal studies in non-CKD mice suggest that lanthanum ions may reduce inflammatory mediator generation and secretion by the liver and macrophages (tumor necrosis factor-α and interleukin-β) in response to bacterial lipopolysaccharide [Guo et al. 2010, 2011].

Systemic inflammation in dialysis recipients can exacerbate anemia and impair response to anemic agents; thus the effect of sevelamer (potentially reducing inflammatory stimuli) on anemia management is being evaluated. Preliminary data in 45 hemodialysis patients [Ike et al. 2012] showed that sevelamer dose independently predicted responsiveness to erythropoietin-stimulating agents (exemplified by reduced ‘ESA resistance index’, weekly erythropoietin dose divided by hemoglobin value); the authors called for further research into the effects of sevelamer on ESA responses.

Atherogenesis. CIMT, a surrogate marker of developing atherosclerosis [Boaz et al. 2011], is increased by inflammatory and oxidative damage [Druke et al. 2002] and independently predicts cardiovascular events in patients with and without CKD [Druke et al. 2002]. CIMT responds to many biochemical perturbations occurring in CKD. In hemodialysis patients, serum FGF-23 and CIMT were significantly correlated (r = 0.497, p = 0.0001), and elevated log FGF-23 independently predicted CIMT [Balci et al. 2010]. In another study, plasma pentosidine correlated with CIMT increases during the first dialysis year [Suliman et al. 2006]. Advanced protein oxidation products were associated with CIMT increases in hemodialysis patients receiving intravenous iron [Druke et al. 2002]. Sevelamer exposure in dialysis patients was associated with significantly reduced CIMT in a nested cross-sectional substudy of the Sevelamer hydrochloride and Ultrasound-Measured femoral and carotid intima Media thickness progression in End-stage Renal disease (SUMMER) trial [Boaz et al. 2011]. The association of reduced CIMT with sevelamer use persisted after controlling for serum calcium, cardiovascular history, and body weight. Importantly, SUMMER analyzed patients with sevelamer exposure regardless of whether they also had received calcium binders.

In apolipoprotein E-deficient mice with chronic renal failure (CRF), both sevelamer hydrochloride and lanthanum carbonate reduced the progression of both atherosclerosis and vascular calcification (VC), and reduced vascular plaque expression of Type 1 collagen [Nikolov et al. 2012]. Sevelamer additionally reduced plaque nitrotyrosine levels. Untreated renal failure mice had increased mineral apposition and bone formation rates, which were reduced by sevelamer but not lanthanum. The study authors concluded that ‘The beneficial effects of La carbonate and sevelamer-HCl on the progression of VC and atherosclerosis in CRF mice could be mainly due to a decrease in phosphate retention and likewise a reduction of arterial Type I collagen expression. The effect of La carbonate differed from that of sevelamer-HCl in that it did not appear to exert its vascular effects via changes in oxidative stress or bone remodeling in the present model’ [Nikolov et al. 2012].

In addition to binding phosphate, sevelamer binds bile acids in vitro and in the gut [Braunlin et al. 2002] [Bays et al. 2008], thus lowering serum LDL cholesterol in people with and without CKD [Braunlin et al. 2002]. These effects of sevelamer are not surprising in view of sevelamer’s similarity to colesvelam, another nonabsorbed resin drug, which was developed as a bile acid sequestrant and hypolipidemic [Bays et al. 2008]. Sevelamer has lowered LDL and total cholesterol in multiple studies of patients with CKD [Gulati et al. 2010] and ESRD [Bleyer et al. 1999; Brandenburg et al. 2010; Braun et al. 2004; Lin et al. 2010; Shantouf et al. 2008; Takenaka and Suzuki, 2005]. High-density lipoprotein (HDL) cholesterol is generally unaffected [Takenaka and Suzuki, 2005]; effects on triglycerides vary among studies. LDL-cholesterol reductions with sevelamer have tended to range from 10% to 20% in predialysis CKD [Di Iorio et al. 2012; Russo et al. 2007; Yilmaz et al. 2012], roughly 20% in incident dialysis patients [Block et al. 2007], and 20% to >30% in prevalent dialysis patients [Bleyer et al. 1999; Braun et al. 2004; Chertow et al. 2002, 2003; Ferramosca et al. 2005; Ferreira et al. 2008; Hervas et al. 2003; Kakuta et al. 2011; Takei et al. 2008], comparable to the ~25% LDL reduction typical of statin use. Reduction of
LDL cholesterol reduces a source of vascular inflammation and an atherogenic substance.

Hyperuricemia. High uric acid concentrations induce endothelial oxidative stress, reduce nitric oxide synthase activity [Hong et al. 2012], and are associated with impaired FMV (endothelial dysfunction) in CKD patients [Yelken et al. 2012] although not in healthy adults [Jalal et al. 2012]. Lowering of serum uric acid with allopurinol ameliorated FMV in CKD patients without any change in oxidative markers [Yelken et al. 2012]. Sevelamer has been shown to adsorb urate ions in vitro [Ohno et al. 2009] and to lower serum uric acid in hemodialysis patients [Garg et al. 2005; Ohno et al. 2009]. In the Ohno and colleagues study, sevelamer lowered uric acid significantly only in patients with baseline serum uric acid >7.0 mg/dl [Ohno et al. 2009]. The Garg and colleagues study [Garg et al. 2005] set an a priori threshold for clinically meaningful serum uric acid reduction at −1.5 mg/dl (20–25% of baseline, depending on gender) and observed that 23% of sevelamer recipients but only 10% of calcium recipients experienced at least this level of uric acid reduction (p = 0.02 for treatment group difference). Patients with baseline serum uric acid >8.0 mg/dl had a mean decrease exceeding −2.5 mg/dl [Garg et al. 2005]. In contrast, in the Brandenburg and colleagues study of hemodialysis patients, sevelamer did not affect serum uric acid [Brandenburg et al. 2010]. Serum uric acid in peritoneal dialysis patients [Evenepoel et al. 2009] was lowered by sevelamer hydrochloride but not by calcium carbonate. Since allopurinol treatment to lower serum uric acid is frequently prescribed to retard progression of CKD [Turner et al. 2012], sevelamer’s effect on serum uric acid also may have potential to reduce endothelial dysfunction and its consequences in CKD/ESRD.

Oxalate. Oxalate excretion in urine is a potential source of pathology in patients who have either CKD without overt nephrolithiasis or histories of nephrolithiasis with normal GFR. Different phosphate binders have been studied for their potential to reduce urinary oxalate. In 20 patients with stage 4 or 5 CKD with no history of kidney stones, either sevelamer or calcium carbonate significantly reduced urinary oxalate in a two-period crossover study (3-week exposure to each binder with 1-week washout between) [Caravaca et al. 2007]. Conversely, in an open-label pilot study of 10 patients with enteric hyperoxaluria, normal GFR, and histories of stone formation [Lieske et al. 2008], sevelamer hydrochloride significantly lowered urinary citrate (23%, p = 0.01) and urinary phosphorus (44%, p = 0.0001) and numerically decreased urinary oxalate (17%, p > 0.05) and the oxalate/creatinine ratio (11%, p > 0.05). Sevelamer decreased brushite supersaturation with borderline statistical significance (p = 0.07). The authors suggested that the observed effects of sevelamer on urinary phosphorus, pH, and brushite supersaturation could be clinically significant in patients with calcium phosphate (as opposed to calcium oxalate) stones, and thus sevelamer merits further investigation in additional patient groups [Lieske et al. 2008].

In preclinical studies, lanthanum carbonate has been observed to bind oxalate in vitro at intestinal pH range and to reduce plasma and urine oxalate and nephrocalcinosis in oxalate-treated rats [Robijn et al. 2012].

Endothelial-mediated effects on vascular calcification. Multiple processes in CKD feed into the development of vascular calcification, which is not a merely passive process of mineral crystallization [Sage et al. 2010]. A study investigating patients with moderate to severe predialysis CKD showed that fetuin-A decreases and endothelial dysfunction develops as GFR declines, and concluded that endogenous calcification inhibitors such as fetuin-A mediate a mechanistic relationship between endothelial dysfunction and intimal vascular calcification [Cottone et al. 2010]. Fetuin-A deficiency contributes to atherosclerotic intimal calcification in patients with CKD, atherosclerosis, hyperphosphatemia, and hypercalcemia [Westenfeld et al. 2009]. Another calcification inhibitor, matrix GLA protein, is thought to protect against the medial calcification that is more specific to CKD-MBD-affected vessels. GLA was upregulated in partial-nephrectomy ApoE−/− mice fed a high-phosphate diet [Westenfeld et al. 2009], which may represent a response for acute prevention of medial calcification.

Effects on bone mineral density. Bone loss in CKD-MBD may be linked to development of vascular calcification [Brandenburg et al. 2009]. Improved bone formation rates, bone mineral density (BMD), and trabecular architecture have been reported with sevelamer use in dialysis patients in several studies [Asmus et al. 2005; Ferreira et al. 2008; Lin et al. 2010; Mathew et al. 2007; Raggi et al. 2005]. Simultaneous evaluation of bone quality and vascular calcification is
relatively infrequent in binder studies. A study by Asmus and colleagues [Asmus et al. 2005] concurrently examined coronary artery and aortic calcification and vertebral BMD by quantitative computed tomography in 72 adults on hemodialysis randomized to 2 years of calcium carbonate or sevelamer. Calcium recipients had significantly greater increases in coronary artery and aortic calcification than sevelamer recipients. Trabecular BMD significantly decreased in calcium recipients and significantly increased in sevelamer recipients; cortical bone density did not differ between treatments. In a pilot randomized trial in dialysis patients, lanthanum and calcium carbonate did not differ in effects on post-treatment lumbar spine BMD [Toussaint et al. 2011].

**Sevelamer in predialysis CKD: primary and pleiotropic effects versus mortality and progression**

A recent exploratory study in predialysis CKD patients [Di Iorio et al. 2012] evaluated the effects of sevelamer versus calcium-based binders on mortality or dialysis initiation, vascular calcification, and pleiotropic effects. INDEPENDENT-CKD [Di Iorio et al. 2012] evaluated mortality, progression to dialysis, coronary artery calcification scores, serum albumin, blood lipids, and CRP in 212 consecutive CKD stage 3–4 outpatients randomized to receive sevelamer or calcium carbonate and followed for ≥36 months. The primary endpoint, all-cause mortality, was significantly lower in sevelamer than calcium carbonate recipients, as was a composite endpoint of mortality or dialysis inception. Dialysis inception alone was lower with sevelamer in unadjusted or baseline-covariate-adjusted models, but lost significance in models adjusted for baseline and time-varying covariates. Among patients with non-zero baseline coronary artery calcification (CAC) scores, 24 sevelamer recipients and 45 calcium recipients experienced regression of calcification. New-onset CAC occurred in 5 sevelamer recipients and 45 calcium recipients. Sevelamer but not calcium significantly reduced total and LDL cholesterol. Sevelamer significantly reduced CRP; calcium increased it. The INDEPENDENT-CKD authors conclude that ‘These results show that sevelamer compared to a calcium-containing phosphate binder improves survival in a cohort of incident hemodialysis patients. However, the better outcomes in the sevelamer group may be due to better phosphate control rather than reduction in calcium load.’ [Di Iorio et al. 2012].

INDEPENDENT-CKD is the first study demonstrating a survival benefit for sevelamer use in predialysis CKD patients (albeit this is off-label in the United States and indicated in hyperphosphatemic CKD in many other countries), complementing RIND and INDEPENDENT-HD evidence for this effect in dialysis recipients.

Thus, the pleiotropic effects of sevelamer complement its primary efficacy as a phosphate binder to address multiple aspects of cardiovascular pathophysiology in patients with CKD or ESRD and their antecedent comorbidities of diabetes and/or hypertension.

Ongoing and planned studies (Table 3) continue to explore the pleiotropic effects of sevelamer carbonate or hydrochloride in CKD/ESRD with the following broad foci:

- advanced imaging of atherosclerotic plaque inflammation;
- effects of sevelamer versus calcium acetate on arterial stiffness and calcification in hemodialysis patients;
- FGF-23 and/or PTH in predialysis CKD;
- vascular health parameters in predialysis CKD;
- anti-endotoxemia and anti-inflammatory effects in patients with HIV infection without CKD.

Thus, sevelamer’s ability to lower serum phosphate (with evidence for lowered mortality risk) in ESRD patients (per US labeling) and hyperphosphatemic CKD patients (approved in many non-US countries) is being augmented by current and planned exploratory studies on phosphate-independent effects within and beyond the CKD and ESRD population.

**Conclusions**

Beyond its labeled effect of serum phosphate reduction in US dialysis recipients and non-US hyperphosphatemic CKD patients of stages 3–5, exploratory data suggest that sevelamer may have additional effects on factors affecting vascular endothelium, such as: arrest of progression of vascular calcification; lowering of total and LDL cholesterol; reduction of FGF-23 (whose elevation is associated with left ventricular hypertrophy); reduction of circulating inflammatory and oxidative molecules, uric acid, and
uremic toxins; and reduced blood absorption of AGEs and endotoxin from the gut. It is reasonable to propose that endothelial pleiotropic effects of sevelamer may have contributed to the reduced mortality observed in the RIND and INDEPENDENT studies.

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