

Sevelamer as a phosphate binder in adult hemodialysis patients: an evidence-based review of its therapeutic value

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Abstract

Introduction: Patients on hemodialysis require phosphate binders to reduce dietary phosphate absorption and control serum phosphate. The standard therapy, calcium salts, can be associated with elevated serum calcium (hypercalcemia). Concern has been raised that hypercalcemia, especially combined with elevated serum phosphate, may be associated with arterial calcification, and this may contribute to increased risk of cardiovascular mortality and morbidity. Sevelamer is a nonmetal, nonabsorbed phosphate binder.

Aims: This review assesses the evidence for the therapeutic value of sevelamer as a phosphate binder in adult hemodialysis patients.

Evidence review: Strong evidence shows that sevelamer is as effective as calcium salts in controlling serum phosphate and calcium-phosphate product, has less risk of inducing hypercalcemia and is more effective at lowering lipid levels. Some evidence indicates that sevelamer reduces arterial calcification progression and loss of bone mineral density, but it may be more likely to induce metabolic acidosis, compared with calcium salts. Sevelamer-containing regimens may improve calcific uremic arteriolopathy, although the evidence is weak. Evidence is divided on whether the incidence of gastrointestinal adverse events with sevelamer is similar to or higher than that with calcium salts. Retrospective and modeling studies suggest lower cardiovascular morbidity and mortality with sevelamer than with calcium salts, with incremental cost-effectiveness of \$US1100–2200 per life-year gained. Further direct evidence is needed on mortality, quality of life, and cost-effectiveness.

Place in therapy: Sevelamer is effective in controlling serum phosphate and lowering lipid levels in hemodialysis patients without inducing hypercalcemia, and may have beneficial effects on arterial calcification.

Key words: sevelamer, calcium salts, phosphate binder, hemodialysis, chronic kidney disease, evidence

Core evidence place in therapy summary for sevelamer as a phosphate binder in adult hemodialysis patients

Outcome measure	Evidence	Implications
Disease-oriented evidence		
Effective control of serum phosphate and $\text{Ca} \times \text{P}$ product to within K/DOQI target range	Clear	Sevelamer is as effective as calcium salts
Absence of hypercalcemia	Clear	Reduced incidence of hypercalcemia with sevelamer compared with calcium salts
Reduction in serum LDL cholesterol and total cholesterol	Clear	Sevelamer is more effective than calcium salts May have beneficial effects on cardiovascular morbidity and mortality
Reduction in vascular calcification	Substantial	Attenuated progression with sevelamer compared with calcium salts May have beneficial effects on cardiovascular morbidity and mortality
Reduction in serum uric acid concentration	Moderate	Greater reduction with sevelamer than with calcium salts
Metabolic acidosis	Moderate	Sevelamer may be more likely than calcium salts to induce metabolic acidosis
Preservation of trabecular bone mineral density	Limited	Better preservation with sevelamer than with calcium salts May improve morbidity due to bone disease
Patient-oriented evidence		
Improvement in cardiovascular morbidity and mortality	Limited	Reduced risk of cardiac mortality and morbidity with sevelamer compared with calcium salts
<i>continued overleaf...</i>		

...table continued		
Outcome measure	Evidence	Implications
Reduction in hospitalization	Limited	Lower risk with sevelamer than with calcium salts
Absence of gastrointestinal adverse events	Limited	Evidence divided on whether the incidence with sevelamer is similar to or higher than with calcium salts
Improved patient acceptability (e.g. reduction of the dose required leading to a lower phosphate binder medication burden)	Limited	No improvement over calcium salts
Improvement of ulcers due to calcific uremic arteriolopathy	Limited	Improvement and/or healing noted after switching to sevelamer in combination with other interventions
Improvement in quality of life	No evidence	
Economic evidence		
Cost-effectiveness as a phosphate binder in hemodialysis patients	Limited	\$US1100–2200 per life-year gained with sevelamer compared with calcium salts
Cost-effectiveness as a lipid-lowering therapy in predialysis patients	Limited	Less cost-effective than atorvastatin (specific lipid-lowering therapy) plus calcium salts

Scope, aims, and objectives

Sevelamer (Renagel®, Genzyme) is indicated for the treatment of hyperphosphatemia in adult patients undergoing hemodialysis for end-stage renal failure. Sevelamer reduces serum phosphate concentrations by binding phosphate ions in the gastrointestinal tract, thus preventing systemic absorption. It differs from other currently available phosphate binders in that it is not a metal salt but a crosslinked polymer containing multiple amine groups. Sevelamer is administered in the hydrochloride form with hydrochloride groups bound to the amine groups. In the gastrointestinal tract, the amine groups become protonated and positively charged, and preferentially bind to phosphate ions, displacing some of the hydrochloride. Maximum phosphate binding occurs at about pH 7, and sevelamer binds phosphate mainly in the duodenum (Anon. 2004). Studies in animals and in healthy volunteers have shown that the sevelamer polymer is not absorbed from the gut, and that both the polymer and the bound phosphate are excreted in the feces (Burke et al. 1997; Plone et al. 2002). Sevelamer contains no metal ion component that could result in potential metal toxicity. The only component of sevelamer that is absorbed is some of the hydrochloride, which could contribute to metabolic acidosis (Loghman-Adham 2003).

This article reviews the evidence for the use of sevelamer as a phosphate binder in adult patients on hemodialysis, and considers its effects on outcomes, including serum phosphate and calcium concentrations, arterial calcification, hospitalization, and cardiovascular morbidity and mortality.

Use in children and in patients not undergoing hemodialysis (e.g. peritoneal dialysis patients or patients not on dialysis) is excluded, as these indications are not presently approved.

Methods

Literature searches were conducted on January 9–21, 2005, in the following databases. The search strategy was “Renagel OR sevelamer” unless otherwise stated. The cut-off date was from the beginning of the database to the date of the search unless otherwise stated.

- PubMed, <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>, 1966 to date. Search strategy: “sevelamer AND (hemodialysis OR haemodialysis)” limited to English-language results only, which was expanded by Automatic Term Mapping to “(‘sevelamer’[Substance Name] OR sevelamer[Text Word]) AND ((hemodialysis[Text Word] OR haemodialysis[Text Word] OR ‘renal dialysis’[TIAB] NOT Medline[SB]) OR ‘renal dialysis’[MeSH Terms]) OR (hemodialysis[Text Word] OR haemodialysis[Text Word] OR ‘renal dialysis’[TIAB] NOT Medline[SB]) OR ‘renal dialysis’[MeSH Terms])) AND English[Lang]”
- EMBASE, <http://www.datastarweb.com>, 1974 to date. Search strategy: “sevelamer AND (hemodialysis OR haemodialysis)” limited to English-language results only
- Database of Abstracts of Reviews of Effectiveness (DARE), NHS Economic Evaluations Database (NHSEED), Health Technology Assessment (HTA), www.york.ac.uk/inst/crd/darehp.htm. All three databases were searched together. All fields searched
- NHS HTA, www.ncchta.org
- National Guideline Clearing House, www.guideline.gov
- National Institute for Health and Clinical Excellence (NICE), www.nice.org.uk
- Cochrane Database of Systematic Reviews (CDSR), www.cochrane.org/index0.htm. Entire site searched
- Clinical Evidence (BMJ), www.clinicalevidence.com

One set of clinical guidelines was identified from the National Guidelines Clearing House (NKF 2003). After removal of duplicates, a total of 142 records were retrieved, two from DARE and the remainder from PubMed or EMBASE. All other databases recorded no matches. Records were manually reviewed and a total of 114 records were excluded: nonsystematic reviews (n=49), animal studies (n=3), *in vitro* studies (n=1), studies in children (n=3), studies in patients other than hemodialysis patients (n=4), letters, editorials, comment and corrections (n=25), and articles that mentioned

Table 1 | Evidence base included in the review

Category	Number of records	
	Full papers	Abstracts
Initial search	142	35
records excluded	114	19
records included	28	16
Additional studies identified	3	n/a
Search update, new records	23	0
records excluded	17	
records included	6	
Total records included	37	16
Level 1 clinical evidence	2	0
Level 2 clinical evidence	11	1
Level ≥ 3 clinical evidence	22	14
trials other than RCT	20	14
case studies	2	0
Economic evidence	2	1
RCT, randomized controlled trial		

sevelamer but did not investigate its clinical use ($n=29$). The remaining 28 records were included in the review. Review of the reference lists of the systematic review and the meta analysis identified two further papers for inclusion. An additional study, submitted to a meeting in 2000 but otherwise apparently unpublished, was identified in a review article and also included, bringing the total to 31 (Table 1).

Meeting abstracts from 2002 to date were identified by searching BIOSIS Previews, <http://www.datastarweb.com>, 1996 to date, using the search strategy "sevelamer AND (hemodialysis OR haemodialysis) AND LG=EN AND PT=MEETING\$ AND (YEAR=2002 OR YEAR=2003 OR YEAR=2004 OR YEAR=2005)" on February 16, 2005. A total of 21 records were retrieved, of which nine were excluded because they were animal studies ($n=1$), studies that did not investigate the clinical use of sevelamer ($n=3$), or duplicate publications of data presented in full papers ($n=5$). The remaining 12 were included in the review. In addition, abstracts from the American Society of Nephrology (ASN) Annual Meeting 2004 were searched on January 20, 2005 (www.abstracts2view.com), using the search terms "(sevelamer OR Renagel) AND hemodialysis." This yielded 14 records, of which 10 were excluded because they were animal studies ($n=3$) or did not investigate the clinical use of sevelamer in hemodialysis patients ($n=7$), leaving four abstracts for inclusion in the review (Table 1).

The searches were updated on April 29, 2005. After excluding duplicates, a total of 23 new records were identified, of which 17 were excluded for the following reasons: nonsystematic reviews ($n=6$), letters ($n=3$), and articles that mentioned sevelamer but did not investigate its clinical use ($n=8$). Six articles remained, all full papers, and were included (Table 1).

For each outcome, preference was given to level 1 and 2 evidence (see Editorial Information on inside back cover). Level 3 evidence was also included where level 1 and 2 evidence was lacking or conflicting. Outcomes from original level 2 or 3 studies, covered in level 1 evidence, were not considered separately in this review. As a result, five level 3 papers (Goldberg et al. 1998; Wilkes et al. 1998; Bleyer et al. 1999; Chertow et al. 1999b; Slatopolsky et al. 1999) and four level 3 abstracts (Marino et al. 2002; Mitsopoulos et al. 2002a; Sonikian et al. 2002; Yamada et al. 2004) which presented data only on outcomes for which substantial level 1 and 2 evidence was identified are not considered in this review. Two level 2 papers presented only outcomes data that were already included in level 1 evidence and are not discussed separately (Chertow et al. 1997; Chertow et al. 1999a).

Disease overview

Chronic kidney disease

Chronic kidney disease (CKD) is classified by the National Kidney Foundation (NKF) guidelines into five stages of severity, defined according to the glomerular filtration rate (GFR) (NKF 2003). Stage 5, kidney failure, is also known as end-stage renal disease (ESRD) or established renal failure (ERF), and requires renal replacement therapy (RRT; regular dialysis or a kidney transplant) if the patient is to survive (NSF 2004). Dialysis must be repeated at regular intervals for the rest of the patient's life or until a successful kidney transplant is performed. The major forms of dialysis are hemodialysis and peritoneal dialysis, though only hemodialysis is considered in this review. CKD is a priority area for the UK National Health Service (NHS), and standards of care are recommended in the National Service Framework for renal services (NSF 2004). These recommend that CKD management should begin before dialysis is required, as this improves outcomes. Treatment should include correction of anemia, improvement of nutrition, preventing the development of renal bone disease, management of comorbid diseases (e.g. cardiovascular disease, diabetes), and helping the patient to choose and prepare for a particular form of RRT (NSF 2004).

CKD is a common disorder, which is increasing in prevalence as the average age of populations increases. In England, there were 547 patients per million population undergoing RRT in 2001, up from 396 per million population in 1992 (NSF 2004). In the USA the number of patients on RRT in 2001 was 1403 per million population, and in Europe it varied from 606 (Norway) to 1022 per million population (Catalonia, Spain) (NSF 2004). In England in 2001, patients on RRT were divided approximately equally between those with a functioning transplant and those on dialysis. However, the number on hospital hemodialysis is projected to increase faster than those on other treatments (NSF 2004).

CKD imposes considerable economic and social burdens on the patients, their families, and healthcare providers (NSF 2004). It has been estimated that the treatment of patients undergoing RRT accounts for 1–2% of the total UK NHS annual budget, while hemodialysis is estimated to cost approximately £21 000 per patient per year (NSF 2004). Mortality in CKD patients is higher compared with the general population; in a survey of 5% of US Medicare recipients (over 1 million people), the 2-year risk of death was 17.7 per 100 patient-years for patients with CKD compared

with 5.5 per 100 patient-years for those without CKD (Foley et al. 2005). Cardiovascular disease accounts for most of this excess mortality (McCullough 2004). Patients with CKD have been shown to have higher risks of congestive heart failure (30.7 vs 8.6 per 100 patient-years) and atherosclerotic vascular disease (35.7 vs 14.1 per 100 patient-years) compared with those without CKD (Foley et al. 2005).

Hyperphosphatemia in CKD

Hyperphosphatemia is common in patients with stages 4 and 5 CKD. In healthy adults, phosphate absorbed from the diet is excreted by the kidney, and average daily excretion balances average daily absorption (Emmett 2004). This is achieved by large amounts of phosphate being filtered from the blood into the renal tubule. More than 90% of the filtered phosphate is then reabsorbed to maintain phosphate balance. Phosphate reabsorption is regulated by parathyroid hormone (PTH); increased serum PTH reduces phosphate reabsorption in the kidney tubule (NKF 2003). In advanced CKD (stage 4 or 5), when the GFR has fallen to <30 mL/min per 1.73 m², the kidney can no longer adequately handle phosphate loads and hyperphosphatemia develops (NKF 2003).

The average phosphorus intake of adults in North America and Europe is approximately 1000 mg/day in women and 1500 mg/day in men, of which about 60–70% is absorbed. A typical 4-h hemodialysis session removes approximately 1000 mg of phosphorus (Emmett 2004). However, since hemodialysis is

normally performed every few days, this is not adequate to remove enough phosphate to restore normal serum phosphate levels (Hergesell & Ritz 2002).

Phosphate balance is closely connected with calcium balance and bone metabolism, and numerous interrelated factors influence the level of serum phosphate in patients with CKD (NKF 2003). Fig. 1 illustrates some of the mechanisms involved.

Normal kidneys produce the active form of vitamin D, which increases absorption of calcium and phosphate from the gut. In CKD, levels of active vitamin D drop, producing hypocalcemia, which in turn stimulates release of PTH. PTH increases bone resorption and release of calcium and phosphate from the skeleton, thereby increasing serum calcium and tending to correct the hypocalcemia. In healthy individuals, PTH also increases urinary phosphate excretion by decreasing tubular reabsorption. However, in advanced CKD the kidneys are unable to remove the excess phosphate and hyperphosphatemia results (NKF 2003). High levels of serum phosphate are associated with hyperplasia of the parathyroid glands (Slatopolsky et al. 2001) and directly stimulate PTH synthesis and secretion (Slatopolsky et al. 2001; NKF 2003), producing a positive feedback loop in which elevated PTH and serum phosphate levels increase each other and move the system further from normal values. Some medical interventions intended to correct aspects of bone and mineral metabolism in CKD may also contribute to hyperphosphatemia. For example, administration of calcitriol (an active form of vitamin D) to patients with CKD may help to correct hypocalcemia and reduce the excess secretion of PTH, but may also aggravate hyperphosphatemia by increasing intestinal absorption of phosphate (NKF 2003).

Consequences of hyperphosphatemia

Hyperphosphatemia, via its effects on PTH, is established as one of the causes of osteitis fibrosa in CKD patients (Drüeke 2000; NKF 2003). Osteitis fibrosa is characterized by high serum PTH, high resorption and high turnover of bone, and may produce skeletal softening and/or deformation. The high bone turnover releases skeletal phosphate and calcium and may further increase serum phosphate levels (see above). The pathogenesis of the other main form of bone disease in patients with CKD, adynamic bone disease, is not fully understood, but is thought to be related to oversuppression of PTH by high calcium intake and/or administration of calcitriol (NKF 2003). Adynamic bone disease is characterized by an unusually low turnover of bone and occurs in 15–60% of dialysis patients (NKF 2003). This low bone turnover means that calcium and phosphate are not absorbed into bone and accumulate in the blood. Adynamic bone disease can thus contribute to hyperphosphatemia and hypercalcemia.

In a study of 202 patients followed for a mean of 45 months after beginning RRT, a serum phosphate level >1.85 mmol/L after 1 year of dialysis was associated with a 2.63 times higher risk of requiring surgical removal of the parathyroid glands (parathyroidectomy) than in those with a serum phosphate level ≤1.85 mmol/L ($P=0.006$) (Jorna et al. 2004). The association between elevated serum phosphate and risk of parathyroidectomy was independent of PTH level, and the authors considered it was likely to be causal (Jorna et al. 2004).

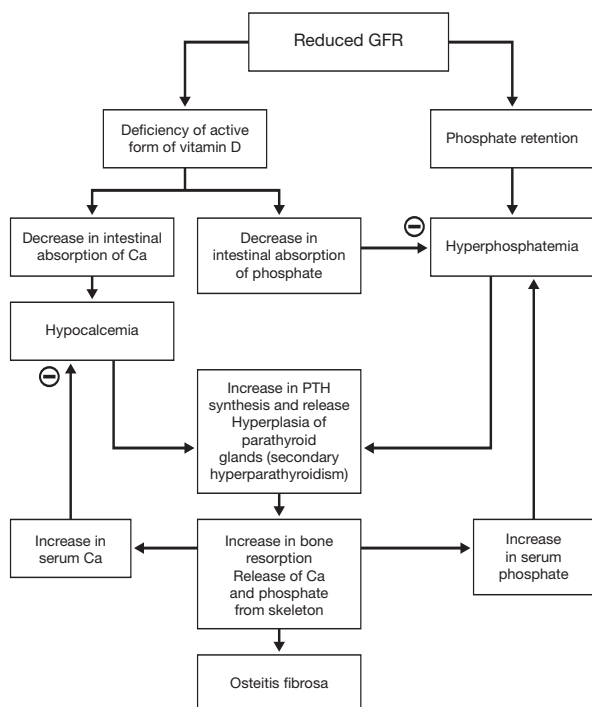


Fig. 1 | Pathogenesis of hyperphosphatemia and abnormalities of mineral and bone metabolism in chronic kidney disease. Ca, calcium; GFR, glomerular filtration rate; PTH, parathyroid hormone

Elevated serum phosphate has been shown to be a risk factor for increased mortality in hemodialysis patients (Block et al. 1998, 2004), and this mortality risk was independent of PTH (Block et al. 1998). A similar risk was observed if the serum calcium-phosphate product ($\text{Ca} \times \text{P}$; the calcium concentration in mg/dL multiplied by the phosphate concentration in mg/dL) exceeded $72 \text{ mg}^2/\text{dL}^2$ (Block et al. 1998). The Dialysis Outcomes and Practice Patterns Study (DOPPS), conducted in over 6000 dialysis patients from seven countries, also observed that high serum phosphate and $\text{Ca} \times \text{P}$ were associated with significantly ($P < 0.0001$) increased cardiovascular and all-cause mortality (Young et al. 2004). High serum calcium was also associated with an increased risk of death in two studies (Block et al. 2004; Young et al. 2004) but not in another (Block et al. 1998). It has been suggested that serum phosphate may be the major determinant of $\text{Ca} \times \text{P}$ product (Jorna et al. 2004).

Hyperphosphatemia and elevated $\text{Ca} \times \text{P}$ product are associated with soft-tissue calcification, in which calcium phosphate minerals are laid down in soft tissues, such as the blood vessels (vascular calcification), eyes (ocular calcification), visceral organs (visceral calcification), skin (cutaneous calcification), and around the joints (periarticular calcification) (Drüeke 2000; NKF 2003). Soft-tissue calcification is most common when $\text{Ca} \times \text{P}$ exceeds $70 \text{ mg}^2/\text{dL}^2$ (NKF 2003), and is a major mortality and morbidity risk factor in CKD patients (NKF 2003). It can occur in patients with elevated PTH and in patients with normal PTH and adynamic bone disease (Drüeke 2000).

Soft-tissue calcification in CKD—effects on morbidity and mortality

The most serious clinical consequences of soft-tissue calcification are due to visceral or vascular calcification, and may be one mechanism underlying the excess mortality risk with high serum phosphate and/or $\text{Ca} \times \text{P}$ observed in hemodialysis patients (Salusky & Goodman 2000; NKF 2003). It should be noted that calcium overload can also occur without hypercalcemia, as can the clinical consequences (e.g. in uremic patients where transfer to the skeletal buffer is the only route available to “eliminate” excess ingested calcium). Visceral calcification of the heart muscle, valves, and/or cardiac conduction system may result in congestive heart failure, cardiac arrhythmias, and heart block, while calcium deposition in the lungs may produce pulmonary fibrosis, pulmonary hypertension, and right ventricular hypertrophy (NKF 2003).

The prevalence of vascular calcification increases with the length of time a patient has been on dialysis; prevalence has been reported as 27% in patients on dialysis for less than 1 year compared with 83% in those on dialysis for more than 8 years (NKF 2003). It can involve any artery and shows little tendency to regress. There are two main forms of vascular calcification (NKF 2003); arteriosclerosis (medial calcification), in which calcium deposits are laid down in the artery wall stiffening it and reducing elastic arterial compliance, and atherosclerosis (intimal calcification), in which calcium deposits are laid down in plaques on the inner surface of the arterial wall which partially occlude the lumen and restrict blood flow. Both forms of arterial calcification have been associated with disturbances of calcium and phosphate balance (Drüeke & Rostand 2002), and both can cause

cardiovascular complications. Reduction in elastic arterial compliance increases the strain on the heart and contributes to the development of left ventricular hypertrophy (Level et al. 2001). In a cohort of 202 hemodialysis patients, individuals with either intimal or medial arterial calcification had a significantly ($P < 0.01$) higher all-cause mortality than patients without calcification (London et al. 2003). A further study in 110 hemodialysis patients found that arterial calcification score (assessed by the presence of calcified plaques detected by ultrasonography and/or calcification visible on soft-tissue radiographs) and arterial elasticity, were the only risk factors independently associated with all-cause and cardiovascular mortality over a mean of 53 months of follow-up (Blacher et al. 2001).

The causes of arterial calcification are not fully understood. It appears to be an active process in which vascular smooth muscle cells actively take up phosphate and begin to express osteoblast markers (osteoblasts are bone-forming cells) (Floege & Ketteler 2004). Endogenous regulators of calcification, such as fetuin A, osteoprotegerin and matrix Gla protein, may be associated with the pathogenesis of vascular calcification, but their precise role remains to be clarified (Kazama 2004; Floege & Ketteler 2004).

Some authorities consider that high doses of calcium salts used as phosphate binders may play an important role, via intestinal absorption of calcium and elevated serum $\text{Ca} \times \text{P}$ product (Salusky & Goodman 2000; Drüeke 2001). In support of this, a study in 120 hemodialysis patients found that, after adjustment for confounding factors, the prescribed dose of calcium carbonate was one of four variables independently associated with arterial calcification (measured by ultrasonography) (Guérin et al. 2000). A further small study in 24 hemodialysis patients found that impaired arterial compliance was associated with duration of hemodialysis and serum total calcium (Level et al. 2001).

Others have argued that dyslipidemia is an important determinant of vascular calcification (McCullough et al. 2004; Qunibi et al. 2004). A systematic review of 30 studies of coronary vascular calcification in patients with CKD found that the most consistent determinants of calcification were increasing age and duration of dialysis (McCullough et al. 2004). Measures of calcium-phosphate balance were found to be associated with calcification in eight studies, while 20 studies found no association (McCullough et al. 2004). The authors also reported that serum lipid profile was associated with vascular calcification in four studies, and concluded that dyslipidemia was possibly associated with vascular calcification, whereas calcium-phosphate balance showed inconsistent results and was “likely not related” (McCullough et al. 2004). However, it seems that results linking lipid profile to vascular calcification may also be inconsistent, since the authors identified two further studies that found no association between vascular calcification and lipid profile (McCullough et al. 2004). In a study of 453 mainly African-American patients on hemodialysis, it was found that 2-year mortality did not correlate with hyperlipidemia (Fleischmann et al. 2001).

There is evidence that the two forms of arterial calcification may differ in their epidemiology. In a cohort of 202 hemodialysis patients, intimal calcification was observed mainly in older patients with typical atherosclerotic risk factors, including dyslipidemia,

Table 2 | Main currently available phosphate binders (adapted from Loghman-Adham 2003; Emmett 2004)

Drug class	Compound	Phosphate-binding effects		Disadvantages
		% of dietary phosphorus absorbed ^a	Phosphorus binding/gram of drug	
Nonaluminum, noncalcium phosphate binders	Sevelamer	Not available	77.5–84 mg	Large doses required (5–7 g/day) Gastrointestinal effects at high doses, similar frequency to high-dose calcium salts Absorption of released hydrochloride may contribute to metabolic acidosis
Aluminum salts	Aluminum hydroxide, aluminum carbonate	Normal subjects: 18% Dialysis patients: 35–49%	Not available	Large doses required Unpleasant taste Can cause constipation Aluminum accumulation and toxicity to skeleton, central and peripheral nervous system, parathyroid glands, and hematopoietic cells
Calcium salts	Calcium carbonate	Normal subjects: 44%	4.65–17 mg	Large doses required (8–10 g/day) Poor phosphate binding at neutral pH Hypercalcemia reported in one-third of patients
	Calcium acetate	Normal subjects: 26%	6.76–27 mg ^b	Large doses required (6–8 g/day) ^c Gastrointestinal effects can occur May be associated with hypercalcemia
Lanthanum salts	Lanthanum carbonate	Not available	Not available	Moderate doses required (1.5–3 g/day) ^d Gastrointestinal adverse events can occur ^d Small amounts of lanthanum are absorbed and there is a possibility of accumulation with chronic use; long-term safety data are needed to assess this

^aWithout phosphate binders, 66–77% of dietary phosphate is absorbed (Emmett 2004).
^bOriginal reference (Loghman-Adham 2003) gives the lower end of the range as 46.76, but this does not agree with the mmol value given in the same source, which is 0.218. However, a value of 6.76 mg for the lower end of the range does match the mmol value.
^cSource: PhosLo® US package insert.
^dSource: Fosrenol® prescribing information (available at: <http://www.fosrenol.com/prescribingInfo.pdf>).

while medial calcification was observed in young and middle-aged patients and was associated with CKD-specific factors, including longer duration of hemodialysis and high serum phosphate (London et al. 2003). Such differences in epidemiology between the two forms may explain the apparent inconsistency of reported associations between vascular calcification and risk factors, but further research is required to clarify this.

A small number of patients with vascular calcification and advanced CKD develop progressive skin ulcerations and tissue necrosis, a syndrome called calciphylaxis or calcific uremic arteriolopathy (Llach 2001; NKF 2003). The mechanism is not well understood, although hyperphosphatemia is an important factor (NKF 2003), and calcium toxicity may also be involved (Llach 2001). The prognosis of patients with calcific uremic arteriolopathy is poor, with most dying of sepsis or ischemic events (Llach 2001).

Metabolic acidosis in CKD

Blood pH, partial pressure of carbon dioxide (CO₂), and serum bicarbonate concentration are chemically related to one another by a fixed equation, and the key determinant of blood pH is the ratio of dissolved CO₂ to bicarbonate in the serum. In healthy individuals, the lungs adjust the partial pressure of CO₂ (which determines the concentration of dissolved CO₂) and the kidneys adjust the

concentration of bicarbonate. A fall in blood pH resulting from an increase in CO₂ is termed respiratory acidosis, while a fall in blood pH resulting from a fall in serum bicarbonate is termed metabolic acidosis.

Metabolic acidosis in patients with kidney failure may be linked to malnutrition and inflammation (Kalantar-Zadeh et al. 2004), and it has been suggested that acidosis could be associated with an increased risk of death and increased dissolution of bone (Brezina et al. 2004). The NKF Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines recommend that predialysis serum levels of total CO₂ should be maintained at ≥22 mmol/L (NKF 2003). Total CO₂ is readily measured by automated analyzers and is considered an appropriate proxy for serum bicarbonate (Bommer et al. 2004). However, the NKF K/DOQI guidelines consider that acidosis does not play an important role in the pathogenesis of bone disease in CKD (NKF 2003). Furthermore, results from the DOPPS study found that patients with moderate acidosis (predialysis serum total CO₂ levels of 20.1–22 mmol/L) had lower mortality and hospitalization risks than patients with either severe acidosis (predialysis serum total CO₂ levels of ≤17 mmol/L) or high predialysis serum total CO₂ level (>27 mmol/L) (Bommer et al. 2004). There is a lack of evidence for reducing acidosis with bicarbonate supplementation, and its true clinical impact on calcification is unclear.

Table 3 | Phosphate binder usage (values may not sum as patients may have been taking more than one agent. The USRDS data were collected prior to 1996 and pre-date the introduction of sevelamer)

	Lorenzo et al. 2004	Manley et al. 2004 (DCI)	Manley et al. 2004 (USRDS)
Patient population	1312 HD patients from 7 centers in Spain	10 474 HD patients treated at DCI units in the US	Data on a sample of 1998 HD patients from the USRDS
Phosphate binder used (% of patients)			
Any phosphate binder	71%	88%	80%
Calcium acetate	NR ^a	43.4%	35%
Calcium carbonate	NR ^a	24%	35%
Any calcium salt	51%	NR	NR
Sevelamer	21%	31.1%	NR
Aluminum	16%	2.8%	6.1–10%

^aOriginal source did not distinguish between individual calcium salts.
DCI, Dialysis Centre Inc; HD, hemodialysis; NR, not reported; USRDS, United States Renal Data System.

Current therapy options

There are three components to a strategy for controlling serum phosphate in ESRD: phosphate removal by dialysis, dietary restriction of phosphate, and use of oral phosphate binders (Emmett 2004). The effect of dietary restriction and dialysis is limited because phosphate is abundant in all food groups, and maintaining an adequate protein intake will also result in a phosphate intake that exceeds the amount that can be removed by most forms of dialysis (Loghman-Adham 2003; Emmett 2004). However, there is some recent evidence that quotidian (i.e. short daily dialysis) is more effective than conventional hemodialysis in reducing serum phosphate and the need for phosphate binders (Achinger & Ayus 2005).

Oral phosphate binders are normally required for most patients (Emmett 2004). The main currently available phosphate binders are

Table 4 | NKF K/DOQI targets for parameters of calcium–phosphate balance in patients with CKD stage 5 (adapted from NKF 2003)

Parameter	Target
Serum phosphate (mg/dL)	3.5–5.5
Serum calcium (mg/dL)	8.4–9.5
Serum Ca × P (mg ² /dL ²)	<55
Serum intact PTH (pmol/L)	150–300
Elemental calcium intake from phosphate binders (mg/day)	≤1500

Ca × P, calcium–phosphate product; PTH, parathyroid hormone.

listed in Table 2. Other compounds are used occasionally or are in development (e.g. magnesium salts and iron preparations) (Hergesell & Ritz 2002; Loghman-Adham 2003; Emmett 2004).

The occurrence of progressive and sometimes fatal aluminum intoxication in some patients taking aluminum salts has been described as a “medical catastrophe” (Hergesell & Ritz 2002), and calcium salts have become the most widely used class of phosphate binder (Salusky & Goodman 2000). Table 3 shows the usage of phosphate binders reported in various surveys. Lanthanum carbonate has only recently been approved (October 2004 in the USA) and did not feature in the surveys.

Unmet needs

Significant problems remain with calcium salts. Large doses are required, especially with calcium carbonate. Calcium carbonate binds phosphate poorly at neutral pH and may have lower effectiveness in patients with impaired gastric acid secretion (Loghman-Adham 2003). Calcium acetate has about twice the phosphate-binding capacity of calcium carbonate, expressed per milligram of elemental calcium, and can be given at a somewhat lower dose. However, it can cause gastrointestinal adverse effects (Loghman-Adham 2003). As discussed in the previous section, calcium salts have been associated with an increased incidence of arterial calcification, which has been associated with elevated cardiovascular mortality, although the nature of the relationship is not known (Emmett 2004). The lower dose of elemental calcium required with calcium acetate compared with calcium carbonate should theoretically reduce the amount of calcium absorbed and hence the risk of hypercalcemia, but a subanalysis of a randomized controlled trial (RCT) found that changes in arterial calcification (as measured by electron beam tomography) in patients receiving calcium acetate were similar to those in patients receiving calcium carbonate (Chertow et al. 2003).

Lanthanum carbonate has only recently become available (FDA approval October 2004). It has the potential to reduce the dosage somewhat compared with calcium salts; median dose required for phosphate control reported as 2.25 g/day for lanthanum carbonate compared with 3 g/day for calcium carbonate (Loghman-Adham 2003). However, small amounts of lanthanum are absorbed and concerns remain that chronic exposure may lead to lanthanum accumulation and potential toxicity (Hergesell & Ritz 2002; Emmett 2004). Long-term safety data are needed to address these concerns (Hergesell & Ritz 2002; Loghman-Adham 2003).

Compliance with treatment guidelines

The NKF K/DOQI treatment guidelines set out targets for various components of calcium–phosphate balance (Table 4).

Several surveys have shown that few patients successfully attain these targets. In a survey of 188 dialysis patients in the USA, only 11 (5.9%) were within the recommended ranges for all five parameters (Tomasello et al. 2004). In another survey among 1312 patients on hemodialysis at seven centers in Spain, only 13% met K/DOQI targets for Ca × P, serum phosphate, and PTH (Lorenzo et al. 2004). While more than half the patients surveyed in the DOPPS

Table 5 | Effects of sevelamer on serum phosphate, calcium (Ca), calcium-phosphate product (Ca × P), parathyroid hormone (PTH), and incidence of hypercalcemia

Level of evidence	Design	Treatment and mean dose	Outcome					Reference
			Serum phosphate	Serum Ca	Incidence of hypercalcemia (≥11 mg/dL or >2.8 mmol/L) ^a	Serum Ca × P	Serum PTH	
1	Meta analysis	Sevelamer	Mean decrease 2.14 mg/dL vs baseline (<i>P</i> <0.001) (11 studies)	Mean increase 0.09 mg/dL vs baseline (NS) (9 studies)	NR	Mean decrease 15.9 mg ² /dL ² vs baseline (<i>P</i> <0.001) (9 studies)	Mean decrease 35.99 pg/mL vs baseline (<i>P</i> =0.026) (3 studies)	Burke et al. 2003
1	Systematic review	Sevelamer Sevelamer plus supplemental Ca Placebo CaAc CaCO ₃	Lower with S vs placebo (<i>P</i> <0.04) (1 study) NSD S vs Ca salts (4 studies) NSD S vs S+Ca (1 study)	NSD S vs placebo (1 study) NSD S vs CaCO ₃ (1 study) NSD S vs S+Ca (1 study) Smaller increase with S vs Ca salts (<i>P</i> <0.01) (3 studies)	Lower with S vs CaAc or CaCO ₃ (<i>P</i> <0.0001) (2 studies)	NSD S vs Ca salts (3 studies) NSD S vs S+Ca (1 study)	NSD S vs Ca salts (4 studies) NSD S vs S+Ca (1 study)	Manns et al. 2004
2	Open, RCT, 34 weeks, n=40 in total	Sevelamer 4.09 g/day CaAc 3.9 g/day	Similar decrease for S and CaAc ^b	NSD vs baseline for S and CaAc ^b	NSD S vs CaAc	Similar decrease for S and CaAc ^b	Similar decrease for S and CaAc ^b	Hervás et al. 2003
2	Open, RCT, 52 weeks, n=36 (S), n=46 (CaCO ₃) ^c	Sevelamer 5.9 g/day CaCO ₃ 3.9 g/day	NSD S vs CaCO ₃	Smaller increase with S vs CaCO ₃ (<i>P</i> <0.01)	Lower with S vs CaCO ₃ (<i>P</i> <0.01)	NSD S vs CaCO ₃	Decrease for CaCO ₃ vs baseline (<i>P</i> <0.01); NSD vs baseline for S ^b	Braun et al. 2004
2	Double-blind, RCT, 8 weeks, n=50 (S), n=48 (CaAc)	Sevelamer 6.9 g/day CaAc 7.1 g/day	Higher with S vs CaAc (<i>P</i> =0.0006)	Lower with S vs CaAc (<i>P</i> <0.0001)	Lower with S vs CaAc (<i>P</i> <0.0001)	Higher with S vs CaAc (<i>P</i> =0.022)	NSD S vs CaAc	Qunibi et al. 2004

^aDefinition varied between studies; 2.8 mmol/L = 11.2 mg/dL.
^bNo between-group statistical comparison reported.
^cNinety-three of the 114 patients randomized were included in the primary publication of the Treat To Goal study (Chertow et al. 2002), which was one of the studies included in Manns et al. (2004).
 CaAc, calcium acetate; CaCO₃, calcium carbonate; NR, not reported; NS, not statistically significant; NSD, no statistically significant difference; RCT, randomized controlled trial; S, sevelamer.

study were outside the target ranges for serum calcium, serum phosphate, and PTH across all seven countries, there was a trend towards improvement between the first DOPPS survey in 1996–2001 and the second in 2002–2004 (Young et al. 2004). In a small survey in 69 hemodialysis patients at a single center in the Czech Republic (not included in DOPPS), only 20% of patients met all the targets (Smrzova et al. 2004). The low level of compliance with the NKF K/DOQI guidelines thus indicates that substantial unmet needs still remain in the control of hyperphosphatemia in hemodialysis patients.

One problem is that patient adherence to phosphate binder therapy is poor (Hergesell & Ritz 2002); in a survey of 188 US dialysis patients, 37.8% of patients admitted noncompliance (compliance defined as at least 80% of phosphate binders taken correctly) (Tomasello et al. 2004). The main reasons given for noncompliance were being unaware of the correct prescription (37% of noncompliant patients) and forgetting the dose (30%). However, the burdensome nature of the large doses was also mentioned by some patients: 6% said there were too many pills, 8% said they

missed a dose because they were eating out, and 4% said the binder doses were too big to carry (Tomasello et al. 2004).

Although current phosphate binders may be effective, they have limitations and adverse effects that may compromise optimal treatment. Alternative agents with improved therapeutic value should retain or improve on the effectiveness of current treatments while avoiding or reducing their limitations. The attributes of an ideal phosphate binder include effective control of serum phosphate and Ca × P product to within K/DOQI target range; avoidance of hypercalcemia; absence of metal absorption that may lead to toxicity; absence of troublesome adverse events; improved patient acceptability (e.g. reduction of the dose required leading to a lower tablet burden) and/or improved patient adherence; wide dose range and flexible dosing to accommodate individual differences in dietary phosphate intake; reduction in the risk of soft-tissue and especially vascular calcification; improvement in the morbidity due to bone disease; improvement in cardiovascular morbidity and mortality; improvement in quality of life; and demonstrated cost-effectiveness.

Clinical evidence with sevelamer

Numerous outcomes have been measured in the published evidence. The majority of the evidence related to disease-oriented outcomes, such as effects on serum phosphate, serum calcium, dyslipidemia, serum uric acid, metabolic acidosis, arterial calcification and bone mineral density. Patient-oriented outcomes included cardiovascular morbidity and mortality, improvement of calcific uremic arteriopathy, and risk of hospitalization, but the evidence base for these outcomes was smaller.

Serum phosphate

The evidence demonstrates that sevelamer is effective in reducing serum phosphate from pretreatment (baseline) values. Most of the evidence (all five studies in the systematic review, and two of three further RCTs) shows that sevelamer is as effective as calcium salts in reducing serum phosphate, and that sevelamer alone is as effective as sevelamer plus supplemental calcium (Table 5). However, one RCT (Qunibi et al. 2004) reported that serum phosphate was significantly higher with sevelamer than with calcium acetate (Table 5), although at 8 weeks' duration this study was shorter than most of the other trials [six of the seven studies reviewed by Manns et al. (2004) were >8 weeks]. Furthermore, this study used a formulation of sevelamer (403 mg capsules) that is no longer available, and did not use a dose of sevelamer that was equipotent to the dose of calcium acetate. The Qunibi et al. (2004) study used a double-blind design, whereas the other comparisons between sevelamer and calcium salts were open label and thus could be considered weaker. However, blinding should have had little, if any, effect on objective measurements of absolute values such as serum phosphate. Qunibi et al. (2004) also used a different measure of serum phosphate, time-averaged serum phosphate over 1–8 weeks as opposed to mean change from baseline to end of treatment, compared with the other studies, and it is possible that this may account for the different results.

Serum calcium

Burke et al. (2003) found in their meta analysis that sevelamer had a small and statistically insignificant effect on serum calcium (see Table 5). The results of the review by Manns et al. (2004) are consistent with this, as the four RCTs comparing sevelamer with calcium salts showed only small mean changes in serum calcium, ranging from an increase of 0.2 mg/dL to a decrease of 0.05 mg/dL with sevelamer (Manns et al. 2004). This wide range may be due in part to variations in the dialysate calcium concentration utilized in the studies. In all four studies the mean increase with sevelamer was lower than with the calcium salt; the difference was statistically significant in three studies ($P<0.01$) and not statistically significant in one study (Manns et al. 2004). There was no statistically significant difference between sevelamer alone and sevelamer with supplemental calcium (see Table 5).

On balance, the current evidence shows that sevelamer has little effect on serum calcium levels, and is less prone to increase serum calcium levels than calcium salts, although none of these trials was powered to detect a difference.

Incidence of hypercalcemia

There is strong evidence that sevelamer is associated with a statistically significantly ($P<0.01$) lower incidence of hypercalcemia than calcium salts (both the trials in the systematic review that reported data on this outcome, and two of three further trials) (see Table 5). Although one RCT reported no statistically significant difference between sevelamer and calcium acetate, it was not powered to detect a difference (Hervás et al. 2003).

Serum $\text{Ca} \times \text{P}$ product

Most of the evidence demonstrates that sevelamer is as effective as calcium salts in decreasing serum $\text{Ca} \times \text{P}$ (see Table 5). One exception, the RCT of Qunibi et al. (2004), reported that calcium acetate decreased $\text{Ca} \times \text{P}$ significantly more than sevelamer. However, as discussed in the section on serum phosphate, this study was of short duration compared with the others and used time-averaged concentrations rather than change from baseline to endpoint.

Parathyroid hormone

Evidence from the meta analysis, systematic review, and two of three further RCTs shows that sevelamer was as effective as calcium salts in reducing serum PTH, and that addition of supplemental calcium did not produce a statistically significant difference (see Table 5).

Intact PTH, the form measured in the studies in Table 5, consists of 84 amino acids (1–84 PTH). The N-terminally-truncated molecule (7–84 PTH) may have different effects from the intact molecule, being associated with hypocalcemia and decreased bone turnover (rather than hypercalcemia and increased bone turnover). In a small study of 17 hemodialysis patients, sevelamer treatment for 5 weeks significantly ($P=0.03$) reduced serum 1–84 PTH, but had no statistically significant effect on 7–84 PTH (Chudek et al. 2003). The clinical significance of effects on different forms of PTH remains unresolved.

Vascular calcification

There is evidence from the RCT conducted by the Treat to Goal Working Group (Chertow et al. 2002) that sevelamer is associated with significantly greater reductions in calcification scores (using electron beam tomography) than calcium salts after 52 weeks of treatment (Table 6). Subanalyses of the primary study (Chertow et al. 2003; Braun et al. 2004) found that this remained true when sevelamer was compared with either calcium acetate (US patients; Chertow et al. 2003) or calcium carbonate (German and Austrian patients; Braun et al. 2004) (see Table 6). The benefit in reduced calcification was greatest in patients with poorly controlled phosphate and $\text{Ca} \times \text{P}$ product (Braun et al. 2004). A further analysis (Raggi et al. 2004) reported that mitral and aortic valve calcification scores were not significantly different between the treatment groups, but that significantly more sevelamer patients experienced a regression in total calcification burden (derived by combining vascular and valve calcification scores) compared with calcium-treated patients (see Table 6).

A further subanalysis presented data from 150 patients in the Treat to Goal study who had electron beam tomography data at baseline and after either 26 or 52 weeks of treatment with sevelamer or

Table 6 | Effects of sevelamer compared with calcium salts on vascular calcification (all level 2 evidence)

Design	Treatment and mean dose	Outcome						Reference
		Mean change in coronary artery calcification score vs baseline at 52 weeks	Mean change in aorta calcification score vs baseline at 52 weeks	Mean change in mitral valve calcification score vs baseline at 52 weeks	Mean change in aortic valve calcification score vs baseline at 52 weeks	Patients with no progression of total calcification burden	Patients with regression of total calcification burden	
Open, 52 weeks, n=62 (S), n=70 (Ca salts) ^a	Sevelamer 6.5 g/day Ca salts 4.3 g/day	S decrease 46 Ca salts increase 151	S decrease 532 Ca salts increase 185	NR	NR	NR	NR	Chertow et al. 2002
Calcification score assessor blinded to study treatment		($P<0.04$ S vs Ca salts)	($P=0.01$ S vs Ca salts)					
Subanalysis of Chertow et al. 2002, US patients only, n=108 randomized	Sevelamer 6.7 g/day CaAc 4.6 g/day	S increase 64 (NS vs baseline) CaAc increase 182 ($P=0.002$ vs baseline)	S decrease 127 (NS vs baseline) CaAc increase 181 ($P<0.0001$ vs baseline)	NR	NR	NR	NR	Chertow et al. 2003
Subanalysis of Chertow et al. 2002, German and Austrian patients, with 11 additional patients randomized, n=36 (S), n=46 (CaCO ₃) ^a	Sevelamer 5.9 g/day CaCO ₃ 3.9 g/day	S decrease 130 CaCO ₃ increase 200 ($P=0.02$ S vs CaCO ₃)	S decrease 897 CaCO ₃ increase 240 ($P<0.01$ S vs CaCO ₃)	NSD vs baseline for S and CaCO ₃	NSD vs baseline for S and CaCO ₃	NR	NR	Braun et al. 2004
Re-analysis of Chertow et al. 2002, to include data on heart valve calcification	Sevelamer 6.5 g/day Ca salts 4.3 g/day	NR	NR	S decrease 655 Ca salts increase 98 (NS S vs Ca salts)	S increase 24 Ca salts increase 24 (NS S vs Ca salts)	S 45% Ca salts 28% ($P=0.047$ S vs Ca salts)	S 26% Ca salts 10% ($P=0.02$ S vs Ca salts)	Raggi et al. 2004
^a Patients with data at 52 weeks. Ca, calcium; CaAc, calcium acetate; CaCO ₃ , calcium carbonate; NR, not reported; NS, not statistically significant; NSD, no statistically significant difference; S, sevelamer.								

calcium salts (Chertow et al. 2004). In patients treated with calcium salts, the change in coronary calcification was significantly correlated with serum phosphorus ($r=0.22$, $P=0.04$) and $\text{Ca} \times \text{P}$ product ($r=0.26$, $P=0.02$), and the change in aortic calcification was significantly correlated with serum calcium ($r=0.28$, $P=0.01$). None of the corresponding correlations were statistically significant in the sevelamer group (Chertow et al. 2004).

As discussed in the Disease overview section above, medial calcification is associated with arterial stiffening. A separate study in Japan measured the change in pulse wave velocity in 15 patients during the 6 months before they were switched from calcium carbonate to sevelamer and during the 6 months after the switch (level 3 evidence; Takenaka & Suzuki 2005). Increased pulse wave velocity indicates increased arterial stiffness (London et al. 2004). In the 6 months before the switch, mean pulse wave velocity increased by 46 cm/s per month, while in the 6 months after switching to sevelamer pulse wave velocity decreased by 20 cm/s per month ($P<0.01$ for comparison between the two

periods). These findings indicate that calcium carbonate treatment was associated with a progressive increase in pulse wave velocity, which was reversed by sevelamer treatment (Takenaka & Suzuki 2005).

Calcific uremic arteriolopathy

An observational study reported data from eight patients with calcific uremic arteriolopathy (calciphylaxis) who were managed with zero-calcium dialysate and switched from calcium-based phosphate binders to sevelamer (Llach 2001). Six of the eight patients showed "dramatic improvement" (no criteria specified) in their skin lesions, according to the author, and four showed total healing (Llach 2001).

Case reports of three patients have described similar results. Russell et al. (2002) described a 73-year-old man with calcific uremic arteriolopathy and leg ulcerations, whose lesions healed after switching from calcium-based phosphate binders to sevelamer, discontinuing vitamin D analogs and receiving

Table 7 | Effects of sevelamer on serum low-density lipoprotein (LDL) cholesterol and total cholesterol

Level of evidence	Design	Treatment and mean dose	Outcome		Reference
			LDL cholesterol	Total cholesterol	
1	Meta analysis (10 studies)	Sevelamer	Mean decrease 31.38 mg/dL vs baseline ($P<0.001$)	Mean decrease 30.58 mg/dL vs baseline ($P<0.001$)	Burke et al. 2003
1	Systematic review	Sevelamer	Lower with S vs placebo (1 study)	Lower with S vs placebo (1 study)	Manns et al. 2004
		Placebo	Lower with S vs Ca salts (3 studies)	Lower with S vs Ca salts (2 studies)	
		CaAc CaCO ₃			
2	Open, RCT, 34 weeks, n=40 in total	Sevelamer 4.09 g/day CaAc 3.9 g/day	Decrease vs baseline for S ($P<0.05$); NSD vs baseline for CaAc	Decrease vs baseline for S ($P<0.05$); NSD vs baseline for CaAc	Hervás et al. 2003
2	Open, RCT, 52 weeks, n=36 (S), n=46 (CaCO ₃) ^a	Sevelamer 5.9 g/day CaCO ₃ 3.9 g/day	Decrease vs baseline for S ($P<0.01$); NSD vs baseline for CaCO ₃	Decrease vs baseline for S ($P<0.01$); NSD vs baseline for CaCO ₃	Braun et al. 2004

^aNinety-three of the 114 patients randomized were included in the primary publication of the Treat To Goal study (Chertow et al. 2002), which was one of the studies included in Manns et al. (2004). Ca, calcium; CaAc, calcium acetate; CaCO₃, calcium carbonate; NSD, no statistically significant difference; RCT, randomized controlled trial; S, sevelamer.

aggressive wound care. The healing was paralleled by a decrease in serum phosphate and Ca × P product (Russell et al. 2002). Don and Chin (2003) described two women with calcific uremic arteriolopathy whose lesions healed after switching from calcium-based phosphate binders to sevelamer and undergoing more frequent hemodialysis with a low-calcium dialysate. This treatment also resulted in a reduction in serum phosphate and Ca × P product (Don & Chin 2003).

These case reports and case series indicate that using sevelamer as part of a treatment regimen to reduce Ca × P product may have a beneficial effect in patients with calcific uremic arteriolopathy. However, it should be noted that other calcium-sparing phosphate binders may be equally effective, and no evidence has compared sevelamer with alternative noncalcium phosphate binding compounds in calcific uremic arteriolopathy.

Serum lipids

Strong evidence shows that sevelamer significantly reduces low-density lipoprotein cholesterol (LDL cholesterol) and total cholesterol, and that it is significantly more effective on these outcomes than calcium salts (Table 7).

Serum uric acid

Elevated serum uric acid concentrations are common in patients with advanced CKD and are associated with the development of gout, although clinically it is relatively insignificant. Nevertheless, evidence indicates that sevelamer treatment is associated with a statistically significant reduction in mean serum uric acid concentration compared with baseline, and in one RCT (Garg et al. 2005) the reduction observed with sevelamer was greater than that observed with calcium salts (Table 8).

Metabolic acidosis

Since some of the hydrochloride component of sevelamer is absorbed, this may theoretically promote the development of

acidosis, in contrast to the calcium-based phosphate binders. Absorption of hydrochloride increases the amount of H⁺ ions absorbed (acid load); the H⁺ ions react with bicarbonate ions in the serum to form CO₂ and water, reducing the serum bicarbonate concentration. If the excess CO₂ can be removed by the lungs (respiratory compensation), the ratio between CO₂ and bicarbonate (and hence blood pH) may be maintained within the normal range, although at lower absolute levels of CO₂ and bicarbonate.

Evidence is divided on whether sevelamer lowers serum bicarbonate more than calcium salts (Table 9). Of the studies reported in the systematic review, one showed no difference from placebo, one showed no difference between sevelamer with and without supplemental calcium, one showed no difference from calcium salts, and one showed lower serum bicarbonate with sevelamer compared with calcium salts (19.2 mmol/L vs 22.1 mmol/L, $P<0.0001$). A further RCT reported that after 8 weeks of treatment, mean serum bicarbonate was significantly lower with sevelamer than with calcium acetate (19.3 mmol/L vs 21 mmol/L, $P<0.0001$). A retrospective study in 17 patients treated with sevelamer for 2 years found that mean serum bicarbonate declined significantly during treatment (from 20 mEq/L to 17.9 mEq/L, $P=0.002$), while there was no statistically significant change in serum bicarbonate in seven control patients who received calcium- or aluminum-based phosphate binders for the same length of time (Sonikian et al. 2005). This study also reported significant increases in serum potassium (from 5.45 mEq/L to 5.75 mEq/L, $P=0.02$) and mean intact parathyroid hormone (from 132.8 pg/mL to 326.9 pg/mL, $P=0.0008$) in the sevelamer-treated patients, with no statistically significant change in the controls, and the authors suggest that secondary hyperparathyroidism and elevated serum potassium could be related to metabolic acidosis. However, they also reported that correlations between serum bicarbonate changes and sevelamer dose, and between serum bicarbonate and intact parathyroid hormone, were not significant (Sonikian et al. 2005). Two retrospective studies presented in abstract form reported that a higher proportion of sevelamer-treated patients had serum bicarbonate <20 mmol/L compared with patients receiving

Table 8 | Effects of sevelamer on serum uric acid

Level of evidence	Design	Treatment and mean dose	Outcome				Reference
			Mean change in serum uric acid vs baseline at 52 weeks	Patients with clinically significant decrease in uric acid concentration ^a	% change in mean serum uric acid vs baseline at end of treatment (12 weeks)	Mean serum uric acid during each treatment period	
2	Open, RCT, 52 weeks, n=81 (S), n=88 (Ca salts) ^b Subanalysis of Chertow et al. 2002	Sevelamer 6.5 g/day Ca salts ^c	S decrease 0.64 mg/dL Ca salts decrease 0.26 mg/dL (<i>P</i> =0.03 S vs Ca salts)	S 23% Ca salts 10% (<i>P</i> =0.02 S vs Ca salts)	NR	NR	Garg et al. 2005
2	Open, RCT, 52 weeks, n=36 (S), n=46 (CaCO ₃) ^b	Sevelamer 5.9 g/day CaCO ₃ 3.9 g/day	S decrease 40 µmol/L (<i>P</i> <0.0001 vs baseline) CaCO ₃ NR	NR	NR	NR	Braun et al. 2004
3	Open, 12 weeks, n=18 patients with severe secondary hyperparathyroidism	Sevelamer	NR	NR	Decrease 9% (<i>P</i> <0.05 vs baseline)	NR	Castro et al. 2002
3	Switching study in 45 patients	Standard phosphate binders for 6 months, then 1 month cotreatment, then S for 6 months	NR	NR	NR	S 5.9 mg/dL Standard binders 7 mg/dL (<i>P</i> =0.0001, S period vs standard period)	Sandberg et al. 2002

^aDefined by the authors as a reduction of 1.5 mg/dL or more.
^bPatients for whom both baseline and follow-up data were available.
^cMean dose not given, but in the primary analysis (Chertow et al. 2002), the mean dose was 4.3 g/day.
Ca, calcium; CaCO₃, calcium carbonate; NR, not reported; RCT, randomized controlled trial; S, sevelamer.

calcium salts (see Table 9), although since these studies were not randomized they may have been subject to selection bias.

A nonrandomized study reported in abstract form (Vlahakos et al. 2004) found that 2 years of treatment with sevelamer produced a reduction in the mean partial pressure of CO₂ and a slight reduction in serum pH, though serum pH remained within the normal range (see Table 9). This pattern is consistent with chronic metabolic acidosis in the sevelamer group (reflecting the increased acid load from the hydrochloride component), with respiratory compensation reducing the partial pressure of CO₂ to maintain serum pH in the normal range.

Thus, it seems that sevelamer can produce modest reductions in serum bicarbonate, but does not consistently do so. It is not clear whether such reductions are of clinical significance; the K/DOQI guidelines recommend that serum total CO₂ should not fall below 22 mmol/L (NKF 2003), but results from the DOPPS study found that a moderate acidosis (predialysis serum total CO₂ levels of 20.1–22 mmol/L) was associated with a reduction in hospitalization and mortality risk (Bommer et al. 2004). As mentioned earlier, there is a lack of evidence on the clinical significance of acidosis, the impact of bicarbonate supplementation, and what constitutes an appropriate endpoint.

Gastrointestinal tolerability

Gastrointestinal adverse events were not consistently defined and reported in the published studies. In the studies that provided some evidence on the occurrence of gastrointestinal adverse events for sevelamer compared with calcium salts the evidence was conflicting, with two studies reporting a higher incidence of gastrointestinal adverse events for sevelamer and four reporting no difference (Table 10).

In a single-group study in 19 hemodialysis patients in Italy switched from calcium carbonate (with or without additional aluminum salts) to sevelamer, two patients withdrew because of gastrointestinal adverse events (one for diarrhea, one for nausea and heartburn), and a further patient reported dyspepsia as an adverse event (Gallieni et al. 2001). A second single-group study in 27 hemodialysis patients in France reported that sevelamer treatment was associated with “minor but poorly tolerated adverse events” including constipation (32%), vague abdominal pain (27%), diarrhea (23%), and gastric dyspepsia (18%) (Huu et al. 2002). The authors noted that the incidence of adverse events progressively diminished after the first few months of treatment, from 63% of patients after 1 month to 8% after 6 months, but commented that digestive adverse events were a barrier to compliance in their

Table 9 | Effects of sevelamer on measures of metabolic acidosis

Level of evidence	Design	Treatment and mean dose	Outcome				Reference
			Serum bicarbonate	% patients with serum bicarbonate <20 mmol/L	Mean serum pH after 2 years	Mean partial pressure CO ₂ after 2 years	
1	Systematic review	Sevelamer Sevelamer plus supplemental Ca Placebo CaAc CaCO ₃	NSD S vs placebo (1 study) NSD S vs CaCO ₃ (1 study) NSD S vs S+Ca (1 study) Lower with S vs Ca salts ($P<0.0001$) (1 study)	NR	NR	NR	Manns et al. 2004
2	Double-blind, RCT, 8 weeks, n=50 (S), n=48 (CaAc)	Sevelamer 6.9 g/day CaAc 7.1 g/day	Lower with S vs CaAc ($P<0.0001$)	NR	NR	NR	Qunibi et al. 2004
3	Retrospective, 2 years, n=17 (S), n=7 (Ca or Al salts)	Sevelamer Ca or Al salts	Decrease with S ($P=0.002$) NSD with Ca or Al salts	NR	NR	NR	Sonikian et al. 2005
3	Retrospective, n=583 (S), n=2923 (CaCO ₃), n=3664 (CaAc)	Sevelamer CaCO ₃ CaAc	Lower with S vs Ca salts ($P<0.0001$ S period vs Ca salts period)	S 46.9% CaCO ₃ 42.4% CaAc 40.8%	NR	NR	Walters et al. 2002a
3	Retrospective, n=30 (S), n=25 (Ca salts)	Sevelamer Ca salts	Lower with S vs Ca salts ($P<0.05$)	S 77% Ca salts 36% ($P<0.05$ S vs Ca salts)	NR	NR	Ciampi & Reilly 2002
3	Switching study, 7 patients with high Ca × P product and severe hyperparathyroidism switched to S, 7 control patients with well-controlled Ca × P and mild hyperparathyroidism continued on calcium salts	Sevelamer Ca salts	NSD vs baseline for S and Ca salts	NR	S 7.37 (decline from 7.40 at baseline, $P<0.05$) Ca salts NSD vs baseline	S 36 mmHg (decline from 42.5 mmHg at baseline, $P<0.05$) Ca salts NSD vs baseline	Vlahakos et al. 2004

Ca, calcium; CaAc, calcium acetate; CaCO₃, calcium carbonate; NR, not reported; NSD, not statistically significantly different; RCT, randomized controlled trial; S, sevelamer.

patients (Huu et al. 2002). In a group of 34 patients switched to sevelamer for previously uncontrolled hyperphosphatemia, gastrointestinal complaints were reported in 23 patients (67%) (Almirall et al. 2004).

On balance, this suggests that sevelamer can be associated with the occurrence of troublesome gastrointestinal adverse events, but the evidence does not clearly show whether the incidence is higher with sevelamer than with calcium salts. Some of the earlier evidence of adverse gastrointestinal effects may have resulted from the high pill counts associated with the earlier sevelamer 403 mg formulation, rather than the 800 mg formulation now in use.

Bone mineral density

Limited evidence, from a subanalysis of patients in the Chertow et al. (2002) study for whom data on bone mineral density [measured by computed tomography densitometry and expressed in Hounsfield Units (HU)] were available at baseline and after 52 weeks of treatment, indicates that patients treated with calcium salts (n=68) experienced significant loss in trabecular bone mineral density during treatment (median absolute change from baseline -7.9 HU, $P<0.05$), while sevelamer-treated patients (n=57) showed no loss of trabecular bone mineral density (median absolute change from baseline 0, $P=NS$) (Raggi et al. 2003). The difference between the two groups was statistically significant ($P=0.01$; Raggi et al. 2005). Further evidence is needed to confirm this finding and to

Table 10 | Effects of sevelamer compared with calcium salts on occurrence of gastrointestinal adverse events

Level of evidence	Design	Treatment and mean dose	Outcome	Reference
2	Open, 5 months, n=21 (S), n=21 (CaCO ₃)	Sevelamer, initial dose 2.4 g/day increasing to 4.4 g/day CaCO ₃ 4.8 g/day	Patients who discontinued due to digestive intolerance S 5/21 CaCO ₃ 0	Sadek et al. 2003
2	Double-blind, 8 weeks, n=50 (S), n=48 (CaAc)	Sevelamer 6.9 g/day CaAc 7.1 g/day	NSD S vs CaAc in subjective symptom score for gastrointestinal side effects	Qunibi et al. 2004
2	Open, 34 weeks, n=40 total	Sevelamer 4.09 g/day CaAc 3.9 g/day	NSD S vs CaAc in occurrence of "constipation, diarrhea and other adverse events"	Hervás et al. 2003
2	Open, 52 weeks, n=36 (S), n=46 (CaCO ₃) ^a Subanalysis of Chertow et al. 2002, German and Austrian patients, with 11 additional patients randomized	Sevelamer 5.9 g/day CaCO ₃ 3.9 g/day	Gastrointestinal adverse events: S 74% CaCO ₃ 53% (<i>P</i> =0.02 S vs CaCO ₃) Dyspepsia: S 26% CaCO ₃ 5% (<i>P</i> <0.01 S vs CaCO ₃)	Braun et al. 2004
2	Open, 52 weeks, n=108 randomized	Sevelamer 6.7 g/day CaAc 4.6 g/day	NSD S vs CaAc in occurrence of gastrointestinal adverse events	Chertow et al. 2003
3	Open, crossover, 8 weeks for each treatment period, n=20	Sevelamer 5.2 g/day CaCO ₃ 9 g/day	Occurrence of gastrointestinal complaints: S 28% CaCO ₃ 35%	Shaheen et al. 2004

^aNumber who completed the trial.
CaAc, calcium acetate; CaCO₃, calcium carbonate; NSD, no statistically significant difference; S, sevelamer.

investigate the influence of sevelamer on other aspects of bone morbidity (e.g. incidence of fractures and bone pain).

Cardiovascular morbidity and mortality

As arterial calcification is associated with increased mortality (London et al. 2003), the reduction in arterial calcification observed with sevelamer compared with calcium salts could have important potential survival benefits. A modeling study (Huybrechts et al. 2005) has explored this area, using data on arterial calcification obtained from an RCT (Chertow et al. 2002) combined with data on cardiovascular risk from a cohort study. Multivariate regression analysis of the data from Chertow et al. (2002) was used to develop an equation to predict the arterial calcification score from baseline clinical characteristics and medical history. This equation was then applied to data from a cohort of 179 patients from a single dialysis center in France, who were followed up for a mean of 4 years. The calcification score for each of these patients was estimated using the equation developed from the Chertow et al. (2002) data, and this predicted score was then included in regression analysis of cardiovascular risk. The predicted calcification score was significantly associated (*P*<0.0001) with the 4-year cardiovascular risk, and an equation was developed to estimate the cardiovascular risk from the calcification score (Huybrechts et al. 2005). Applying this equation to the calcification score data in the treatment groups from Chertow et al. (2002) allowed the authors to estimate that in a population of 100

patients, treatment with sevelamer rather than calcium salts would prevent a total of nine cardiovascular events over the patients' lifetimes (Huybrechts et al. 2005).

Further results from this modeling study have been presented in abstract form (Caro et al. 2003). This estimated that in a cohort of 100 patients, sevelamer treatment for 1 year would prevent nine future cardiovascular events and save 18 life-years compared with calcium acetate treatment, and prevent 10 future cardiovascular events and save 18 life-years compared with calcium carbonate (Caro et al. 2003).

A retrospective study in dialysis patients receiving sevelamer (n=696), calcium acetate (n=4018), or calcium carbonate (n=3279) during 2001 reported data on cardiac mortality (Walters et al. 2002b). Among the sevelamer patients, 10.8% died of cardiac disease in 2001, compared with 16.6% of patients treated with calcium acetate (*P*<0.001 vs sevelamer) and 12.6% of patients receiving calcium carbonate (*P*=NS vs sevelamer). However, this study was not randomized and the sevelamer group had a significantly (*P*<0.001) lower mean age, a higher percentage of women and a higher percentage of patients on peritoneal dialysis compared with the other two groups (Walters et al. 2002b), which may have affected the results.

Sevelamer also sequesters bile acids and has been shown to reduce serum lipid levels; this action may also have favorable cardiovascular effects (Loghman-Adham 2003).

Direct evidence from prospective RCT is required to fully assess the effect of sevelamer on cardiovascular mortality and morbidity.

Hospitalization

A case-control study compared rates of hospitalization in sevelamer-treated Medicare patients ($n=152$) enrolled in the study published by Chertow et al. (1999b) and nonsevelamer-treated Medicare patients ($n=152$) from the same dialysis facilities over the same time period, matched for age, sex, race, diabetic status, and geographic location (Collins et al. 2000). After adjusting for prior medical history and severity of disease, Cox regression analysis showed a significant reduction in the risk of hospitalization for any reason in the 17-month study period in the sevelamer group (46–54% lower than in the control group, $P<0.03$) (Collins et al. 2000). However, significantly more of the control subjects had a history of cerebral vascular accidents or transient ischemic attacks and gastrointestinal disease associated with bleeding, compared with the sevelamer group. The sevelamer patients were selected from a clinical study population with defined inclusion/exclusion criteria, and the possibility that differences in the patient population may have biased the results cannot be excluded, as acknowledged by the authors (Collins et al. 2000). Evidence from randomized trials is needed to assess this point.

Compliance

One observational study presented data on compliance with phosphate binders (Tomasello et al. 2004). Interviews were conducted with 188 dialysis patients (129 on hemodialysis), and found that 37.8% of patients admitted noncompliance with their phosphate binder (compliance defined as taking 80% of the tablets prescribed). The noncompliant patients were prescribed higher doses of phosphate binders than the compliant patients (9.3 vs 8.2 pills/day), but actually took smaller doses (4.2 vs 7.6 pills/day). Noncompliant and compliant patients did not differ with respect to the type of phosphate binder prescribed (categorized by the authors into calcium binders vs noncalcium binders) (Tomasello et al. 2004). This study did not provide specific evidence on rates of compliance with sevelamer treatment. However, as the phosphate binder medication burden with sevelamer is not notably different from that with calcium salts (both require daily doses of several grams), little difference would be expected, and the findings of Tomasello et al. (2004) are consistent with this expectation.

Quality of life

No evidence was identified in the search on the effects of sevelamer on health-related quality of life.

Other comparisons

A crossover study in six hemodialysis patients found that colestimide, a bile-acid sequestrant with a similar chemical structure to sevelamer, was significantly less effective than sevelamer as a phosphate binder (Tajiri et al. 2004).

Combination treatment

Concern has been expressed over the cost of sevelamer compared with calcium salts (McIntyre et al. 2002; Manns et al. 2004; Sturtevant et al. 2004). It has been suggested that combination

treatment with low-dose sevelamer and low-dose calcium salts could achieve effective phosphate control at a lower cost (Hergesell & Ritz 2002). There has also been concern that Japanese patients may be less tolerant of sevelamer treatment and more prone to develop hypocalcemia because average dietary calcium intake is lower in Japan than in Europe or the USA, leading to the suggestion that combination treatment may be a useful alternative in this population (Ogata et al. 2005). As the K/DOQI guidelines recommend targets for various parameters without specifying how these targets should be achieved, a number of investigators have examined combination therapy as a possible means of achieving K/DOQI targets.

McIntyre et al. (2002) selected 23 hemodialysis patients with hypercalcemia (serum calcium >2.6 mmol/L), and exchanged 50% of their initial calcium binder dose for sevelamer. After 4 weeks, if serum calcium was still above 2.6 mmol/L, a further 50% of the calcium dose was replaced by sevelamer, and if serum calcium was normal but serum phosphate was >2 mmol/L, the dose of sevelamer was increased by 25%. Patients were then followed for a further 4 weeks. Mean serum calcium declined significantly during the study (from 2.8 to 2.56 mmol/L, $P<0.0005$), mean serum phosphate showed no statistically significant change, and mean intact PTH increased (from 166 to 276 ng/L, $P=0.02$). The percentage of patients with hypercalcemia declined from 100 to 26%. The mean sevelamer dose was 2.77 g/day and the mean calcium dose (measured as elemental calcium) was 1.03 g/day. The authors concluded that combination treatment could achieve control of serum phosphate without inducing hypercalcemia in the majority of patients who had been hypercalcemic on their previous phosphate binder treatment (McIntyre et al. 2002).

A further study replaced part of the calcium binder dose with sevelamer in a group of 18 dialysis patients with serum phosphate >1.8 mmol/L who were intolerant of other available phosphate binders (Sturtevant et al. 2004). Sevelamer was added at an initial dose of 403 mg three times daily and titrated to a maximum of 1209 mg three times daily. Mean serum phosphate and $\text{Ca} \times \text{P}$ product were significantly ($P=0.02$) lower after addition of sevelamer than before, with no significant change in serum calcium or PTH. The mean dose of sevelamer was 2.4 g/day and the mean dose of elemental calcium decreased from 3.4 g/day to 1.2 g/day ($P=0.04$).

A study in Japan treated a cohort of 210 patients with sevelamer plus calcium carbonate, gradually increasing the sevelamer dose and reducing the calcium carbonate dose over a period of 24 weeks (Shishido et al. 2004; Ogata et al. 2005). After 24 weeks, the sevelamer dose was further increased to 3.29 g/day and the calcium carbonate dose was decreased by 54%. Serum calcium significantly decreased ($P=0.0012$), although there was also a small increase in serum phosphate (from 5.89 mg/dL to 6.25 mg/dL, $P=0.017$) (Ogata et al. 2005). Among patients with a baseline PTH <150 pg/mL, PTH and phosphate increased and serum calcium decreased compared with baseline (all $P<0.05$); while in those with a baseline PTH 150–300 pg/mL, serum PTH increased without statistically significant changes in calcium or phosphate; and in those with a baseline PTH ≥ 300 pg/mL, there were no significant changes in serum PTH, calcium, or phosphate. Vitamin D treatment could be started or intensified in 23 of 66 patients with baseline

PTH ≥ 300 pg/mL, because of improved calcium and phosphate control (Shishido et al. 2004). It is important to note that this study utilized sevelamer to introduce or escalate vitamin D therapy in order to avoid low calcium, which may have been the main determinant of serum calcium and phosphate levels. The overall doses of binder were low, which may explain the suboptimal control of serum phosphate.

Economic evidence

The major cause of death in patients with CKD is cardiovascular disease (McCullough 2004; Foley et al. 2005). There is evidence that sevelamer can reduce the rate of progression of arterial calcification in hemodialysis patients compared with calcium salts, perhaps due to the lower incidence of hypercalcemia with sevelamer (Chertow et al. 2002), as discussed above in the Clinical evidence section. Arterial calcification has been linked to cardiovascular morbidity and mortality (London et al. 2003), and thus a reduction would be expected to produce a corresponding reduction in cardiovascular events and deaths. Such an improvement in cardiovascular disease could potentially provide substantial economic benefits, which in turn could offset the higher acquisition price of sevelamer compared with calcium salts [in the USA the mean annual cost of sevelamer was estimated at \$US3644 per patient, compared with \$US154 for calcium carbonate and \$US463 for calcium acetate (Manns et al. 2004)].

The economic effects of the reduction in arterial calcification with sevelamer have been explored in a modeling study published in abstract form (Caro et al. 2003). The model estimated cardiovascular disease risk by combining calcification scores for sevelamer and calcium salts, reported in an RCT (Chertow et al. 2002), with equations relating calcification score to cardiovascular disease risk derived from a cohort study. In a cohort of 100 patients, the model estimated that 1 year of sevelamer treatment would save 18 life-years and prevent nine future cardiovascular events that would have cost \$US205 600 to manage, resulting in a net cost of \$US37 900 for sevelamer compared with calcium acetate (Caro et al. 2003). The corresponding values for sevelamer compared with calcium carbonate were 18 life-years, 10 cardiovascular events prevented that would have cost \$US226 700 to manage, and a net cost of \$US19 500. The incremental cost-effectiveness ratios for sevelamer compared with calcium acetate were \$US2200 per life-year gained and \$US4400 per cardiovascular event prevented; for sevelamer compared with calcium carbonate the corresponding values were \$US1100 per life-year gained and \$US2300 per cardiovascular event prevented (Caro et al. 2003). The authors comment that these results show that sevelamer is highly cost-effective, as the median cost-effectiveness of dialysis is \$US46 000 per life-year gained (Caro et al. 2003). However, there has been debate over the cost-effectiveness of sevelamer (Quinibi & Nolan 2005), and direct evidence of the economic effects of sevelamer is required to confirm these estimates.

A case-control study reported that average total Medicare expenditure during the 17-month study was lower in patients receiving sevelamer than in matched controls not receiving sevelamer (\$US4422 vs \$US5866 per patient per month) (Collins et

al. 2000). However, there were baseline differences in the medical history of the two groups that may have affected the results, and these findings need to be replicated in randomized trials.

As discussed above in the Disease overview section, it has been suggested that dyslipidemia may be a major determinant of cardiovascular mortality in dialysis patients. A decision-analysis model estimated the costs and cost-effectiveness of sevelamer compared with calcium carbonate plus atorvastatin for reducing LDL cholesterol in patients with CKD (Brophy et al. 2000). The authors state that the modeled population represents patients with CKD, hyperphosphatemia, and dyslipidemia who are not yet on dialysis (Brophy et al. 2000). However, the sevelamer data used to populate the model were derived from seven published sevelamer trials, six of which were conducted in hemodialysis patients (the other was in healthy volunteers), so the study is relevant to a review of sevelamer in hemodialysis patients. The study estimated that the total annual cost of treatment with calcium carbonate (1 g three times per day) plus atorvastatin (10 mg/day) was \$US1029 per patient, while the cost of treatment with sevelamer (2 \times 403 mg capsules three times per day) was \$US1579 per patient. The estimated percentage of patients achieving a 35% reduction in LDL cholesterol concentration was 74.2% in the calcium carbonate+atorvastatin group, and 50.2% in the sevelamer group. These results indicate that calcium carbonate+atorvastatin was both more effective and less costly than sevelamer for reducing LDL cholesterol in predialysis patients (Brophy et al. 2000).

However, the study has a number of serious limitations. First, although the modeled population is stated to be predialysis patients with hyperphosphatemia and dyslipidemia, the sevelamer data were derived from studies in healthy volunteers or hemodialysis patients, whereas the data for the calcium carbonate+atorvastatin group were derived from studies of atorvastatin alone in patients with hypercholesterolemia and/or cardiovascular risk factors without CKD. Thus, the efficacy data used to populate the model are derived from different patient populations, neither of which is the modeled population. Second, the sevelamer studies did not report data on the percentage of patients who achieved a 35% reduction in LDL cholesterol, so the authors assumed that the probability would be 50%. Third, the authors assumed that hypercalcemia was "generally not of concern" and did not consider possible effects of hypercalcemia on costs or effectiveness. Fourth, the model did not take account of any costs associated with adverse events. Fifth, the effectiveness data were derived from trials lasting 8–16 weeks (atorvastatin) or 15 days–44 weeks (sevelamer), and these data may not be capable of extrapolation to the modeled period of 1 year. Sixth, the choice of effectiveness measure (reduction in LDL cholesterol by 35%) relies on an assumption that this is a key determinant of cardiovascular risk in CKD patients and does not take account of other potential cardiovascular risk factors in these patients, such as arterial calcification score, elevated serum calcium, and/or Ca \times P product. It is not unexpected that atorvastatin, designed and used specifically as a lipid-lowering agent, should prove to be more effective at lipid-lowering than sevelamer, which was designed and used as a phosphate binder. These limitations, most of which are acknowledged by the study authors, limit the potential applicability of the model's findings.

Some evidence indicates that sevelamer may be associated with better preservation of trabecular bone mineral density than calcium salts (Raggi et al. 2003). This may have the potential to save costs associated with the management of bone disease (e.g. costs of managing fractures or treating bone pain). However, direct evidence is required on this issue.

Further economic studies on a range of outcomes are required to evaluate the cost-effectiveness of sevelamer as a phosphate binder in hemodialysis patients.

Resource utilization

The acquisition price of sevelamer is substantially higher than that of calcium salts. The potential budget impact of using sevelamer in all patients who meet the K/DOQI guideline criteria for its use (see Patient population section below) has been estimated for the USA and Canada (Manns et al. 2004). In Canada, 51% of a cohort of dialysis patients (407 hemodialysis, 92 peritoneal dialysis) met the K/DOQI criteria for use of sevelamer. Extrapolating this figure to the total Canadian dialysis population, the authors estimated that using sevelamer in all patients meeting the K/DOQI criteria would result in an expenditure of \$US26 million per year on sevelamer. Of a cohort of 1600 hemodialysis patients and 400 peritoneal dialysis patients in the USA, 64% met the K/DOQI criteria for sevelamer use, and extrapolating this to the total US dialysis population projected that \$US781 million per year would be spent on the drug (Manns et al. 2004). The authors estimated that hospitalization costs for ESRD patients would have to be reduced by 45% in Canada and by considerably more (detailed estimate not provided) in the USA to offset the additional cost of sevelamer (Manns et al. 2004).

It has been suggested that using a combination of sevelamer and a low dose of calcium salts may be effective in controlling serum phosphate and result in a lower cost than with sevelamer alone (Hergesell & Ritz 2002), but there is little evidence on this point at present.

Sevelamer has been shown to attenuate the progression of arterial calcification compared with calcium salts, which has the potential to reduce the excess cardiovascular morbidity and/or mortality seen in hemodialysis patients. A modeling study has estimated that sevelamer treatment could reduce the costs of managing cardiovascular events in a cohort of 100 patients by \$US205 600 compared with calcium acetate and \$US226 700 compared with calcium carbonate (Caro et al. 2003). These savings offset most of the additional acquisition cost of sevelamer, resulting in net costs for the cohort of \$US37 900 compared with calcium acetate and \$US19 500 compared with calcium carbonate (Caro et al. 2003). Direct evidence is required to confirm these potential savings in cardiovascular treatment costs.

A case-control study has estimated that the risk of hospitalization over the 17-month study period was 46–54% lower in US Medicare patients treated with sevelamer compared with matched controls receiving other phosphate binders (Collins et al. 2001), and this could indicate substantial potential savings in direct treatment costs for patients receiving sevelamer. However, as previously discussed, this study reported significant baseline differences in medical history between the two groups, which may have influenced its results.

Prevention of cardiovascular morbidity should also reduce indirect costs (e.g. more patients may be able to work and/or undertake normal activities) and provide intangible benefits (e.g. improved quality of life), but the search identified no direct evidence relating to these potential economic benefits.

There is, at the time of writing, insufficient evidence to estimate the overall effect of sevelamer on resource utilization. Some evidence from retrospective and modeling studies suggests that higher expenditure in the drug budget (which follows from the higher acquisition cost of sevelamer compared with calcium salts) could be offset by savings elsewhere or justified by additional health benefits, but this needs to be confirmed by direct evidence from prospective controlled studies designed to measure economic endpoints.

Patient group/population

Sevelamer is indicated for the treatment of adult patients on hemodialysis. While it may have potential benefits for other groups, such as children, patients on peritoneal dialysis, or predialysis patients, such off-label use is outside the scope of this review.

The NKF K/DOQI guidelines recommend sevelamer as a phosphate binder in the following clinical situations:

- In dialysis patients who remain hyperphosphatemic (serum phosphate >5.5 mg/dL) despite the use of calcium-based binders or other noncalcium-, nonaluminum-, nonmagnesium-containing binders, a combination should be used
- In dialysis patients, the total dose of elemental calcium from calcium-based phosphate binders should not exceed 1500 mg/day. For comparison, the recommended daily dose of calcium acetate (3–4 capsules three times per day) equates to 1521–2028 mg/day elemental calcium (PhosLo® US package insert <http://www.fda.gov/cder/foi/label/2001/21160lbl.pdf>)
- In dialysis patients, calcium-based binders should not be used in patients with hypercalcemia (serum calcium >10.2 mg/dL) or with serum PTH <150 pg/mL
- In dialysis patients with severe soft-tissue calcifications, noncalcium-based phosphate binders are preferred
- Adynamic bone disease should be treated by increasing PTH to ≥ 100 pg/mL by decreasing or eliminating calcium-based phosphate binders.

It has been estimated that 64% of US and 51% of Canadian dialysis patients would meet the K/DOQI criteria for the use of sevelamer (Manns et al. 2004).

Patients with uncontrolled hyperphosphatemia

A study in 34 patients with uncontrolled hyperphosphatemia (serum phosphate >6.5 mg/dL and/or toxicity or intolerance to calcium- or aluminum-based phosphate binders) found that the addition of sevelamer provided better control of serum phosphate and $\text{Ca} \times \text{P}$ product and allowed a reduction in the dose of other binders (Almirall et al. 2004). However, 13 of 34 patients (38%) dropped out because of intolerance to sevelamer, mainly (no number or

percentage specified) due to gastrointestinal adverse effects (Almirall et al. 2004). In a crossover study of 10 patients with uncontrolled hyperphosphatemia (serum phosphate 6.6–10.4 mg/dL), the effect of sevelamer on serum phosphate was similar to that of standard phosphate binders (Apostolou et al. 2002). A study in 18 patients with hyperphosphatemia [serum phosphate >1.8 mmol/L (>5.6 mg/dL)] who were intolerant of other currently available phosphate binders found that combination treatment with sevelamer and calcium carbonate reduced serum phosphate and $\text{Ca} \times \text{P}$ product significantly ($P=0.02$) more than calcium carbonate alone (Sturtevant et al. 2004).

Patients with severe secondary hyperparathyroidism

In 18 patients with severe secondary hyperparathyroidism (mean serum intact PTH concentration 810 pg/mL), switching to sevelamer produced significant ($P<0.05$) reductions in serum phosphate and serum calcium, with no change in PTH, leading the authors to conclude that sevelamer is an effective phosphate binder in such patients (Castro et al. 2002). A further study, in which sevelamer replaced aluminum hydroxide in 11 hemodialysis patients with secondary hyperparathyroidism, reported that sevelamer significantly reduced mean serum phosphate and mean serum intact PTH after 8 weeks (both $P<0.003$), but that there was no statistically significant change in mean serum calcium (Mitsopoulos et al. 2002b).

Patients taking concurrent vitamin D and/or calcium supplements

A subgroup analysis of a cohort of patients who received sevelamer for 1 year (Chertow et al. 1999b) found that sevelamer significantly reduced serum phosphate and $\text{Ca} \times \text{P}$ regardless of whether patients were also taking vitamin D, calcium supplements, or both (Chertow et al. 2000).

Japanese patients

It has been suggested that Japanese patients may be less tolerant of sevelamer treatment and more prone to develop hypocalcemia because average dietary calcium intake is lower in Japan than in Europe or the USA (Ogata et al. 2005). A cohort study in 210 hemodialysis patients in Japan concluded that a combination of sevelamer and calcium carbonate could reduce calcium load compared with calcium carbonate alone, while still avoiding the development of hypocalcemia (Ogata et al. 2005).

Dosage, administration, and formulations

Sevelamer (Renagel®) is indicated for the control of hyperphosphatemia in adult patients on hemodialysis. It is available as film-coated tablets each containing sevelamer 800 mg.

For patients who are not taking phosphate binders and whose serum phosphate concentration is 1.94–2.42 mmol/L, the recommended starting dose is 1×800 mg tablet three times daily, increasing to 2×800 mg tablets three times daily if the serum phosphate concentration is >2.42 mmol/L. In patients who are being switched from alternative phosphate binders, the starting dose of sevelamer should be the milligram equivalent of the patient's previous dose of calcium-based phosphate binder. Serum

phosphate concentrations should be measured every 2–3 weeks, and the dose of sevelamer titrated with the goal of reaching a serum phosphate concentration of 1.94 mmol/L or less. The dose range may vary between 1 and 5×800 mg tablets three times daily. Sevelamer should be taken with meals (Anon. 2004).

Place in therapy

The evidence summary table at the beginning of the article summarizes the clinical evidence for the impact of sevelamer on clinical and economic outcome measures. The strongest evidence was found for disease-oriented outcomes, such as arterial calcification score and reduction of serum phosphate, calcium and lipid concentrations. Although these may be markers of beneficial effects on patient-oriented outcomes (e.g. arterial calcification may be linked to a reduction in cardiovascular morbidity and mortality), in themselves they do not demonstrate improved length or quality of life. The evidence on patient-oriented outcomes was less clear. There was an indication of reduced cardiovascular mortality and morbidity, but the evidence on this outcome is derived from a modeling study and requires confirmation by direct observation. Among other patient-oriented outcomes, sevelamer may reduce hospitalization risk but this is derived from a case-control study and requires confirmation by randomized trials. Limited evidence from case reports and a small observational study suggests that reduction of $\text{Ca} \times \text{P}$ product by treatment interventions including sevelamer may improve healing of ulcers associated with calcific uremic arteriopathy. This is of clear potential benefit to patients with this uncommon but serious and distressing condition, but it should be noted that there is no evidence comparing sevelamer with other noncalcium binders.

There is strong evidence that sevelamer is as effective as calcium salts in lowering serum phosphate and serum $\text{Ca} \times \text{P}$ product, with only one study finding to the contrary. Similarly, there is strong evidence that sevelamer is associated with a lower incidence of hypercalcemia than calcium salts. Only one study failed to show a statistically significant difference in hypercalcemia incidence in favor of sevelamer, and this study was not powered to detect a difference (Hervás et al. 2003). There is also strong evidence that sevelamer reduces LDL cholesterol more than calcium salts, with no results to the contrary.

Some evidence indicates that sevelamer reduces serum bicarbonate concentration more than calcium salts. Two studies have reported no statistically significant difference, but neither was powered on this endpoint. Data from a small single-group study, reported in abstract form, indicates that respiratory compensation (reduction in partial pressure of CO_2) maintains serum pH in the normal range.

Evidence from one RCT (and several subanalyses) from the Treat to Goal Working Group study shows that sevelamer reduces the progression of arterial calcification compared with calcium salts. There is limited evidence that may indicate a beneficial effect of sevelamer as part of a therapeutic regimen for the management of calcific uremic arteriopathy, with improvement and/or healing of ulcerations reported in a small observational study and two case reports. Some evidence also indicates that sevelamer reduces serum uric acid concentrations to a greater degree than calcium salts.

The attenuation of arterial calcification is potentially of great therapeutic value, as this has been suggested as a possible mechanism underlying the excess cardiovascular morbidity and mortality in CKD patients. A modeling study has estimated that the reduction in arterial calcification associated with sevelamer treatment could prevent 9–10 future cardiovascular events and save 18 life-years in a cohort of 100 patients. A retrospective study has also observed lower cardiac mortality in sevelamer-treated patients than in those receiving calcium acetate, although the study was not randomized and there were baseline differences between the groups that could have affected the results. Similarly, sevelamer was associated with a lower risk of hospitalization than calcium salts in a case-control study, but this study could also have been biased by significant differences between the groups at baseline.

A subanalysis of data from one RCT showed that sevelamer could preserve trabecular bone mineral density compared with calcium salts. This may suggest a beneficial effect on bone morbidity, but direct evidence is needed to confirm this possibility.

The evidence is divided with regard to the incidence of gastrointestinal adverse events, with six studies providing some comparison between sevelamer and calcium salts, two of which found that sevelamer was associated with a higher frequency of gastrointestinal adverse events than calcium salts while four reported no statistically significant difference. However, the evidence is limited in its applicability, since there was no consistent definition of gastrointestinal adverse events across the studies and so it is difficult to draw a firm conclusion about where the balance lies. Moreover, all but one of the studies were open label, a design known to be subject to potential bias in the reporting of subjective events. It may be significant that the one double-blind comparative study (Qunibi et al. 2004) reported no statistically significant difference between sevelamer and calcium acetate in subjective symptom scores for gastrointestinal adverse events, although the study was not powered to detect a difference. Further evidence on this point is required. No evidence was identified in this review on the effect of sevelamer on quality of life.

Limited evidence from one study suggested that the phosphate binder medication burden and patient adherence to therapy was no different with sevelamer than with calcium salts. Although this evidence is weak in itself, it is consistent with the fact that average doses of sevelamer are several grams per day, which is not dissimilar to the doses of calcium salts. No marked improvement in phosphate binder medication burden would thus be expected.

Considering economic evidence, it is clear that the acquisition cost of sevelamer is higher than that of calcium salts. However, a modeling study estimated that this increased acquisition cost could be largely offset by reduced cardiovascular mortality and morbidity, and estimated the incremental cost-effectiveness ratio for sevelamer compared with calcium salts at \$US1100–2200 per life-year gained. However, direct evidence is needed to confirm these estimates before the true economic benefits and cost-effectiveness of sevelamer can be assessed.

In summary, there is strong evidence that sevelamer is as effective as calcium salts in controlling serum phosphate and $\text{Ca} \times \text{P}$

product, has less risk of inducing hypercalcemia, and is more effective at lowering lipid levels. Some evidence also indicates that sevelamer is more effective than calcium salts in reducing the progression of arterial calcification, which may in turn be associated with reduced cardiovascular mortality and/or morbidity. It has been estimated that savings in treatment costs associated with cardiovascular events could offset most of the additional acquisition cost of sevelamer compared with calcium salts. However, direct evidence is required to confirm the effects of sevelamer on cardiovascular morbidity and mortality and to assess its cost-effectiveness.

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