Use of phosphate binders in chronic kidney disease

Date written: April 2005
Final submission: December 2005
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GUIDELINES

a. **Calcium-containing phosphate binders are effective. (Level II evidence)**

b. **Calcium acetate (CA) is more effective than calcium carbonate. (Level I evidence)**

c. **Calcium salt-based binders should be minimised when serum calcium is above the target range (2.4 mmol/L) or serum parathyroid hormone (PTH) is below the upper limit of the reference range. (Level II evidence)**

d. **Sevelamer is an effective phosphate binder. (Level II evidence)**

e. **Lanthanum is an effective phosphate binder. (Level II evidence)**

Suggestions for Clinical Care

(Suggestions are based on Level III and IV evidence)

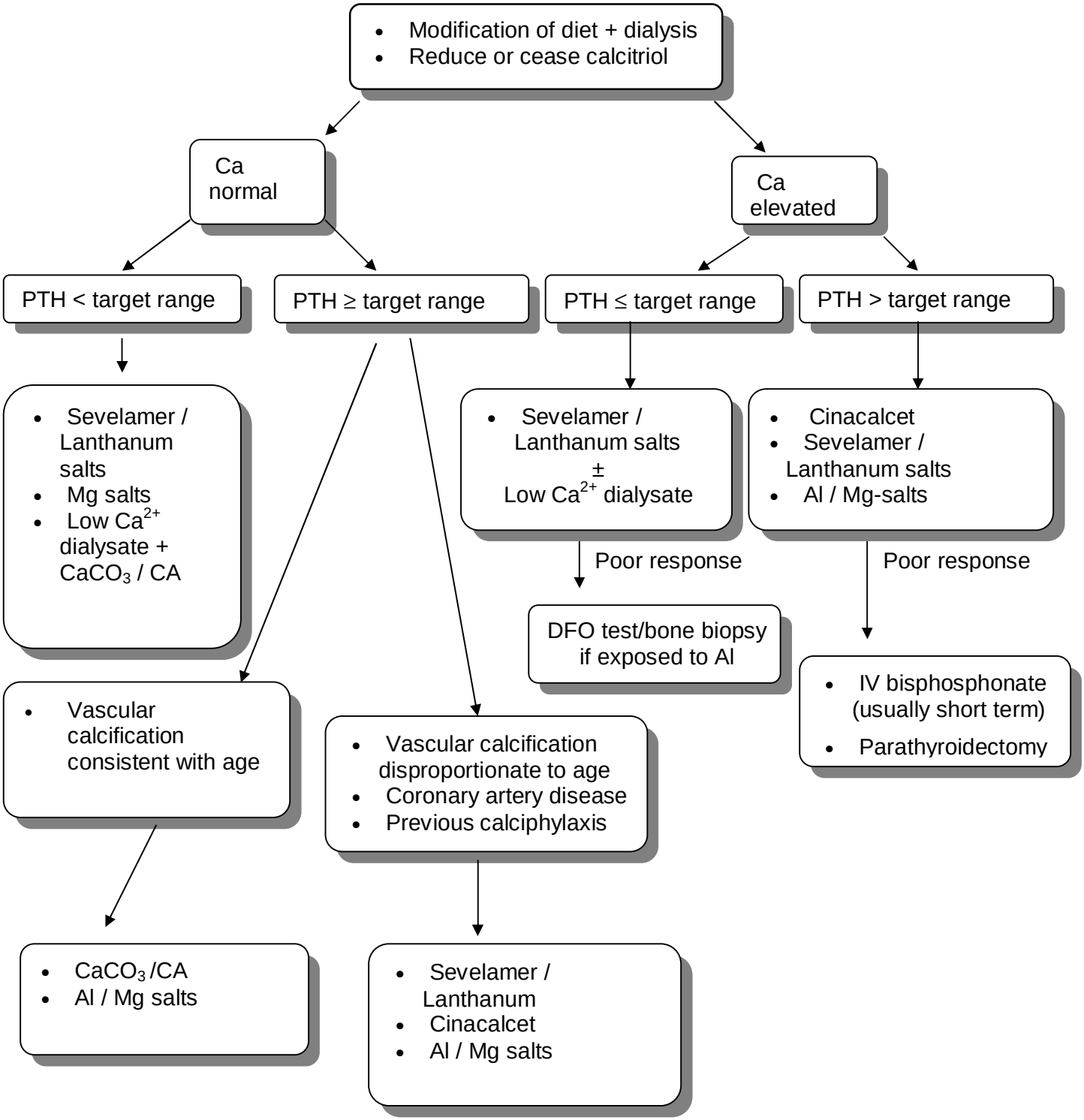
- **Factors influencing the choice and effectiveness of a phosphate binder include serum PTH, tendency towards hypercalcaemia, side effects, diet and compliance of the patient. (Opinion)**
- **Initial management of serum phosphate levels above the target range (> 1.6 mmol/L) should include optimization of dialysis, when possible, by increasing the duration and/or the number of treatments (Level III evidence) (Fajardo et al 2003, Musci et al 1998), dietary advice and efforts to ensure patient compliance with medications. (Opinion)**
- **Calcium-containing phosphate binders should be the initial choice in patients with levels of serum calcium < 2.4 mmol/L and PTH in the target range (Opinion), but should be avoided when levels of PTH are below the target range. (Level lll evidence) (Kurtz 1994).**
- **Calcium carbonate ($CaCO_3$) should be taken before or with meals and may be less effective than CA when used with inhibitors of gastric acidity. (Level III evidence) (Janssen et al 1996).**
- **Aluminium salts should be avoided when PTH is below the target range (Level lll evidence). Aluminium use is associated with an increased risk of low bone turnover and abnormal bone mineralisation and should be avoided in at-risk patients, including children. (Level III evidence) (Clarkson et al 1972, Jespersen et al 1991).**
- **Monitoring of serum aluminium levels at regular intervals is suggested when aluminium-containing binders are used. If no aluminium-containing binders are used, it is sufficient to monitor reverse osmosis water supplies for heavy metal contamination, and perform serum aluminium levels and**

desferrioxamine testing in patients when the clinical state suggests that aluminium toxicity is possible (Gault et al 2005).

- **Calcium citrate may increase aluminium absorption and should be avoided. (Level III evidence) (Coburn et al 1991).**
- **The use of sevelamer should be considered when levels of calcium are above the target range. (Opinion)**
- **The use of sevelamer should be considered when levels of PTH are below the target range. (Opinion)**
- **Compared with calcium, magnesium-containing salts are an alternative but less efficient phosphate binder. (Level III evidence) (Delmez et al 1996). There are few long-term studies of safety. If used, serum magnesium levels should be monitored. Consider the use of low magnesium dialysate. (Opinion)**
- **Care should be taken to avoid hypercalcaemia when calcium salts are used in conjunction with calcitriol or vitamin D analogues. (Opinion)**
- **A maximum daily dose of calcium salts to be used in CKD is not suggested in this guideline (see note under "What do the other guidelines say?").**

Flow diagram for suggested control of serum phosphate in Stage 5 CKD

Adapted from Elder GJ. 'Targets for Phosphate Control in Chronic Kidney Disease' *Nephrology* 2004; 9: 2-6.



Background

The objective of this guideline is to provide clinicians with suggestions for the safe use of phosphate-binding agents, based on published clinical trial data, where possible. This guideline should be read in conjunction with the CARI guideline on target levels for serum calcium, phosphate and PTH levels.

As renal function and phosphate excretion declines, continued phosphate ingestion, reduced bone uptake of phosphate or increased release of phosphate from high turnover bone results in hyperphosphataemia. Dialytic therapies may not redress this imbalance and short, interval dialysis in patients with minimal residual renal function leads to phosphate accumulation. Hyperphosphataemia exacerbates hyperparathyroidism and is associated with cardiovascular morbidity and mortality. Oral phosphate binders are used to overcome the obligatory phosphate load associated with an adequate protein intake.

Aluminium salts are excellent phosphate binders but their use is limited by the adverse consequences of aluminium accumulation in bone, brain and nerve tissues (Jespersen et al 1991, Lerner et al 1986). Use should be avoided in low bone turnover states and in children. As a result, aluminium-based binders have been largely replaced by the calcium salts CA and $CaC0_3$. Most randomised trials in the area have compared these salts. Hypercalcaemia is reported to be less common when CA is used (National Kidney Foundation 2003) although vascular calcification is progressive with both salts (Chertow et al 2002). High doses of calcium-containing phosphate binders and increased frequency of hypercalcaemic episodes are associated with vascular calcification and poor outcome (Bleyer et al 1999, Ganesh et al 2001). Calcium-containing binders should be avoided in hypercalcaemic patients or in those with extra-vascular calcification. Magnesium-based phosphate binders, often combined with aluminium are effective, but long-term studies of safety and efficacy are lacking. Other agents such as calcium ketoglutarate and ferric citrate are expensive, have limited availability, and are not well studied.

Two newer agents not yet widely available in Australia are sevelamer and lanthanum carbonate. Studies comparing sevelamer with calcium salts show equivalent phosphate control and less hypercalcaemic events with sevelamer. With sevelamer use, calcium supplementation or higher dialysate calcium levels may be required to maintain serum calcium levels in the desired range (Izumi et al 2005). The finding in one study of reduced vascular and cardiac calcification (a surrogate measure for cardiac disease) with sevelamer holds promise for better patient management, however, at the time of the literature search, no survival benefit had been established.

Lanthanum carbonate is at an early stage of clinical use and studies have reported good phosphate control. The concern with lanthanum is long-term accumulation of this rare earth metal in the body. Some rat studies suggest that accumulation may occur, although human studies so far have not detected accumulation (Lacour et al 2005, Behets et al 2004, Finn and Joy 2005).

Adequate, safe control of phosphate and calcium levels with binders is therefore difficult and multiple agents may be required. Recent Japanese publications using

both $CaCO_3$ and sevelamer suggest that multiple phosphate binders may be needed for optimal management (Ogata et al 2005, Koiwa et al 2005). Manipulation of dialysate calcium concentration may also be required (Ando et al 2005). Dietary advice and adequate dialysis must also be provided. This guideline will provide suggestions for evidence-based optimal use of phosphate binders.

Search strategy

Databases searched: MeSH terms and text words for phosphate were combined with MeSH terms and text words for blood or serum, then combined with MeSH terms and text words for aluminium, magnesium, and calcium, lanthanum and sevelamer then combined with MeSH terms for kidney disease or dialysis, and then combined with the Cochrane highly sensitive search strategy for randomised controlled trials. The search was carried out in Medline (1966 – September Week 1 2004). The Cochrane Renal Group Trials Register (which covers EMBASE) was also searched for trials not indexed in Medline. The Cochrane register search was updated in August 2005.
Date of searches: 10 September 2004; update August 2005.

What is the evidence?

Sevelamer vs calcium

"Treat to Goal" study (Chertow et al 2002). This was a randomised multi-centre open label trial with 200 haemodialysis patients randomised to sevelamer or $CaCO_3$ or CA, and followed for a year. The study had targeted ranges for calcium (2.13–2.63 mmol/L), phosphate (0.96–1.6 mmol/L) and PTH (15–30 pmol/L). Aluminium was used as a rescue binder and dialysate calcium and Vitamin D analogues could be used at the clinician's discretion. Endpoints of interest were:

1. calcium-phosphate product and achievement of biochemical targets, and
2. calcification scores of coronary arteries and thoracic aorta using electron beam computed tomography (EBCT).

The results showed that the calcium salts were associated with more hypercalcaemia (16% vs. 5%). Phosphate control was equivalent with both drugs, however, PTH was below target more commonly in subjects randomised to calcium salts (57% vs. 30%). No significant statistical difference in calcium x phosphate product was found. Vascular calcification scores progressed in the calcium group, but not in the sevelamer group. This difference was apparent as early as 6 months and was statistically significant.

Limitations: Dialysate calcium concentrations and the use of night-time calcium supplementation in the sevelamer group were not stated. Hence, changes in vascular calcification may not be due to calcium use but related to other properties of sevelamer, such as effects on lowered LDL cholesterol. Statin use has also been shown to reduce coronary calcification. EBCT is unable to detect the difference between intimal and medial calcification. The study was conducted by Genzyme Corporation and data supplied to investigators.

Heart calcification studies

The same authors also looked at valvular calcification (a surrogate marker for cardiovascular events) (Chertow et al 2002). At baseline, mitral calcification was seen in 46% of subjects and aortic calcification in 33%. Most subjects with no calcification at baseline (younger and less time on dialysis, lower C-reactive protein [CRP]) did not progress over 12 months. Aortic but not mitral valve calcification increased significantly in calcium-treated subjects. A composite 'total calcification burden' was used. The sevelamer group had a higher percentage of patients with no progression (45% vs 28%) and with regression (26% vs 10%) compared with those who were treated with calcium salts.

A subgroup analysis, which included 108 dialysis patients was performed, restricting the comparison to CA and sevelamer. Phosphate control was similar in both groups, but more CA-treated subjects developed hypercalcaemia (36% vs 13%). Over the 12-month study, vascular calcification scores only increased in the patients treated with CA.

Asmus et al (2005) randomly allocated 72 haemodialysis patients to $CaCO_3$ or sevelamer for 2 years. EBCT scans to assess vascular calcification were performed at 6, 12 and 24 months. Bone density was also measured by CT. Results showed that calcium x phosphate was similar in the two groups. However, $CaC0_3$-treated patients had more hypercalcaemic episodes and greater increases in coronary artery and aortic calcification scores. There was no difference in cortical bone density, however, the $CaC0_3$ group had a decrease in trabecular bone density.

Chertow et al (1999) performed a randomised study of 71 patients comparing sevelamer and calcium salts (900 mg elemental calcium at night) vs. sevelamer alone for 16 weeks. Both reduced phosphate equivalently. No differences in the calcium x phosphate product were seen between the groups. The supplemental calcium with sevelamer group had a non-significant increase in calcium of 0.08 mmol/L and tended towards a lower serum PTH level (P = ns).

The CARE Study (2004) was an 8-week randomised, double-blind study of sevelamer vs. CA in 100 haemodialysis patients. The study aimed to see which drug best met the recommended targets for serum phosphate (< 1.76 mmol/L) and calcium x phosphate product (< 4.4 $mmol^2/L^2$). Serum calcium (target range: 2.13–2.75 mmol/L) was also measured weekly. Results were reported in binary terms 'goal attained or not' and by mean values at each weekly time point. Drug was administered half before and half after meals. Doses were increased weekly as needed to achieve the serum phosphate target. Dialysate calcium (1.25 mmol/L) and vitamin D were held constant throughout the study. No aluminium or magnesium was allowed. Results showed that CA users had lower serum phosphate (0.35 mmol/L difference), higher serum calcium (0.16 mmol/L difference) and lower calcium x phosphate (0.49 $mmol^2/L^2$), than sevelamer users. Hypercalcaemia occurred in 16.7% of CA users and 0% of sevelamer users. Hypercalcaemia occurred in the presence of vitamin D (65% CA vs. 60% sevelamer). Clinically significant predictors of always attaining goal were centre and compliance. No difference in PTH levels was found at week 8. Bicarbonate levels were significantly lower with sevelamer.

Serum bicarbonate levels of 14.9%–22.2% of sevelamer users were below 17 mmol/L, while 0%–8.5% were below this level with CA.

Sevelamer lowered LDL cholesterol to a degree equivalent to that of the statins. Sevelamer cost US$4283 per patient per year vs US$732 for CA.

Limitations: There were artificial limitations on the adjustment of dialysate calcium concentration (which was low) and vitamin D use. This was only an 8-week study. The study was sponsored by Braintree Laboratories (Braintree, MA, USA) and Nabi Biopharmaceuticals (Boca Raton, FLA, USA).

Hervas et al (2003) conducted a randomised study of 40 haemodialysis patients randomly allocated to sevelamer or CA and followed them over 34 weeks. Doses were increased by protocol to control serum phosphate. Similar reductions in both phosphate and calcium x phosphate product were seen. Vitamin D dosage was 'stable' but not stated (70% taking this) and dialysate calcium was 1.25 mmol/L in 79% of cases. The mean change in serum phosphate from baseline to end of treatment was similar with both drugs. Hypercalcaemia was found in 7.1% of patients taking sevelamer and 8.9% of patients taking CA.

Limitations: Insufficient information to differentiate between the two groups at baseline.

Bleyer et al (1999) ran a randomised 20-week cross-over study of 84 patients using sevelamer and CA. The dose of binder was titrated upwards to achieve target phosphate levels (0.80–1.76 mmol/L). The dialysis regimen remained unchanged throughout the study (most using dialysate calcium 1.25 mmol/L) but of the patients using calcitriol (50/84 patients), 16 had dose increases during the study. CA dose was reduced if hypercalcaemia occurred. Nocturnal $CaCO_3$ was added if the serum calcium fell below 2.13 mmol/L.

The mean change in serum phosphate was similar with both treatments. Hypercalcaemia (> 2.75 mmol/L) occurred in 5% of sevelamer-treated patients and 22% of CA-treated patients. Also, in 4% of patients during wash-out, 23% of sevelamer-treated patients required an evening supplement of $CaCO_3$. Sevelamer led to a 27% reduction in LDL cholesterol.

Limitations: This was a short-term study.

Koiwa et al (2005) conducted a randomised open-label 3-phase trial of sevelamer vs. $CaC0_3$ in 86 Japanese patients. All patients were initially on 3.0 g $CaC0_3$ for 4 weeks, followed by 3.0 g/day of sevelamer for 4 weeks. Patients were then randomly allocated to one of three groups:
a. sevelamer 6 g/day,
b. sevelamer 3.0 g/day plus $CaC0_3$ 3.0 g/day, and
c. $CaC0_3$ 3.0 g/day.

Of the high dose sevelamer group, 44% dropped out of the study due to side-effects. Combination therapy showed better tolerability and patient compliance. Phosphate control was best in the combination group, however, serum calcium levels did increase in both calcium-containing regimens.

Limitations: A short-term study that highlights compliance issues. The fixed doses of binders used may not be realistic in many patients.

Shaheen et al (2004) published a short-term (8-week) cross-over study of sevelamer vs. $CaC0_3$ in 20 haemodialysis patients. This study showed similar phosphate control using both regimens, which allowed titration of drug to control phosphate level. Of those on $CaC0_3$, 52% developed hypercalcaemia (> 2.75 mmol/L) while in the sevelamer phase, only 26% developed hypercalcaemia (Shaheen et al, 2004).

The common finding in these studies comparing sevelamer with calcium salts, is that phosphate control is similar with the two agents. Calcium-treated patients tend to have more hypercalcaemic episodes and this may be associated with increased vascular and cardiac calcification. Lower calcium levels in the sevelamer groups may lead to hyperparathyroidism, but less low turnover bone disease. Mortality studies are needed to clarify the overall impact of sevelamer use. Sevelamer may exacerbate acidosis but leads to improvements in lipid profile – hence extrapolation from surrogate endpoint data is difficult. Patient compliance may also be an issue with this agent. To date, no safety concerns have emerged.

Calcium acetate vs. calcium carbonate

The Kidney Disease Outcomes Quality Initiative (National Kidney Foundation 2003) performed a meta-analysis of trials in this area, published prior to 1 January 2001. This showed that CA led to less hypercalcaemia than $CaCO_3$.

Pflanz et al (1994) performed a randomised cross-over study in 23 patients, over 14 weeks.

Equimolar doses of CA and $CaCo_3$ were used.

Results: Serum phosphate was significantly lower with CA (1.51 vs 1.80 mmol/L) as was the calcium x phosphate (3.59 vs 4.18 $mmol^2/L^2$). Serum calcium was significantly higher after the CA (2.40 vs 2.32 mmol/L), and intact PTH was lower with CA (17.8 vs 25.4 pmol/L).

Limitations: This was a small study with many dropouts.

Schaefer et al (1991) performed a randomised, cross-over comparison of CA vs $CaC0_3$, in 47 haemodialysis patients, divided into 4 groups:

a. CA for 7 weeks then 1 week washout then $CaC0_3$ for 7 weeks,
b. as for group 1 plus 4 μg calcitriol twice weekly, orally,
c. as for group 1 plus 0.5 μg calcitriol daily, orally,
d. aluminium hydroxide as a binder for the entire study but 4 μg calcitriol orally, twice weekly for the first 7 weeks, then 0.5 μg calcitriol daily in the second study period. Dialysate 1.5 mmol/L calcium. Dietician input was given with counselling of all patients.

Results: The same phosphate reduction was achieved with both salts. Serum calcium increased with both salts, however, more hypercalcaemia occurred with

$CaC0_3$ and calcitriol. Three cases of hypercalcaemia occurred in the CA group and 6 with $CaC0_3$, leading to calcitriol being ceased. More elemental calcium was used with $CaC0_3$. Most of the 4 mcg twice-weekly calcitriol treatment had to be discontinued due to high calcium levels. Even in the aluminium group on the low dose of calcitriol, 7/13 had hypercalcaemic episodes. All hypercalcaemic episodes occurred within 2 weeks of starting calcitriol. No differences were seen in compliance.

Limitations: The multiple groups and several experiments make this a confusing study. Less elemental calcium was used with CA and less hypercalcaemia seen.

D'Almeida Filho et al (2000) conducted a randomised, cross-over, double-blind study of CA 5.6 g/day (1.4 g elemental calcium) for 4 weeks followed by a 2-week washout period and switched to $CaC0_3$ 6.2 g/day (2.5 g elemental) in 23 subjects. Dialysate calcium was 1.75 mmol/L. Calcitriol was withdrawn from all patients.

Results: Significant increase in serum calcium occurred only after $CaC0_3$ (2.34 vs. 2.48 mmol/L). A ratio of phosphate binding to hypercalcaemic tendency was calculated. This was 4.4 times greater for CA and 3.7 for $CaC0_3$, favouring the CA.

Limitations: There were many dropouts, with only 23/52 finishing. Mathematical calculations, while consistent with the literature, are theoretical.

Almirall et al (1994) conducted a randomised cross-over study over 24 weeks, in 7 selected haemodialysis patients, to compare CA with $CaC0_3$.

Results: There was no difference in phosphate control and mean serum calcium levels were similar. The incidence of hypercalcaemia was similar between the two treatments. Less elemental calcium was used in the acetate form, but this made no difference to the incidence of hypercalcaemia or a raised calcium x phosphate product.

Limitations: This was a very small study.

Caravaca et al (1992) randomised unblinded parallel groups in a clinical trial in 80 haemodialysis patients to compare CA vs $CaC0_3$. The trial ran over 2.5 months. Dialysate calcium was 1.62 mmol/L. No patient was on H_2 antagonists and all calcitriol was withdrawn prior to the study. The dose of the binder was titrated to achieve an acceptable serum phosphate. Compliance was assessed.

Results: The mean serum phosphate at the time of group allocation was 1.8 mmol/L in the CA group and 1.93 mmol/L in the $CaCO_3$ group. CA led to no significant increase in serum calcium (2.42–2.47 mmol/L), while in the $CaC0_3$ group it did rise significantly (2.40–2.55 mmol/L). No difference in serum bicarbonate or PTH was found. CA was slightly less well tolerated (but a powder form was used). Hypercalcaemia in the CA group was 16% of participants and in 30.5% in the $CaC0_3$ group.

Limitations: This study had larger patient numbers and fewer patient dropouts than most other studies.

Ring et al (1993) conducted a double-blind, randomised cross-over study of CA vs. $CaC0_3$ in 15 selected haemodialysis patients. Dialysate calcium was 1.74 mmol/L. No patients had calcitriol or H_2 antagonists. Diet diaries, compliance assessment and side-effects were examined. The daily calcium dose (median: 1440 mg, range: 540–2700 mg) was kept constant throughout the study for each patient.

Results: Serum phosphate was lower during the CA phase by 0.11 mmol/L. Due to a time-treatment interaction, it was difficult to interpret serum calcium changes. However, with this caveat, hypercalcaemia was more common during the CA period with 17 episodes vs. 7 with $CaC0_3$. No differences were found in serum PTH, bicarbonate was slightly higher with CA, and no difference in side-effects was noted.

Limitations: This was a very small study.

Aluminium

Aluminium is normally excreted by the kidney. As aluminium has a high affinity for transferrin, in renal failure it is not well cleared by dialysis. Gastrointestinal absorption is markedly increased by citrate or citric acid (Coburn et al 1991). Diabetes and iron deficiency also increase aluminium absorption and toxicity. Aluminium should also be avoided after renal transplantation and parathyroidectomy, when bone re-calcification occurs (Reichel 1992).

The key studies examining aluminium toxicity in kidney disease patients were done in the 1970s and 1980s, and were not randomised controlled studies (RCTs). Nevertheless, examination of this data provides a note of caution on the use of aluminium. Andreoli et al (1984) published a series of case reports in children and neonates who were pre-dialysis and were treated with aluminium as a phosphate binder. This study reported the pattern of osteomalacia with myopathy and bone fractures with biochemically-suppressed alkaline phosphatase (ALP), PTH and clinically, episodes of hypercalcaemia. Bone biopsies showing aluminium accumulation and osteomalacia were also provided. In these children, serum aluminium level corresponded with dose of aluminium taken, and inversely with age of the patient, with infants suffering the most ill-effects. The infants concerned were receiving > 100 mg/kg body weight of aluminium daily.

Alfrey et al (1976) published a study that compared the aluminium content of muscle, bone and brain in control subjects (mostly people who died in traffic accidents) and dialysis patients. A subgroup of dialysis patients who had died from a neurological syndrome of unknown cause had much higher brain aluminium levels of 25 ppm, compared with 6.5 ppm in uraemic patients and 2.2 ppm in control subjects. No other significant findings were seen at autopsy, and no evidence of viral cause was found. All patients had routinely received aluminium gels for at least 2 years prior to the onset of this illness and most were receiving about 2g per day. No information on water aluminium levels was provided.

Clarkson et al (1972) published a pivotal study examining the effect of daily aluminium hydroxide ($Al(OH)_3$) [1.5–3.4 g/day] use in uraemic patients for 20–32 days. Investigations were performed in a metabolic ward. Patients absorbed 100–568 mg of aluminium daily. In a balance study in 3 patients receiving 2 g aluminium per day, the mean daily absorption was 276 mg/day. During the control period, 4.7 mg/day was absorbed. In 2/3 patients, the aluminium content of the iliac bone increased over this time.

In all patients, there was a decrease in serum phosphate. However, phosphate balance studies were negative or neutral in most patients. Hence, the authors suggested that absorbed aluminium may bind to phosphate in bone and other tissues. In 5/8 patients, serum calcium increased as phosphate decreased. Plasma aluminium concentration showed no consistent change throughout the study while serum PTH was variable.

Hence, the above data suggests that aluminium should be avoided in children, especially neonates. It also suggests that we should limit the daily aluminium dose as much as possible. The data also implies that serum aluminium levels may be unreliable but hair and nail samples are no better (de Wolff 1985).

Janssen et al (1996) performed a randomised study over 12 months in 37 haemodialysis patients with dialysate calcium of 1.75 mmol/L. Patients were randomised to CA (mean dose = 4.90 g/day), $CaC0_3$ (mean dose = 3.46 g/day) or aluminium hydroxide (mean dose = 3.16 g/day). The target phosphate level was 1.6 mmol/L and extra aluminium was allowed if required, to achieve phosphate goals. Vitamin D was used if the serum calcium was less than 2.20 mmol/L.

Results: No difference was found between the groups in serum phosphate or PTH over time. The $CaC0_3$ group tended towards higher serum calcium levels than the CA group, who in turn were higher than the aluminium group. Sixty-four per cent in the CA group and 92% in the $CAC0_3$ group had hypercalcaemia > 2.80 mmol/L but none in the aluminium group did. Aluminium seemed to be the most efficient phosphate binder, with no accompanying hypercalcaemia.

Limitations: Many in the calcium phase required aluminium ‘rescue’. No comment was made about aluminium toxicity.

Jespersen et al (1991) investigated 11 haemodialysis patients in a cross-over study of $CaC0_3$ vs. $Al(OH)_3$, with each arm lasting 6 months. Serum phosphate was maintained in the range 1.50–2.0 mmol/L. Dialysate calcium was 1.49 mmol/L and no calcitriol was used. Bone mineral content was assessed with single photon absorptiometry of the forearm. Osteocalcin, ALP and vitamin D levels were also measured. Mean $Al(OH)_3$ dose was 2.28 g/day, 6 tablets per day (range: 3–10/day). Mean $CaCo_3$ dose was 5 tablets per day (range: 3–10/day).

Results: Serum calcium was higher in the $CaC0_3$ group and no difference was seen in serum phosphate. PTH, osteocalcin and ALP decreased with $CaC0_3$ and increased with $Al(OH)_3$. No change in vitamin D levels was found. Bone mineral content declined more during the $Al(OH)_3$ phase (10% per 6 months), probably due to

higher PTH activity. Serum aluminium increased during the $Al(OH)_3$ phase and decreased slowly with $CaC0_3$.

Limitations: This was a very small study.

Lerner et al (1986) did a 6-month comparison of $CaC0_3$ (10.6 g/day) vs. $Al(OH)_3$ gel (5.1 g/day) in 16 haemodialysis patients in a cross-over (non-randomised) study. Seven patients were on vitamin D.

Results: Serum phosphate was similar in both groups. Bicarbonate increased and PTH decreased with $CaC0_3$. Three of the 7 patients on vitamin D developed hypercalcaemia > 2.88 mmol/L. This resolved on discontinuation in 2/3. PTH did not rise in these patients when calcitriol was discontinued.

Aluminium monitoring

Little data exists to guide clinicians in this area. Measurement of plasma levels is a poor reflection of the total body load of aluminium, which has a high volume of distribution. Routine bone biopsy is not acceptable. A recent UK audit of plasma and water aluminium results in the UK suggests that plasma monitoring of aluminium is not indicated when aluminium-based binders are not used. Reverse osmosis-treated water was used in all units involved in the study and water was monitored for aluminium (Gault et al 2005).

Magnesium

[NB: "Mylanta" = 200 mg of $Mg(OH)_2$ and 200 mg $Al(OH)_3$]

Delmez et al (1996) conducted a prospective, randomised, cross-over study in 15 haemodialysis patients, comparing $CaC0_3$ (at half usual dose) plus magnesium carbonate ($MgC0_3$) vs $CaC0_3$ alone in the usual dose. Outcome measures were control of phosphate, calcium and the size of calcitriol dose possible. A magnesium dialysate of 0.2 mmol/L (0.6 mg/dL) was used, and no calcitriol was given prior to the start of the study. Subjects were given $CaC0_3$ for 4–8 weeks to establish a stable dose leading to serum phosphate less than 1.92 mmol/L and calcium between 2.63 and 2.38 mmol/L. Subjects were then randomised to half $CaC0_3$ dose plus $MgC0_3$ 750 mg/day titrated to achieve phosphate target. If targets were maintained, a calcitriol phase was then started at 2 mcg thrice weekly (iv) and this was titrated upwards to a maximum of 4 mcg thrice weekly, for 10 weeks. After 4 weeks back on $CaC0_3$ alone (dialysate Mg = 0.7 mmol/L), subjects then crossed over to the other arm. Calcium dialysate was 1.25 mmol/L. Compliance and diet intake was monitored.

Results: No significant differences were found for mean calcium, phosphate and magnesium levels in both phases. The magnesium group could tolerate twice the dose of calcitriol in comparison with the $CaC0_3$ group.

Limitations: This was a small study with magnesium carbonate only (not hydroxide or trisilicate).

Other non-randomised magnesium studies

Magnesium hydroxide is an effective binder (Guillot et al 1982) but caused diarrhoea in 4/9 patients. Magnesium trisilicate had no phosphate binder effect (Mactier 1987). Magnesium hydroxide is a less effective phosphate binder than $Al(OH)_3$ (Oe et al 1987). However, O'Donovan et al (1986) switched 28 patients from $Al(OH)_3$ to $MgC0_3$ over a 2-year period and had similar phosphate levels with magnesium compared with the control phase. A further study of $CaC0_3$ plus magnesium hydroxide as needed, vs magnesium hydroxide alone was done by Moriniere et al (1988). The second group (magnesium only) had higher phosphate levels. Several studies noted unexplained hyperkalaemia in the magnesium phase. In vitro studies in subjects with normal renal function suggest that magnesium hydroxide is probably a less potent phosphate binder than $CaC0_3$ (Sheikh et al 1989).

Ferric citrate

Yang et al (2002) ran an open-label, random order, cross-over (each arm was 4 weeks) comparison study between ferric citrate 3 g/day and $CaC0_3$ 3 g/day in 45 haemodialysis patients. All iron therapy was discontinued. The dialysate calcium was 1.25 mmol/L and no patient was using calcitriol during the study.

Results: Both compounds reduced serum phosphate, however, $CaC0_3$ was the more effective phosphate binder. However, binder doses were fixed and may not be equivalent in phosphate-binding ability. Calcium levels rose with $CaC0_3$ but not ferric citrate. Ferritin rose marginally with ferric citrate and PTH decreased only with $CaC0_3$. Ferric citrate was associated with mild gastrointestinal side-effects.

Limitations: The fixed-dose study design makes the comparison meaningless. Clearly ferric citrate merits more evaluation as a phosphate binder.

Calcium ketoglutarate

Birck et al (1999). This was a 24-week, open-label, cross-over study in 28 haemodialysis patients of CA vs. calcium ketoglutarate. All patients received equimolar doses of elemental calcium with both treatments.

Results: Both treatments reduced serum phosphate to a plateau level after 4 weeks of treatment. The CA group had 8 episodes of hypercalcaemia (> 2.8 mmol/L) while the calcium ketoglutarate group had 1 episode. There were no differences in PTH or serum bicarbonate. No particular side-effects occurred with calcium ketoglutarate.

Limitations: The dose of both compounds was too small. Higher doses may lead to more side-effects. The drug is expensive.

Bro et al (1998). This study was a randomised, open-label cross-over study of $CaCo_3$ vs. calcium ketoglutarate in 19 haemodialysis patients. Dialysate calcium was 1.25 mmol/L and calcitriol was held at a fixed dose, in all subjects. Each study arm was of 12 weeks' duration. Ten subjects completed both treatments.

Results: Ionised calcium was lower in the calcium ketoglutarate arm. No difference in phosphate and PTH levels was found. Two patients in the $CaC0_3$ arm required

extra aluminium as a phosphate binder and 5/17 patients were withdrawn from the calcium ketoglutarate arm due to gastrointestinal side-effects (most of these had some pre-existing symptoms).

Limitations: The cost of calcium ketoglutarate was 10 times that of $CaC0_3$. This was a small study with frequent dropouts. This drug merits more study.

Lanthanum carbonate

This substance is a rare earth element, a trivalent cation, and has a high affinity for phosphate. It is excreted mainly via the liver and gastrointestinal absorption is said to be minimal (D'Haese et al 2003). However, the drug is still in the relatively early stages of clinical evaluation with few comparison studies against other binders over long time periods.

Joy et al (2003). This was a randomised, placebo-controlled, dose-titration study to assess safety and efficacy of lanthanam over 16 weeks in renal failure patients. This study showed that lanthanum improved phosphate control, calcium x phosphate product and lowered PTH levels, compared with placebo. There were no safety or adverse events reported.

Results of an open-label extension study were published by Finn & Joy in 2005. A total of 77 patients who were involved in two previous lanthanum studies were followed for a further 12 months. They were treated with lanthanum at an optimal dose for phosphate control. Safety and tolerability were assessed. The most commonly reported adverse events were nausea, peripheral oedema, and myalgia. No treatment-related serious adverse events were reported. No bone biopsies were performed. The mean serum phosphate level was 1.84 ± 0.5 mmol/L (54% of patients with 'controlled' phosphate levels) [Finn and Joy 2005].

Animal studies have raised some concerns about lanthanum. A study in rats (Behets et al 2004) suggested that there may be a dose-dependent decrease in bone formation rate and osteomalacia. This was seen at a dose of 1000 mg/kg per day. Lanthanum levels in the femur, however, remained low and did not correlate with the bone changes seen. Other concerns with the drug in animals include cytotoxicity for pulmonary alveolar macrophages in vitro and neurotoxicity in chicks (Basu et al 1982, Palmer et al 1987, Briner et al 2000).

D'Haese et al (2003). This randomised clinical trial is the major study of lanthanum, comparing it to $CaCO_3$ in 98 dialysis-dependent patients over 12 months. Bone biopsies were taken at the start of the study and at 12 months, in 63 patients. Biochemistry and adverse events were compared.

Results: Serum phosphate was well-controlled in both groups. The lanthanum group had a 6% incidence of hypercalcaemia compared with 49% in the $CaCO_3$ group, although the mean calcium levels in the groups were not significantly different. Comparison of the 12-month bone biopsies showed that only one patient in the lanthanum group had evolved towards a low bone turnover state, compared with six in the calcium group. There was little change in either group for PTH or bone-specific

alkaline phosphatase (BSALP) levels. This would seem to differ from the unexplained bone findings in the Behets et al (2004) rat study.

Serum lanthanum levels were higher in the lanthanum group, however, this did not appear to be related to the drug dose. Levels appeared to plateau after 12 weeks of dosing. The median bone concentration of lanthanum at 12 months for those taking the drug was 1.8 mcg/g with the highest value being 5.5 mcg/g. Bone levels of lanthanum also increased in the calcium group, where the highest level was 1.0 mcg/g.

Dialysis

Studies in both long haemodialysis (e.g. 21 h/week) and nocturnal haemodialysis have shown that better serum phosphate and lower calcium x phosphate product were achieved (Fajardo et al 2003, Musci et al 1998). Changing patients from 12 to 15 h per week with the same dialysis dose as assessed by Kt/V has also been shown to increase the amount of phosphate removed in the dialysate, but no change in serum phosphate was shown in this short-term study (Vaithilingam et al 2004).

Diet

(This is a summary of the K/DOQI guideline, 2003). Dietary phosphate restriction should be initiated in CKD as the serum phosphate and serum PTH begin to rise. This may occur at creatinine clearances of 20–30 mL/min/1.73m^2, as this is the level at which no further increase in urinary excretion of phosphate can occur. In children, dietary phosphate restriction is also important but close monitoring of growth is required.

Studies in dialysis-dependent adults where careful dietician input is available do not show an adverse nutritional outcome from a prescribed low phosphate diet. However, in the typical clinical setting, such close monitoring is not always available and a prescribed diet is not always the same as the consumed diet. In general, the phosphate level in the diet should be as low as possible while adequate protein intake is supplied.

Summary of the evidence

With the emergence of data suggesting that both calcium and phosphate serum level targets should be lower than previously thought, clinicians may wonder how these targets can be met in the real world.

There is evidence that longer dialysis hours can lead to better serum phosphate levels. This is not suitable for all patients.

This area is plagued by a multitude of small studies with different aims and study designs. This includes different timing of phosphate binders with respect to meals, differing use of vitamin D analogues and different dialysis calcium concentrations. It is difficult to reach a definitive conclusion.

Sevelamer is a newer agent recently available in Australia. Available trial data suggests that sevelamer is an equivalent but not better binder of phosphate, compared with calcium salts. There is evidence that sevelamer use leads to less hypercalcaemia than calcium salts. Sevelamer also lowers LDL cholesterol. It is associated with a lower serum bicarbonate level in kidney disease patients. One trial examined vascular calcification over a 1-year period and found less calcification with sevelamer than with $CaCO_3$ (Chertow et al 2002). Mortality data is awaited.

Another major study is the CARE study (Qunibi et al 2004), an RCT of 98 patients randomised to CA or sevelamer. This well-conducted study showed that CA was able to control serum phosphate and the calcium x phosphate product better than sevelamer, at less cost.

In patients prone to hypercalcaemia, there may be a role for sevelamer. Less coronary calcification progression over 52 weeks was seen for sevelamer (+ 6% increase) vs $CaCO_3$ (+ 23% increase) in the study by Chertow et al (2002). Calcification score is a surrogate marker for cardiovascular events and hard endpoint data is awaited. Some studies with sevelamer have required the use of supplemental calcium to maintain serum calcium levels. It is unclear whether sevelamer is associated with less calcification in such cases and whether the reduction in vascular calcification is due to lower calcium levels or by concomitant improvement in lipid profile. Recent Japanese studies have shown good phosphate control and patient tolerability with a combination of sevelamer and $CaCO_3$ (Koiwa et al 2005).

Calcium salts are the most extensively used phosphate binders. Trial and registry data have shown that calcium salts may be associated with suppression of PTH levels and the development of adynamic bone disease and vascular and ectopic calcification, with increased risk of cardiovascular events.

There are numerous small studies comparing CA and $CaCO_3$. Less elemental calcium is required for the same amount of phosphate binding in the acetate form compared with the carbonate; this translates into a small difference in serum calcium levels in the trials done to date, although several studies show a trend to more hypercalcaemia with the carbonate form. A meta-analysis done as part of the K/DOQI guidelines indicates that CA leads to less hypercalcaemia than do $CaCO_3$ salts (National Kidney Foundation 2003).

Some studies suggested taking the carbonate salt before meals with a higher stomach pH, for better phosphate binding effects. Mid-meal medication with the carbonate makes the salt less soluble. This is not so important for the acetate. Many of the studies did not specify dosing time.

Aluminium salts have led to toxicity issues in the past, and certainly metabolic study data on aluminium absorption is concerning. Nevertheless, aluminium is an excellent phosphate binder for which there remains a role in some patients. There are no good randomised trials examining aluminium use or toxicity. There is no data to suggest a safe threshold dose of aluminium or the optimal monitoring regimen. Magnesium is a weaker binder of phosphate and again, studies on this salt are limited.

Lanthanum is a new rare metal salt, phosphate binder. There is evidence that lanthanum is an effective binder of dietary phosphate compared with placebo (Joy &

Finn 2003). A 12-month clinical study in humans showed no trend towards the development of adynamic bone disease with this salt, although rat studies had suggested that this may occur (Behets et al 2004). The same study showed lanthanum equivalence with $CaCO_3$ in the control of serum phosphate (D'Haese et al 2003). Serum and bone levels of lanthanum did increase over the 12 months in the lanthanum-treated group, although not to a large degree. The $CaCO_3$ group had more episodes of hypercalcaemia compared with the lanthanum group, although mean serum calcium levels were not significantly different.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative:
These guidelines state a maximal total dose of calcium-based binders of 1,500 mg/day elemental calcium, and that total intake of elemental calcium should not exceed 2000 mg per day.

K/DOQI also state that calcium salts should be avoided when serum calcium is above 2.54 mmol/L and PTH less than 16.5 pmol/L.

The writers of this CARI guideline feel that without mortality data showing a benefit for sevelamer (or lanthanum) over calcium, it is not possible to give an upper limit for calcium daily dose. Clinically serum calcium levels may differ widely between patients depending on the use of calcitriol and other variables in addition to the dose of calcium-containing binders. A recommendation for the upper dose of aluminium was not made in K/DOQI or in CARI, as there is no evidence to suggest a threshold dose.

UK Renal Association:
These guidelines suggest that serum phosphate level is a marker for nutrition and that a low serum phosphate may reflect malnutrition.

The guidelines recommend that serum aluminium be measured at least 3-monthly in all dialysis (HDx and CAPD) patients taking aluminium salts.
This CARI guideline has not made a specific recommendation on serum aluminium monitoring due to lack of data (except to say that unit water should be monitored and this may be adequate when aluminium-containing binders are not used.)

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines:
These guidelines suggest that the calcium salt dose be limited to 6 g per day and that calcium binders not be given when active vitamin D derivatives are also being used, due to the risk of extra-skeletal calcification. Calcium citrate should also be avoided in patients who are also on aluminium salts. Optimisation of the dialysis dose is also emphasised.

International Guidelines: No recommendation.

Implementation and audit

Implementation should be on the basis of achieving target serum levels of calcium (< 2.4 mmol/L), phosphate (< 1.6 mmol/L) and PTH (not less than the upper limit of the reference range). As episodes of hypercalcaemia may be a marker for vascular calcification, dialysis units should review blood results monthly in order to minimise hypercalcaemic episodes and improve serum phosphate control. The number of patients with levels out of range could be used as a performance indicator.

Suggestions for future research

1. Mortality studies with newer agents – sevelamer and lanthanum – in comparison with calcium salts are urgently required.
2. An audit of serum aluminium levels. Follow-up data on patients with elevated levels should be collected.
3. Cost-benefit analysis of sevelamer vs. calcium salts should be undertaken as the dose of sevelamer needed to control phosphate will add considerably to the cost of treating end-stage kidney disease.
4. Bone biopsy studies of patients treated long-term with lanthanum should be undertaken to satisfy safety concerns.

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Appendices

Table 1 Characteristics of randomised controlled trial evidence

Author/Year	N	Design	Setting	Subjects	Intervention	Control	Follow Up	Comments
Joy et al, 2003	126	pRCT…	University	HD*	Lanthanum	Placebo	4 weeks	Short study.
D'Haese et al, 2003	98	pRCT	University	HD/PD$^{\delta}$	Lanthanum	$CaC0_3$	12 mths	Bone histology study
Qunibi et al, 2004	100	pRCT	Univercity / multi-centre	HD	Sevelamer	CA	8 wks/ 98 pts	Titrated to phosphate
Hervas et al, 2003	51	pRCT	?	HD	Sevelamer 403 mg	CA 500 mg	34 wks/ 40 pts	Doses titrated
Bleyer et al, 1999	84	RXover	multi-centre	HD	Sevelamer	CA	8 wks each arm	Titrated to phosphate
Chertow et al, 2002	223	MRCT	multi-centre	HD	Sevelamer	Calcium salts	52 weeks	Open label
Chertow et al, 1999	71	RCT	University	Haemo > 3 mths	Sevelamer	Sevel. + 900 mg extra calcium	16 wks/ 55 finished	Interest in "Renegl" by several authors
Raggi et al, 2001	223	pRCT	University	HD	Sevelamer	Calcium	52 weeks	Coronary calcification progressed with Calc No change with sevelamer
Raggi et al, 2004	186	RCT	University	HD	sevelamer	CA/ CaC03	52 weeks	Electron beam tomography of coronary arteries and valves.
D'Almeida Filho et al, 2000	101	RXover$^{\Psi}$	Private centre	HD	CA	CaCO3	64 pts finished	
Pflanz et al, 1994	31	RXover	University	HD	CA	CaCO3	6 wks each arm/23 finished	Equimolar calcium, compliance measured

Table 1 Continued

Author/Year	N	Design	Setting	Subjects	Intervention	Control	Follow Up	Comments
Ring et al, 1993	15	RXover	Hospital	HD	CA 90 mg calcium	$CaCO_3$ 90 mg calcium	3 weeks each arm	Compliance 92%. Same diet intake of phosphate and PCR bicarbonate higher in CA
Caravaca et al, 1992	80	RCT	Hospital	HD	CA	$CaCO_3$	4 mths	No calcitriol No H_2 inhibitors
Almirall et al, 1994	10	RXover	Single hospital	HD	CA	$CaCO_3$	12 weeks each arm	All on calcitriol. No H_2 inhibitors
Yang et al, 2002	45	RXover	University	HD	$CaCO_3$ 3 g/day	Ferric citrate 3 g/day	4 wks each arm/45 finished	
Delmez et al, 1996	29	RXover	University	HD > 6 mths	$CaCO_3$ + mg	$CaCO_3$ alone	10 weeks each arm	
Jespersen et al, 1991	14	RXover	Single centre	11 HD 3 CAPD$^{\beta}$	$CaCO_3$	$Al(OH)_3$	52 weeks	No difference in phosphate
Bro et al, 1998	19	RXover	University	HD	Calcium ketoglutarate	$CaCO_3$	12 weeks each arm	Ketoglutarate expensive and some GI upset
Birck et al, 1999	28	RXover	University	HD	Calcium ketoglutarate	CA	12 weeks	Binder titrated to phosphate initially then fixed
Janssen et al, 1996	53	RCT	Single hospital	HD	Al	CA or $CaCO_3$	52 weeks	Dose titrated to calcium and phosphate levels. Some on vitamin D

...RCT, randomised controlled trial; $^{\Psi}$RXover, randomised crossover clinical trial; *HD, haemodialysis; $^{\delta}$PD, peritoneal dialysis; $^{\beta}$CAPD, continuous ambulatory peritoneal dialysis.

Table 2 Quality of randomised trials

Author/Year	Method of allocation Concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		Subjects	Investigators	Outcome Assessors		
Joy et al, 2003	unclear	yes	yes	Not stated	Not stated	Unclear if any
D'Haese et al, 2003	unclear	no	no	no	yes	30
Qunibi et al, 2004	unclear	yes	yes	Not stated	no	nil
Hervas et al, 2003	unclear	no	no	Not stated	no	22
Bleyer et al, 1999	unclear	no	no	no	no	4
D'Almeida Filho et al, 2000	unclear	yes	yes	Not stated	no	66
Chertow et al, 2002	Computer gen.	no	no	Not stated	Not stated	Not stated
Chertow et al, 1999	unclear	no	no	No	yes	nil
Pflanz et al, 1994	unclear	no	no	Not stated	no	26
Raggi et al, 2001	unclear	no	no	Not stated	Not stated	Not stated
Yang et al, 2002	unclear	no	no	Not stated	no	17
Delmez et al, 1996	unclear	no	no	Not stated	no	49
Ring et al, 1993	Random numbers	yes	yes	Not stated	no	29
Bro et al, 1998	unclear	no	no	Not stated	no	48
Birck et al, 1999	unclear	no	no	Not stated	no	13
Caravaca et al, 1992	unclear	no	no	Not stated	no	18
Janssen et al, 1996	unclear	no	no	Not stated	no	31
Almirall et al, 1994	unclear	no	no	Not stated	no	30
Raggi et al, 2004	Computer gen.	no	no	Not stated	no	29
Jespersen et al, 1991	unclear	no	no	Not stated	no	22

Table 3 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Almirall et al, 1994	Hypercalcaemia	1/7	***1/7***	1.00 (95%CI:0.08, 13.02)	0.00 (95%CI:-0.37, 0.37)
Birck et al, 1999	Hypercalcaemia	1/28	***8/28***	0.13 (95%CI:0.02, 0.93)	-0.25 (95%CI:-0.43, -0.07)
Bleyer et al, 1999	GI complaints	28/83	23/83	1.22 (95%CI:0.77, 1.93)	0.06 (95%CI:-0.08, 0.20)
	Hypercalcaemia	4/83	18/83	0.22 (95%CI:0.08, 0.63)	-0.17 (95%CI:-0.27, -0.07)
Chertow et al, 2002	Hypercalcaemia	5/99	16/101	0.32 (95%CI:0.12, 0.84)	-0.11 (95%CI:-0.19, -0.02)
	Mortality	6/99	5/101	1.22 (95%CI:0.39, 3.88)	0.01 (95%CI:-0.05, 0.07)
	hospitalisation	37/99	48/101	0.79 (95%CI:0.57, 1.09)	-0.10 (95%CI:-0.24, 0.03)
Chertow et al, 1999	Serum phosphorus at or below washout level <5.5 mg/dL	33/35	34/36	1.00 (95%CI: 0.89, 1.12)	0.00 (95%CI: -0.11, 0.11)
D'Haese et al, 2003	GI complaints	18/34	17/34	1.06 (95%CI:0.67, 1.68)	0.03 (95%CI:-0.21, 0.27)
	Hypercalcaemia	2/34	17/34	0.12 (95%CI:0.03, 0.47)	-0.44 (95%CI:-0.63, -0.26)

Table 3 Continued

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
	Normal or increased bone turnover	26/33	23/30	1.03 (95%CI: 0.79, 1.34)	0.02 (95%CI: -0.18, 0.23)
	Adynamic bone disease	1/26	6/23	0.15 (95%CI: 0.02, 1.14)	-0.22 (95%CI: -0.42, -0.03)
	Hyperparathyroid-ism	2/33	5/30	0.36 (95%CI: 0.08, 1.74)	-0.11 (95%CI: -0.26, 0.05)
Hervas et al, 2003	Hypercalcaemia	9/40	15/40	0.60 (95%CI: 0.30, 1.21)	-0.15 (95%CI: -0.35, 0.05)
Janssen et al, 1996	Mortality (Aluminium vs calcium acetate)	2/15	2/18	1.20 (95%CI: 0.19, 7.53)	0.02 (95%CI: -0.20, 0.25)
	Mortality (Calcium carbonate vs. calcium acetate)	2/20	2/18	0.90 (95%CI: 0.14, 5.74)	-0.01 (95%CI: -0.21, 0.18)
Joy et al, 2003	Nausea	3/50	2/44	1.32 (95%CI: 0.23, 7.54)	0.01 (95%CI: -0.08, 0.10)
	Vomiting	3/50	1/44	2.64 (95%CI: 0.28, 24.47)	0.04 (95%CI: -0.04, 0.12)
	Diarrhoea	2/50	3/44	0.59 (95%CI: 0.10, 3.35)	-0.03 (95%CI: -0.12, 0.06)
	Dialysis graft occlusion	3/50	1/44	2.64 (95%CI: 0.28, 24.47)	0.04 (95%CI: -0.04, 0.12)

Table 3 Continued

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Qunibi et al, 2004	Hypocalcaemia	3/46	1/46	3.00 (95%CI: 0.32, 27.79)	0.04 (95%CI: -0.04, 0.13)
	Hypercalcaemia	3/46	0/46	7.00 (95%CI: 0.37, 131.81)	0.07 (95%CI: -0.02, 0.15)
Yang et al, 2002	Upset stomach	1/45	2/45	0.50 (95%CI: 0.05, 5.32)	-0.02 (95%CI: -0.10, 0.05)

Table 4 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Almirall et al, 1994	Serum calcium	10.35 (0.5)	10.20 (0.5)	0.15 (95%CI: -0.37, 0.67)
Birck et al, 1999	PTH (pmol/l) at 12 weeks	18.5 (14.1)	19.4 (16.7)	-0.90 (95%CI: -9.00, 7.20)
	Albumin (g/l) at 12 weeks	39.4 (4.8)	38.3 (4.1)	1.10 (95%CI: -1.24, 3.44)
	Calcitriol (ng/l) at 12 weeks	22.8 (12.2)	19.9 (8.3)	2.90 (95%CI: -2.57, 8.37)
	Venous bicarbonate (mmol/l) at 12 weeks	22.5 (3.5)	21.2 (1.8)	1.30 (95%CI: -0.16, 2.76)
Bleyer et al, 1999	Mean change in serum P (mg/dl)	-2.0 (2.3)	-2.1 (1.9)	0.10 (95%CI: -0.54, 0.74)
	Mean change in serum Ca (mg/dl)	0.2 (0.6)	0.6 (0.8)	-0.40 (95%CI: -0.62, -0.18)
	Mean change in Ca x P (mg^2/dl^2)	-16.5 (19.6)	-15.9 (16.5)	-0.60 (95%CI: -6.11, 4.91)
	Mean change in serum iPTH (pg/ml)	-48.2 (168)	100.6 (289.7)	-52.40 (95%CI: -19.65, 124.45)
	Alkaline phosphatase (U/l) final	114.3 (73.3)	95.8 (49.5)	18.50 (95%CI: -0.53, 37.53)
	Intestinal fraction (%) final	4.2 (9.4)	5.2 (11.6)	-1.00 (95%CI: -4.21, 2.21)
	Bone fraction (%) final	55.7 (23.8)	55.7 (2.1)	0.00 (95%CI: -5.14, 5.14)
	Macrohepatic fraction (%) final	15.7 (9.4)	18.8 (10.2.)	-3.10 (95%CI: -6.08, -0.12)
	Liver fraction (%) final	36.2 (18.4)	36.1 (16.7)	0.10 (95%CI: -5.25, 5.45)
	Total cholesterol (mg/dl) final	146.8 (42.8)	169.9 (51.4)	-23.10 (95%CI: -37.49, -8.71)

Table 4 Continued

	LDL cholesterol (mg/dl) final	77.2 (28.0)	100.9 (34.4)	-23.70 (95%CI: -33.24, -14.16)
	HDL cholesterol (mg/dl) final	38.3 (14.2)	38.6 (14.1)	-0.30 (95%CI: -4.61, 4.01)
	Triglycerides (mg/dl) final	162.8 (157.1)	157.6 (154.6)	5.20 (95%CI: -42.22, 52.62)
	25 hydroxy-vitamin D (mg/ml) final	22.4 (18.3)	23.6 (16.3)	-1.20 (95%CI: -6.47, 4.07)
Bro et al, 1998	Albumin (g/dl) at 12 weeks	4.07 (0.51)	3.87 (0.19)	0.20 (95%CI: -0.14, 0.54)
	Bicarbonate (mEq/l) at 12 weeks	22.4 (3.79)	24.1 (2.21)	-1.70 (95%CI: -4.42, 1.02)
	Creatinine (mg/dl) at 12 weeks	9.5 (2.85)	9.1 (2.21)	0.40 (95%CI: -1.84, 2.64)
	Urea (mg/dl) at 12 weeks	75.1 (27.5)	72.8 (22.14)	2.30 (95%CI: -19.58, 24.18)
	Plasma ionised Ca levels (mg/dl) at 12 weeks	4.8 (0.32)	5.2 (0.32)	-0.40 (95%CI: -0.68, -0.12)
	Plasma ionised Ca x P (mg^2/dl^2)	26.3 (3.48)	21.8 (4.74)	4.50 (95%CI: 0.86, 8.14)
	Plasma PTH (pg/ml)	266 (395.28)	301 (468.02)	-35.00 (95%CI: -415.17, 345.17)
Caracava et al, 1992	Changes in serum phosphorus at end of study (mmol/l)	1.80 (0.50)	1.93 (0.48)	-0.13 (95%CI: -0.37, 0.11)
	Change in serum calcium (mmol/l) at end of study	2.47 (0.17)	2.55 (0.22)	-0.08 (95%CI: -0.17, 0.01)
	Change in serum bicarbonate (mmol/l) at end of study	20.59 (1.9)	20.58 (2.2)	0.01 (95%CI: -0.98, 1.00)
	Dry body weight change (kg)	0.469 (1.430)	0.400 (1.366)	0.07 (95%CI: -0.61, 0.75)

Table 4 Continued

Chertow et al, 2002	Phosphate (mg/dl) final	5.1 (1.2)	5.1 (1.4)	0.00 (95%CI: -0.36, 0.36)
	Ca (mg/dl) final	9.5 (0.6)	9.7 (0.7)	-0.20 (95%CI: -0.38, -0.02)
	Ca x P (mg^2/dl^2) final	48 (12)	49 (14)	-1.00(95%CI: -4.61, 2.61)
	Total cholesterol (mg/dl) final	141 (28)	182 (41)	-41.00 (95%CI: -52.03, -29.97)
	LDL cholesterol (mg/dl) final	65 (21)	103 (43)	-38.00 (95%CI: -47.35, -28.65)
	HDL cholesterol (mg/dl) final	43 (10)	45 (12)	-2.00 (95%CI: -5.06, 1.06)
	Mean change in coronary arteries at 26 weeks	-134 (697)	110 (413)	-244.00 (95%CI: -436.39, -51.61)
	Mean change in coronary arteries at 52 weeks	-46 (692)	151 (471)	-197.00 (95%CI: -401.56, 7.56)
	Mean change in aorta at 26 weeks	-595 (1723)	230 (1697)	-825.00 (95%CI: -1390.95, -259.05)
	Mean change in aorta at 52 weeks	-532 (1706)	185 (3100)	-717.00 (95%CI: -1558.25, 124.25)
Chertow et al, 1999	Mean change of serum phosphorus at 12 weeks (mg/dl)	-2.4 (1.8)	-2.3 (2.2)	-0.10 (95%CI: -0.11, 0.11)
	Mean change in serum calcium (mg/dl)	0.0 (0.6)	0.3 (0.8)	-0.30 (95%CI: -0.63, 0.03)
	Mean serum calcium (mg/dl) at end of study	9.4 (0.6)	9.4 (0.8)	0.00 (95%CI: -0.33, 0.33)
	Ca x P (mg^2/dl^2) at end of study	60.1 (17.3)	55.9 (13.9)	4.20 (95%CI: -3.11, 11.51)

Table 4 Continued

Delmez et al, 1996	Mean tolerated calcitriol dose	1.5 (1.16)	0.8 (1.16)	0.70 (95%CI: -0.13, 1.53)
	Mean PTH (ng/ml)	47 (30.98)	48 (38.73)	-1.00 (95%CI: -26.10, 24.10)
	Mean potatssium (mEq/l)	4.9 (0.39)	4.9 (0.39)	0.00 (95%CI: -0.28, 0.28)
D'Almeida et al, 2000	Calcium plasma (mg/dl) final	9.91 (0.79)	9.34 (0.91)	0.57 (95%CI: 0.08, 1.06)
	Phosphorus (mg/dl)	4.66 (1.32)	4.56 (1.57)	0.10 (95%CI: -0.74, 0.94)
Hervas et al, 2003	Mean change in serum phosphorus (mg/dl)	-2.29 (0.05)	-1.6 (0.1)	-0.69 (95%CI: -0.72, -0.66)
	Intact PTH (pg/ml) final	330 (205)	346 (250)	-16.00 (95%CI: -116.19, 84.19)
	Serum alkaline phosphatase (I/l)	243 (65)	226 (120)	17.00 (95%CI: -25.29, 59.29)
Janssen et al, 1996	Serum $Al(OH_3)$ concentration after 12 months (Al vs. Ca acetate)	116 (123.33)	90 (44.90)	26.00 (95%CI: -53.98, 105.98)
	Serum magnesium after 12 mo (Al vs. Ca acetate)	1.19 (0.16)	1.26 (0.11)	-0.07 (95%CI: -0.18, 0.04)
	Serum $Al(OH_3)$ concentration after 12 months (Al vs. Ca carbonate)	88 (57.69)	90 (44.90)	-2.00 (95%CI: -41.20, 37.20)
	Serum magnesium after 12 months (Al vs. Ca carbonate)	1.24 (0.18)	1.26 (0.11)	-0.02 (95%CI: -0.13, 0.09)
Joy et al, 2003	Phosphorus (mg/dl)	5.9 (1.65)	7.85 (1.96)	-1.95 (95%CI: -2.69, -1.21)
	Calcium (mg/dl)	8.83 (0.68)	8.48 (0.81)	0.35 (95%CI: 0.04, 0.66)
	Ca x P (mg^2/dl^2)	52.4 (14.9)	66.6 (18.3)	-14.20 (95%CI: -21.03, -7.37)
	PTH (pg/ml)	209 (152)	292 (195)	-83.00 (95%CI: -154.63, -1.37)

Table 4 Continued

	Lanthanum (ng/ml)	0.64 (0.60)	0.20 (0.21)	0.44 (95%CI: 0.26, 0.62)
Qunibi et al, 2004	Phosphorus (mg/dl)	6.4 (1.6)	5.5 (1.7)	0.90 (95%CI: 0.25, 1.55)
	Calcium (mg/dl)	9.0 (0.4)	9.6 (0.8)	-0.60 (95%CI: -0.85, -0.35)
	Ca x P (mg^2/dl^2)	57.3 (13.9)	52.7 (16.5)	4.60 (95%CI: -1.43, 10.63)
Yang et al, 2002	Serum phosphorus (mg/dl) at wk 4	5.2 (1.5)	5.7 (1.6)	-0.60 (95%CI: -1.24, 0.04)
	Serum calcium (mg/dl) at wk 4	9.5 (0.7)	9.0 (1.0)	0.50 (95%CI: 0.14, 0.86)
	Ca x P (mg^2/dl^2) at wk 4	49.5 (15.3)	51.8 (15.2)	-2.30 (95%CI: -8.60, 4.00)
	Intact PTH (pg/ml) at wk 4	192 (172)	228 (160)	-36.00 (95%CI: -104.64, 32.64)
	Calcitriol (pg/ml) at wk 4	12.9 (8.6)	12.1 (5.7)	0.80 (95%CI: -2.21, 3.81)
	Aluminium (µg/l) at wk 4	10.6 (6.3)	12.9 (7.5)	-2.30 (95%CI: -5.15, 0.56)
	Haemoglobin (g/dl)	10.0 (1.5)	10.1 (1.3)	-0.10 (95%CI: -0.68, 0.48)
	Haematocrit (%)	29.8 (4.0)	30.3 (3.5)	-0.50 (95%CI: -2.05, 1.05)
	Iron (mg/d)	68.9 (25.4)	71.2 (31.6)	-2.30 (95%CI: -13.42, 8.82)
	Ferritin (mg/d)	233 (122)	248 (143)	-15.00 (95%CI: -69.92, 39.92)
	Serum alkaline phosphatase (U/l)	84.7 (45.4)	85.0 (44.8)	-0.30 (95%CI: -18.94, 18.34)
	Serum albumin (g/dl)	4.0 (0.2)	4.0 (0.2)	0.00 (95%CI: -0.08, 0.08)
	BUN (mg/dl)	72.1 (12.3)	69.9 (12.0)	2.20 (95%CI: -2.82, 7.22)
	Creatinine (mg/dl)	11.3 (1.8)	11.4 (2.1)	-0.10 (95%CI: -0.91, 0.71)