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Calcimimetics for secondary hyperparathyroidism in chronic kidney disease patients (Review)

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[Intervention Review]

Calcimimetics for secondary hyperparathyroidism in chronic kidney disease patients

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ABSTRACT

Background

Calcimimetic agents have recently been evaluated in the treatment of secondary hyperparathyroidism (SHPT) as add-on therapy to calcitriol and vitamin D analogues and dietary phosphate binders.

Objectives

To evaluate the benefits and harms of calcimimetics for the prevention of secondary hyperparathyroid bone disease (including osteitis fibrosa cystica and adynamic bone disease) in dialysis patients with chronic kidney disease (CKD).

Search methods

MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials and conference proceedings were searched for randomised controlled trials (RCTs) evaluating any calcimimetic against placebo or another agent in pre-dialysis or dialysis patients with CKD.

Selection criteria

We included all RCTs of any calcimimetic agent, cinacalcet HCl (AMG-073, Sensipar®), NPS R-467 or NPS R-568 administered to patients with CKD for the treatment of SHPT.

Data collection and analysis

Data were extracted on all relevant patient-centred and surrogate outcomes. Analysis was by a random effects model and results expressed as risk ratio (RR) or mean difference (MD) with 95% confidence intervals.

Main results

Eight studies (1429 patients) were identified, which compared a calcimimetic agent plus standard therapy to placebo plus standard therapy. The end of treatment values of parathyroid hormone (pg/mL) (MD -290.79, 95% CI -360.23 to -221.34), serum calcium (mg/dL) (MD -0.85, 95% CI -1.14 to -0.56), serum phosphorus (mg/dL) (MD -0.29, 95% CI -0.50 to -0.08) and the calcium by phosphorus product (mg^2/dL^2)(MD -7.90, 95% CI -10.25 to -5.54) were significantly lower with calcimimetics compared to placebo. No significant effects on patient-based

endpoints were demonstrated except for the risk of hypotension which was significantly reduced with calcimimetics compared to placebo (RR 0.53, 95%CI 0.36 to 0.79).

Authors' conclusions

Calcimimetic treatment of SHPT leads to significant improvements in biochemical parameters that observational studies have shown to be associated with increased mortality, cardiovascular risk and osteitis fibrosa, but patient-based benefits have not yet been demonstrated in trials. For patients with SHPT, the benefits of calcimimetics over standard therapy remain uncertain until further RCTs become available.

PLAIN LANGUAGE SUMMARY

Calcimimetics for secondary hyperparathyroidism in chronic kidney disease patients

Abnormalities of calcium and phosphorus metabolism are present in all individuals with chronic kidney disease (CKD). These biochemical changes lead to a condition known as secondary hyperparathyroidism (SPTH), resulting in an excessive production of parathyroid hormone which in turn causes bone and metabolic disorders. These disorders are associated with an increased incidence of fracture, bone and muscular pain and abnormalities of bones and joints. Standard management of patients with CKD, particularly those on dialysis, includes treatment to control levels of calcium, phosphorus and parathyroid hormone. This can be achieved initially by dietary restrictions of phosphorus, calcium supplementation, and/or the use of calcitriol. Once patients have commenced dialysis, standard treatment generally includes calcitriol, vitamin D analogues or derivatives, calcium or other phosphate-binding agents and parathyroidectomy. The aim of this review was evaluate the benefits and harms of calcimimetics for the prevention of SHPT in patients with CKD. Eight studies (1429 patients) were identified. After treatment, parathyroid hormone, serum calcium, serum phosphorus and the calcium by phosphorus product were all significantly lower for calcimimetics when compared to placebo. The only patient level outcome which was been found to be reduced with the use of calcimimetics is the risk of hypotension. For patients with SHPT, the benefits of calcimimetics over standard therapy remain uncertain until further RCTs become available.

BACKGROUND

Abnormalities of calcium and phosphorus metabolism are present in all individuals with chronic kidney disease (CKD). These biochemical changes cause many bone and metabolic disorders, including renal osteodystrophy that is characterized by abnormalities of bone turnover (ranging from high turnover osteitis fibrosa to adynamic bone disease), mineralization defects (osteomalacia) and architectural change. Renal osteodystrophy is associated not only with an increased incidence of fracture, bone and muscular pain and abnormalities of bone and joint morphology, but also with vascular and soft tissue calcification. In addition to causing reduced quality of life, these complications and the associated abnormalities of elevated phosphorus, calcium, the calcium by phosphorus product and levels of parathyroid hormone (PTH) have been associated with increased mortality (Block 2004b; Ganesh 2001; Malluche 2004b; Marco 2003; Martin 2004; Stehman-Breen 2004).

Standard management of patients with CKD, particularly those on dialysis, includes treatment to control levels of calcium, phosphorus and PTH, so as to prevent bone and soft-tissue complications. Based on a number of association studies, (Block 2004b; Ganesh 2001; Kestenbaum 2005; Marco 2003; Stevens 2004) including studies of bone histomorphometry, (Hutchison 1993; Qi 1995; Wang 1995; Ziolkowska 2000) optimal ranges for serum phosphorus, calcium, the calcium by phosphorus product and PTH have been suggested (CARI 2005; NKF 2003). However, success in achieving these targets has been limited (Young 2004).

Specific management of secondary hyperparathyroidism (SHPT) in CKD stages 3 and 4 may be accomplished by restriction of dietary phosphorus, calcium supplementation, and/or the use of calcitriol. Once patients have commenced dialysis, standard therapy of SHPT generally includes calcitriol, vitamin D analogues or derivatives, calcium or other phosphate-binding agents and parathyroidectomy (Albaaj 2003; Courant 1993). Recently the use of a novel class of drugs, the calcimimetics, has been proposed as a strategy to reduce PTH secretion and possibly to reduce parathyroid cell proliferation, while decreasing levels of serum calcium, phosphorus and the calcium by phosphorus product (Goodman 2000; Ott 1998). Use of these agents has been advocated whenever there is inability to control SHPT with other agents. Results of randomised controlled trials (RCTs) testing the efficacy and safety of calcimimetics in patients undergoing dialysis are becoming available. With the aim of preventing complications associated with SHPT, cinacalcet HCl has now been incorporated into many treatment algorithms.

However, several aspects of calcimimetic therapy require further evaluation. In the dialysis population, for which these drugs are approved, the most important question is the degree to which calcimimetics will impact on clinically relevant end-points such as parathyroidectomy rates, fracture, renal osteodystrophy, cardiovascular disease and death, as well as surrogate markers for these conditions, such as abnormalities of serum calcium and phosphorus. Other important questions include the optimal time for commencement of calcimimetic therapy, the influence of calcimimetics on standard treatment regimens and the effectiveness of calcimimetics at different stages of CKD and after transplantation.

This systematic review was performed at an early phase of calcimimetic usage, but one year after licensing by the FDA (FDA 2004), in order to assess available efficacy and safety data and to highlight research questions that need further investigation.

OBJECTIVES

To evaluate the benefits and harms of calcimimetics for the prevention of secondary hyperparathyroid bone disease (including osteitis fibrosa cystica and adynamic bone disease) in dialysis patients with CKD.

METHODS

Criteria for considering studies for this review

Types of studies

We included all RCTs of any calcimimetic agent, cinacalcet HCl (AMG-073, Sensipar®), NPS R-467 or NPS R-568 administered to patients with CKD for the treatment of SHPT.

Types of participants

Patients with CKD needing treatment for SHPT.

Types of interventions

Any calcimimetic agent (e.g. cinacalcet HCl (AMG-073, Sensipar®), NPS R-467 or NPS R-568).

Types of outcome measures

1. All-cause mortality
2. At least 30% decrease in mean PTH level
3. Fractures
4. Hypocalcaemia (as defined by the authors)
5. Nausea
6. Vomiting
7. Dyspnoea
8. Muscle weakness
9. Hypotension
10. Upper respiratory tract infection
11. Parathyroidectomy
12. Headache
13. Paresthesia
14. Abdominal pain
15. Diarrhoea
16. Mixed uraemic osteodystrophy
17. Bone histomorphometry
18. End of treatment PTH levels (any measure)
19. End of treatment serum calcium concentrations (mg/dL or mmol/L)
20. End of treatment serum phosphorus concentrations (mg/dL or mmol/L)
21. End of treatment calcium x phosphorus product (mg^2/dL^2)

Search methods for identification of studies

The literature searching was performed independently by two authors. Relevant studies were obtained from the following sources

without language restriction (see Table 1 - *Electronic search strategies*).

1. The Cochrane Renal Group's specialised register and the Cochrane Central Register of Controlled Trials (CENTRAL) in T*he Cochrane Library,* (issue 4 2005)
2. MEDLINE (1966 to November 2005) using the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of RCTs (Dickersin 1994) with a specific search strategy developed with input from the Cochrane Renal Group's Trial Search Co-ordinator.
3. EMBASE (1980 to November 2005) using a search strategy adapted from that developed for the Cochrane Collaboration for the identification of RCTs (Lefebvre 1996) together with a specific search strategy developed with input from the Cochrane Renal Group's Trial Search Co-ordinator.
4. Reference lists of nephrology textbooks, review articles and relevant trials.
5. Letters seeking information about unpublished or incomplete trials to investigators known to be involved in previous trials.

Data collection and analysis

Search strategy

The results of the above searches were analysed in title and abstract form by two authors according to the inclusion criteria in consultation with a third author. Reference lists from the identified articles were also searched and information about unpublished or ongoing trials was sought from experts in the field and pharmaceutical companies. Trials were considered without language restriction.

Data extraction and trial quality assessment

Each trial was assessed independently by two authors. From all included trials, data were extracted on study sample characteristics, the type of agent, dose, and route of administration, the trial methods and outcomes. The methods and quality of included trials were assessed using standard criteria (allocation concealment, blinding of participants, investigators and outcome assessors, analysis by intention to treat and completeness of follow-up). Discrepancies in data extraction were resolved by discussion among the authors, and when data were missing or incomplete, the investigators of the trial were contacted for clarification.

Quality checklist

Allocation concealment

- Adequate (A): Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study
- Unclear (B): Randomisation stated but no information on method used is available
- Inadequate (C): Method of randomisation used such as alternate medical record numbers or unsealed envelopes; any information in the study that indicated that investigators or participants could influence intervention group

Blinding

- Blinding of investigators: Yes/no/not stated
- Blinding of participants: Yes/no/not stated
- Blinding of outcome assessor: Yes/no/not stated
- Blinding of data analysis: Yes/no/not stated

The above are considered not blinded if the treatment group can be identified in > 20% of participants because of the side effects of treatment.

Intention-to-treat

- Yes: Specifically reported by authors that intention-to-treat analysis was undertaken and this was confirmed on study assessment.
- Yes: Not stated but confirmed on study assessment
- No: Not reported and lack of intention-to-treat analysis confirmed on study assessment. (Patients who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation)
- No: Stated but not confirmed upon study assessment
- Not stated

Completeness of follow-up

Per cent of participants excluded or lost to follow-up.

Statistical analysis

The estimate of effect of an experimental versus a control intervention on categorical outcomes (e.g. fracture rate, all-cause mortality including sudden death) was analysed using the risk ratio (RR) measure and its 95% confidence interval (CI) for each trial. For continuous variables, the mean difference (MD), and its 95% CI were calculated using the end of treatment values of the variable in the experimental and control groups. Heterogeneity of treatment effects between studies was tested formally using the Q (heterogeneity chi-square) and the I^2 statistic (Higgins 2003). When appropriate, summary estimators of treatment effects were calculated by using a random-effects model and expressed as a RR or MD, with 95% CI.

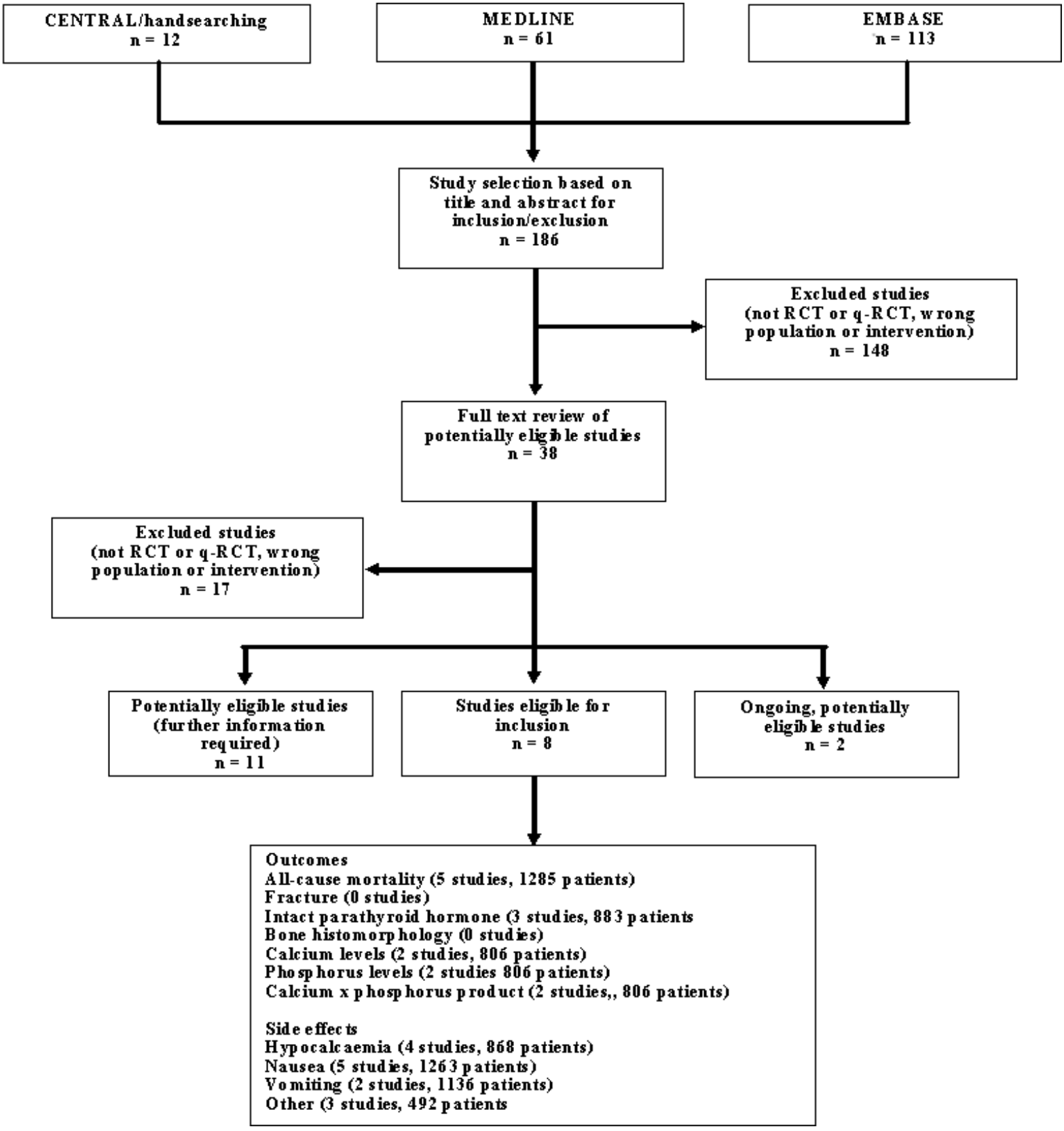
RESULTS

Description of studies

Our search for RCTs of calcimimetic interventions to treat SHPT identified 186 articles (see Figure 1 - *Flowchart of study identification)*. Of these, 148 were excluded after title and abstract review because they were clearly ineligible (non randomised studies, RCTs of interventions not relevant to SHPT, non calcimimetic interventions, duplicate articles of the same trial, or review articles). Of the remaining 38 potentially eligible studies (either full-text or abstract publications), thirty were excluded because we could not confirm from the full-text analysis or from contacting authors that they were RCTs, or that they were not a duplicate publication. Two attempts were made to contact all authors of the trials for clarifications of study designs and request supplemental data but we were not able to obtain some of the data nor to ascertain if some reports (Coburn 2003; Goodman 2003; Martin 2003; Quarles 2003; Sterrett 2004; Cunningham 2003; Cunningham 2004; Fournier 2004;de Francisco 2004; Frazao 2004) (presented in abstract form at the American Society of Nephrology (ASN) and the European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA) meetings of years

2003 and 2004)) were subsets of other publications which had subsequently appeared as full-text articles in scientific journals or were unique unpublished trials. These studies could therefore not be included (*see* Characteristics of studies awaiting classification).

Figure 1. Flow chart of study identification



Eight studies (eight publications) enrolling 1429 patients were finally included (Block 2004b; Goodman 2000; Goodman 2002; Harris 2004; Lindberg 2003; Lindberg 2005; Malluche 2004a; Quarles 2003a). The eight included studies compared cinacalcet HCl (845 patients) to placebo (584 patients). Three of these studies reported cinacalcet HCl as AMG-073. One study reported on the first-generation calcimimetic R-568. This drug has been withdrawn from clinical use because of poor bioavailability, variable serum concentrations and potential drug interactions caused by cytochrome P-450 activity (Goodman 2000; Urena 2003). There were also two ongoing studies identified which will be included in a future update of this review (CONTROL 2004; TARGET 2004)

In addition to these randomised interventions, patients received vitamin D for suppression of PTH and phosphate binders for management of hyperphosphataemia as co-interventions in all studies in a non-randomised fashion. There were no significant differences in the proportions of patients who were prescribed calcitriol, vitamin D analogues and phosphate binders as co-interventions between the calcimimetic and placebo groups of the studies. Entry to some studies was restricted when patients had severe SHPT (e.g. iPTH > 800 pg/mL) while others stratified patients according to the severity of hyperparathyroidism. The mean age of patients enrolled in the trials ranged from 47 to 55 years. All patients had SHPT. On average, a higher proportion of males were enrolled in the trials (388 males compared to 220 females in the six trials that reported gender distribution).

Follow up of the studies ranged from three to 26 weeks. All studies were supported by Amgen Inc., Thousand Oaks, CA, which holds the cinacalcet HCl patent. Of note, the largest report published (Goodman 2002) was based on the pooled results of two separate trials.

Risk of bias in included studies

By current standards, the methodological quality of all but two trials was suboptimal (see *Table of included studies*), even though all trials were published after the Consolidated Standards for Reporting Trials (CONSORT) Statement (a checklist designed to improve quality of trial reporting) was released (Moher 2001).

Allocation concealment

Allocation concealment was unclear in 6/8 (75%) of the trials.

Blinding

All studies were reported as double-blinded, (presumably to indicate that participants and investigators were blinded to the intervention), but no study mentioned the blinding of outcome assessors.

Intention-to-treat analysis

Intention-to-treat analysis (i.e. the analysis of all patients according to randomised allocations rather than actual intervention) was performed in 3/8 (38%) of the trials.

Completeness of follow-up

The proportion of patients lost to follow-up ranged from 0% to 56%. The proportion of patients who stopped taking the medication was unclear from the reports of most trials, and was either not reported or reported to be minimal.

Effects of interventions

All-cause mortality

There was no statistically significant reduction in the risk of all-cause mortality with calcimimetics compared to placebo/no treatment (Analysis 1.1 (5 trials, 1285 patients): RR 0.75, 95% CI 0.30 to 1.88). There was no significant heterogeneity across the trials (χ^2 = 0.23; P = 0.63; I^2 = 0%).

30% or more decrease in mean PTH level

There was a significant increase in achieving a greater or equal to 30% decrease in mean parathyroid hormone level with calcimimetics compared to placebo/no treatment (Analysis 1.2 (4 trials, 1284 patients): RR 4.49, 95% CI 3.04 to 6.64). There was no significant heterogeneity across the trials (χ^2 = 5.69; P = 0.13; I^2 = 47.3%).

Fractures

There were no reported episodes of fractures in the included studies. There were two abstracts with some data, although in one the data reported was insufficient to ascertain eligibility of this study for the review (Cunningham 2003) and in one other there where insufficient data to estimate observed treatment effects (Malluche 2004a).

Hypocalcaemia

There was no statistically significant increase in the risk of hypocalcaemia with calcimimetics compared to placebo/no treatment (Analysis 1.4 (4 trials, 868 patients): RR 2.89, 95% CI 0.71 to 11.73). There was no significant heterogeneity across the trials (χ^2 = 1.08; P = 0.78; I^2 = 0%).

Nausea

There was no statistically significant increase in the risk of nausea with calcimimetics compared to placebo/no treatment (Analysis 1.5(5 trials, 1263 patients): RR 1.40, 95% CI 1.00 to 1.95). There was no significant heterogeneity across the trials (χ^2 = 5.83; P = 0.21; I^2 = 31.4%).

Vomiting

There was a statistically significant increase in the risk of vomiting with calcimimetics compared to placebo/no treatment (Analysis 1.6 (2 trials, 1136 patients): RR 1.89, 95% CI 1.47 to 2.43). There was no significant heterogeneity across the trials (χ^2 = 0.01; P = 0.91; I^2 = 0%).

Dyspnoea

There was no statistically significant increase in the risk of dyspnoea with calcimimetics compared to placebo/no treatment across the trials (Analysis 1.7 (1 trial, 77 patients): RR 1.44, 95% CI 0.50 to 4.14).

Asthenia, muscle weakness or paraesthesia

There was no statistically significant increase in the risk of asthenia with calcimimetics compared to placebo/no treatment (Analysis 1.8.1 (1 trial, 396 patients): RR 4.12, 95% CI 0.99 to 17.14).

Goodman 2000 combined muscle weakness and paraesthesia as one outcome measure. There was no statistically significant increase in the risk of muscle weakness or paraesthesia with calcimimetics compared to placebo/no treatment across the trials (Analysis 1.8.2 (1 trial, 20 patients): RR 3.24, 95% CI 0.21 to 49.01).

Hypotension

There was a statistically significant reduction in the risk of hypotension with calcimimetics compared to placebo/no treatment (Analysis 1.9 (2 trials, 1136 patients): RR 0.53, 95% CI 0.36 to 0.79). There was no significant heterogeneity across the trials (χ^2 = 0.20; P = 0.66; I^2 = 0%).

Upper respiratory tract infection

There was no statistically significant reduction in the risk of upper respiratory tract infection with calcimimetics compared to placebo/no treatment (Analysis 1.10 (2 trials, 1136 patients) RR 0.86, 95% CI 0.34 to 2.18). There was significant heterogeneity across the trials (χ^2 = 6.65; P = 0.01; I^2 = 85.0%). This may be explained by the fact that Lindberg 2005 enrolled patients on PD and HD and Block 2004a enrolled HD patients only. Also Lindberg 2005 enrolled a smaller proportion of white patients (39%) compared to Block 2004a (56% to 61%).

Parathyroidectomy

There was no statistically significant reduction in the risk of parathyroidectomy with calcimimetics compared to placebo/no treatment (Analysis 1.11 (1 trial, 395 patients): RR 0.07, 95% CI 0.00 to 1.43).

Headache

There was no statistically significant reduction is the risk of headaches with calcimimetics compared to placebo/no treatment (Analysis 1.12 (1 trial, 395 patients): RR 0.86, 95% CI 0.54 to 1.37).

Abdominal pain

There was no statistically significant reduction in the risk of abdominal pain with calcimimetics compared to placebo/no treatment (Analysis 1.13 (1 trial, 395 patients): RR 0.67, 95% CI 0.40 to 1.13).

Diarrhoea

There was no statistically significant increase in the risk of diarrhoea with calcimimetics compared to placebo/no treatment (Analysis 1.14 (1 trial, 395 patients): RR 1.28, 95% CI 0.82 to 2.02 1.28).

Mixed uraemic osteodystrophy

There was no statistically significant reduction in the risk of mixed uraemic osteodystrophy with calcimimetics compared to placebo/no treatment (Analysis 1.15 (1 trial, 32 patients): RR 0.34, 95% CI 0.07 to 1.60).

Bone histomorphometry

There were no reports of bone histomorphometry in included trials.

End of treatment value for parathyroid hormone

There was a statistically significant reduction in the end of treatment value for parathyroid hormone (pg/mL) with calcimimetics compared to placebo/no treatment (Analysis 1.17 (4 trials, 1278 patients): MD -290.49, 95% CI -360.23 to -221.34). There was no significant heterogeneity across the trials (χ^2 = 4.08; P = 0.25; I^2 = 26%).

End of treatment value for serum calcium

There was a statistically significant reduction in the end of treatment value for serum calcium (mg/dL) with calcimimetics compared to placebo/no treatment (Analysis 1.18 (3 trials, 1201 patients): MD -0.77, 95% CI -0.93 to -0.60). There was no significant heterogeneity across the trials (χ^2 = 4.53; P = 0.10; I^2 = 56%).

End of treatment value for serum phosphorus

There was a statistically significant reduction in the end of treatment value for serum phosphorus (mg/dL) with calcimimetics compared to placebo/no treatment (Analysis 1.19 (3 trials, 1195 patients): MD -0.29, 95% CI -0.50 to -0.08). There was no significant heterogeneity across the trials (χ^2 = 2.50; P = 0.29; I^2 = 20.0%).

End of treatment value for serum calcium x phosphorus

There was a statistically significant reduction in the end of treatment value for serum calcium x phosphorus product with calcimimetics compared to placebo/no treatment (Analysis 1.20 (3 trials, 1204 patients): MD -7.90, 95% CI -10.25 to -5.54). There was no significant heterogeneity across the trials (χ^2 = 3.09; P = 0.21; I^2 = 35.3%).

DISCUSSION

Trials of calcimimetic compounds in patients with CKD are restricted almost exclusively to haemodialysis patients with SHPT, where calcimimetics have been added to standard therapy with outcomes measured up to six months. In this population, calcimimetic agents compared to placebo were effective in decreasing parathyroid hormone levels, serum calcium, phosphorus and the calcium-phosphorus product. All-cause mortality was reported in five studies and was not reported in three. Analysis of these studies suggests that cinacalcet HCl may be associated with a 25% relative risk reduction in all-cause mortality, but the estimate is very imprecise with wide confidence intervals consistent with a 70% reduction up to a 90% increase in risk. No difference between calcimimetics and placebo was demonstrated for all-cause mortality. This may be due to insufficient power because these events are relatively infrequent, artefactual lack of power by failure to measure and/or report patient-based outcomes, or a true lack of benefit. The annual mortality of patients undergoing dialysis is high, at around 15 deaths/hundred patient-years at risk, of which approximately 40% are cardiac and 11% vascular (ANZDATA 2004). There also was no reported data on fractures. Use of calcimimetics has been found to be associated with a significant reduction in the risk of hypotension. Based on this considerations, cinacalcet HCl is a potentially important intervention to improve survival and other patient-level endpoints in patients with SHPT receiving dialysis treatment, but existing RCTs have not confirmed the hypothesized benefits of this drug.

In general the trials reported transient and mild to moderate toxicity with only few participants withdrawing from therapy due to adverse events. However, rates of withdrawal and valid, precise estimates of adverse effects such as hypotension and nausea were often not available. One trial (Block 2004a) reported

that in the calcimimetic group 6/17 patients withdrew due to gastrointestinal events (nausea/vomiting). The few trials reporting toxicity individually suggest that calcimimetics increase the risk of nausea and vomiting and reduce the number of hypotensive episodes and upper respiratory tract infection, but our meta-analysis of data from all trials that reported these events did not confirm these findings.

Despite their adoption into clinical practice and approval by the FDA in the US, the efficacy and tolerability of calcimimetics and their role in the treatment of high turnover bone disease due to SHPT has not yet been adequately investigated. Animal studies have shown an improvement of bone histology and bone strength with calcimimetics (Sherrard 1998) but these findings are yet to be demonstrated in humans and there are no major clinical data demonstrating an effect on bone histomorphometry, which is the best determinant of renal bone disease. In addition, there are no adequate clinical data demonstrating an effect of calcimimetics on fracture risk and subsequent morbidity in patients with CKD. Given the recent introduction of calcimimetic therapy, many of these questions may be answered in coming years. Critics of our review may regard it as premature, however Cinacalcet HCl is approved for clinical use by many national regulatory agencies (FDA 2004), is in widespread clinical use, and clinicians need to decide whether they should prescribe calcimimetics now.

The argument in favour of calcimimetic use hinges on the acceptance of improvements in Ca-P metabolism and levels of PTH as valid surrogates of clinically important outcomes such as mortality. A surrogate is a measurable outcome such as a laboratory or imaging test, which is responsive to the effect of an intervention (e.g. reduction of total cholesterol with statins) and is also causally associated with a clinically important outcome (e.g. reduction in all-cause or cardiovascular mortality with statins). A valid surrogate end-point therefore captures the full effect of an intervention but earlier in the causal chain of events. (Bucher 1999; Psaty 1999; Temple 1999) Surrogate end points are used in preference to hard end points in RCTs because cost and sample size can be reduced and feasibility increased substantially. Compared with hard endpoints, surrogates allow for shorter study duration, and either occur more commonly or are continuous measures and so more sensitive to differences in treatment. In kidney disease, surrogates are commonly used in trials, and include dialysis adequacy, haemoglobin levels, left ventricular hypertrophy, and episodes of acute rejection, which have been the basis for the regulatory approval and clinical use of various drugs (Churchill 1997; Besarab 1998; Borrows 2004; McMahon 2004). However, not all surrogates are valid proxies of clinically important patient-entered outcomes. In order for a surrogate to be valid, two criteria must be met. First, there must be a strong, independent and consistent association between the surrogate and the clinically important outcome, which comes from observational studies. For calcium, phosphorus and PTH this criterion has been met from a number of large-scale cohort and cross sectional studies (Avram 1996; Ganesh 2001; Kestenbaum 2005; Stevens 2004). Second, and more importantly, for a surrogate to be valid there must also be evidence that using an intervention changes a surrogate (e.g. reduction of PTH with a calcimimetic) and results in an expected change in the patient-based outcome distal to the surrogate in the same causal pathway for the disease in question (e.g. reduction of deaths with a calcimimetic). This criterion requires a RCT, which measures both the surrogate and the hard endpoint. Our study has shown that the second criterion has not yet been met for calcimimetics.

Critics of the second criterion argue that it is too stringent and will mean potentially life-saving interventions will be withheld. Proponents invoke the usual arguments for superiority of RCTs compared with observational studies (selection bias and unmeasured confounders) to estimate the true effects of interventions. In addition some interventions that positively affect a surrogate have been reported to have possible harmful effects on the major patient-based outcome. A recent example is that high dose erythropoietin increases haemoglobin levels in patients with metastatic breast cancer but has also been associated with an increase in the risk of death and disease progression in this population (Leyland-Jones 2004). Such results suggest that validation of surrogates in disease specific populations, should be mandatory when adopting novel interventions and that trial results based on unvalidated surrogates should be used cautiously.

We identified four other problems in the trial basis supporting calcimimetics. First, despite the widespread adoption of CONSORT, a standardized checklist to improve the quality of reporting of RCTs, the majority of trials of calcimimetics either did not state or did not use (or both) secure methods of allocation, blinded outcomes assessors, or reduced loss to follow-up to a minimum. These design and reporting problems tend to bias results in favour of the intervention (Schulz 1995).

Second, to illustrate the importance of prospective registration of trials recently adopted by all major biomedical journals and kidney journals, in order to ensure that all trials evaluating an intervention can be known and linked with publications to avoid publication bias (Simes 1986) and duplication bias (Egger 1998), we found it very difficult to link publications with studies. We identified eight unequivocally separate studies with unique data, but also seven other studies (published in abstract form), which could be duplicates of data already available in full-text published reports. Duplicate reporting is known to be associated with an overestimation of true treatment effects and spurious precision if the trials are incorporated in meta-analysis (Egger 1998). Prospective registration with a unique identification number for each trial would avoid this.

Third, based upon the published report, the investigators of the largest trial (Block 2004a) combined the results of two separate but similar studies, a method used by the CLASS investigators that has been widely criticized (Juni 2003). When the cinacalcet group of one trial is compared both with the placebo group of the same trial (random allocation) but also the placebo group of the other trial (non-random allocation), outcome differences between the cinacalcet and placebo groups may be due to differences in study populations or co-interventions; which are unknown and therefore cannot be adjusted for. Having identical trial designs does not prevent these effects. Such trial results would be better reported separately. Data could then be combined using meta-analysis to provide a summary weighted estimate of the effects shown in the individual trials (Juni 2003; Block 2004a).

Fourth, CKD is a long-term problem, but except for one study, published trials have reported treatment outcomes to six months only.

It remains an important but unanswered question whether calcimimetic effects on surrogate endpoints, such as biochemical targets, changes in vascular compliance, indices of vascular calcification and bone mineral density will translate into improved patient-based outcomes. The only patient level outcome which has been found to be reduced with use of calcimimetics is the risk of hypotension.

AUTHORS' CONCLUSIONS

Implications for practice

Given reservations relating to the current published trials, calcimimetic therapy of SHPT can be considered of potential but currently unproven benefit to patient-based outcomes including cardiovascular mortality, renal osteodystrophy and fracture.

Implications for research

RCTs with adequate power and longer treatment duration are required to determine the most appropriate use of this important new class of drugs.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Block 2004a

Methods	Country: USA Setting/Design: randomised controlled clinical trial Randomisation method: stratified by disease severity and base-line values for calcium-phosphorus product Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: No - Data analysis: NS Intention-to-treat: No Follow-up period: 26 weeks Loss to follow-up: 202/741
Participants	INCLUSION CRITERIA HD ≥ 3 months iPTH ≥ 300 pg/mL serum Ca ≥ 8.4 mg/dL TREATMENT GROUP Number: 371 Age: 54 (SD14) Sex (M/F): 226/145

Block 2004a *(Continued)*

	CONTROL GROUP Number: 370 Age: 55 (SD15) Sex (M/F): 229/141 EXCLUSIONS: Infection, malignancy, disease causing hypercalcaemia, tricyclic antidepressants
Interventions	TREATMENT GROUP Cinacalcet 30-180 mg/d CONTROL GROUP placebo CO-INTERVENTIONS: NS
Outcomes	1. PTH 2. calcium 3. phosphorus 4. calcium x phosphorus 5. mortality 6. hypocalcaemia 7. nausea 8. vomiting 9. upper respiratory tract infection 10. hypotension 11. transplant 12. 30% ≥ decrease in PTH level
Notes	STOP OR END POINT/S iPTH < 250 pg/mL

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Goodman 2000

Methods	Country: USA Setting/Design: multicentre randomised controlled clinical trial Randomisation method: not specified Blinding - Participants: yes - Investigators: yes - Outcome assessors: no - Data analysis: NS Intention-to-treat: no Follow-up period: 3 weeks Loss to follow-up: 7/20
Participants	INCLUSION CRITERIA HD ≥ 3 months iPTH 300-1200 pg/mL serum Ca ≥ 8.4 mg/dL serum P > 3.0 mg/dL TREATMENT GROUP

Goodman 2000 *(Continued)*

	Number: 16 Age: 48.6 (SE 3.1) Sex (M/F): 13/3 CONTROL GROUP Number: 5 Age: 54.7 (SE 8.4) Sex (M/F): 1/3 EXCLUSIONS: Malignancy, disease causing hypercalcaemia, myocardial infarction previous 6 months, tricyclic antidepressants
Interventions	TREATMENT GROUP R-568 100 mg/d CONTROL GROUP placebo CO-INTERVENTIONS: NS
Outcomes	1. mortality 2. hypocalcaemia 3. nausea 4. muscle weakness
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Goodman 2002

Methods	Country: USA Setting/Design: Multicentre randomised controlled clinical trial Randomisation method: not specified Blinding - Participants: yes - Investigators: yes - Outcome assessors: no - Data analysis: NS Intention-to-treat: yes Follow-up period: 2 weeks Loss to follow-up: 0/52
Participants	INCLUSION CRITERIA HD ≥ 3 months iPTH 250-1500 pg/mL serum Ca > 9.0 mg/dL serum P ≥ 2.5 mg/dL TREATMENT GROUP Number: 40 Age: NS Sex (M/F): NS CONTROL GROUP

Goodman 2002 *(Continued)*

	Number: 12 Age: NS Sex (M/F): NS EXCLUSIONS: Malignancy, disease causing hypercalcaemia, myocardial infarction previous 6 months, tricyclic antidepressants, transaminase or bilirubin > 2x upper limit of normal
Interventions	TREATMENT GROUP AMG 073 5-100 mg/d CONTROL GROUP placebo CO-INTERVENTIONS: NS
Outcomes	1. mortality 2. hypocalcaemia 3. nausea
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Harris 2004

Methods	Country: USA Setting/Design: randomised controlled clinical trial Randomisation method: NS Blinding - Participants: yes - Investigators: yes - Outcome assessors: no - Data analysis: NS Intention-to-treat: no Follow-up period: 1 week Loss to follow-up: 10/23
Participants	INCLUSION CRITERIA HD Serum Ca ≥ 8.4 mg/dL serum P ≥ 3.0 mg/dL TREATMENT GROUP Number: 17 Age: NS Sex (M/F): NS CONTROL GROUP Number: 6 Age: NS Sex (M/F): NS EXCLUSIONS: NS

Harris 2004 *(Continued)*

Interventions	TREATMENT GROUP Cinacalcet 25 to 300 mg/d CONTROL GROUP placebo CO-INTERVENTIONS: NS
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Lindberg 2003

Methods	Country: USA, Canada Setting/Design: Multicentre randomised controlled clinical trial Randomisation method: not specified Blinding - Participants: yes - Investigators: yes - Outcome assessors: no - Data analysis: NS Intention-to-treat: no Follow-up period: 18 weeks Loss to follow-up: 11/78
Participants	INCLUSION CRITERIA HD ≥ 3 months iPTH ≥ 300 pg/mL serum Ca 8.8-11.0 mg/dL CaxP < 70 mg^2/dL^2 TREATMENT GROUP Number: 39 Age: 42.7 (SD 16.4) Sex (M/F): 24/15 CONTROL GROUP Number: 39 Age: 48.8 (SD 15.6) Sex (M/F): 22/17 EXCLUSIONS: Infection, malignancy, disease causing hypercalcaemia, hepatic transaminase or bilirubin >2x upper limit of normal
Interventions	TREATMENT GROUP AMG-073 10-50 mg/d CONTROL GROUP Placebo CO-INTERVENTIONS: NS

Lindberg 2003 *(Continued)*

Outcomes	1. PTH 2. mortality 3. hypocalcaemia 4. nausea 5. dyspnoea 6. ≥ 30% decrease in PTH level
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Lindberg 2005

Methods	Country: USA Setting/Design: Multicentre randomised controlled clinical trial Randomisation method: stratified by dialysis modality, programmatic algorithm using an interactive voice-response system Blinding - Participants: yes - Investigators: yes - Outcome assessors: no - Data analysis: NS Intention-to-treat: yes Follow-up period: 26 weeks Loss to follow-up: 101/395
Participants	INCLUSION CRITERIA HD and PD (CAPD, ADP) > 1 month iPTH = 300pg/mL serum Ca = 8.4 mg/dL serum P = 6.5 mg/dL CaxP = 70 mg^2/dL^2, stable vitamin D dosing > 30 days TREATMENT GROUP Number: 294 Age: 51.8 (SD 14.0) Sex (M/F): 181/113 CONTROL GROUP Number: 101 Age: 53.5 (SD 13.9) Sex (M/F): 64/37 EXCLUSIONS: Parathyroidectomy, previous myocardial infarction (3 months)
Interventions	TREATMENT GROUP Cinacalcet 30-180 mg/d CONTROL GROUP Placebo CO-INTERVENTIONS: NS
Outcomes	1. PTH

Lindberg 2005 *(Continued)*

	2. Calcium 3. Phosphorus 4. calcium x phosphorus 5. mortality 6. parathyroidectomy 7. nausea 8. transplant 9. vomiting 10. upper respiratory tract infection 11. hypotension 12. diarrhoea 13. headache 14. asthenia 15. abdominal pain 16. = 30% reduction in PTH level
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Malluche 2004a

Methods	Country: USA Setting/Design: randomised controlled clinical trial Randomisation method: NS Blinding - Participants: yes - Investigators: yes - Outcome assessors: no - Data analysis: NA Intention-to-treat: Follow-up period: 52 weeks Loss to follow-up: NA
Participants	INCLUSION CRITERIA iPTH ≥ 300 pg/mL TREATMENT GROUP Number: 32 Age: NS Sex (M/F): NS CONTROL GROUP Number: 16 Age: NS Sex (M/F): NS EXCLUSIONS: NA
Interventions	TREATMENT GROUP Cinacalcet 30-180 mg/d CONTROL GROUP Placebo

Malluche 2004a *(Continued)*

	CO-INTERVENTIONS: NS
Outcomes	1. mixed uraemic osteodystrophy
Notes	STOP OR END POINT/S iPTH = 250 pg/mL

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Quarles 2003a

Methods	Country: USA Setting/Design: Multicentre randomised controlled clinical trial Randomisation method: interactive voice response system Blinding - Participants: Yes - Investigators: yes - Outcome assessors: no - Data analysis: NS Intention-to-treat: yes Follow-up period: 18 weeks Loss to follow-up: 6/71
Participants	INCLUSION CRITERIA HD ≥ 3 months iPTH ≥ 300 pg/mL serum Ca 8.8-11.0 mg/dL CaxP < 70 mg^2/dL^2 Stable vitamin D > 21 days TREATMENT GROUP Number: 36 Age: 19.6 (SD 8.5) Sex (M/F): 27/9 CONTROL GROUP Number: 35 Age: 47.9 (SD 14.2) Sex (M/F): 17/18 EXCLUSIONS: Infection, malignancy, disease causing hypercalcaemia, hepatic transaminase or bilirubin > 2x upper limit of normal
Interventions	TREATMENT GROUP AMG-073 25-100 mg/d CONTROL GROUP Placebo CO-INTERVENTIONS: NS
Outcomes	1. PTH 2. calcium 3. phosphorus

Quarles 2003a *(Continued)*

	4. calcium x phosphorus 5. = 30% decrease in PTH level
Notes	STOP OR END POINT/S iPTH reduction = 30%

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

NA - not available; NS - not stated

Characteristics of studies awaiting assessment *[ordered by study ID]*

Coburn 2003

Methods	Data not available to assess if randomised study. Study duration: 18 weeks
Participants	**Inclusion criteria** Nondialysis patients, iPTH ≥ 130 pg/mL Number included: 54 (19 treatment group, 21 control group)
Interventions	**Treatment group** Cinacalcet 30-80 mg/d (iPTH decrease ≥ 30%) **Control group** Placebo
Outcomes	
Notes	

Cunningham 2003

Methods	Study duration: 208 weeks
Participants	**Inclusion criteria** Haemodialysis (iPTH ≥ 300 pg/mL) Number included: 287 (182 treatment group, 115 control group)
Interventions	**Treatment group** Cinacalcet > 180 mg/d **Control group** Placebo

Cunningham 2003 *(Continued)*

Outcomes	
Notes	Analysis of 5 trials, unconfirmed if all RCTs

Cunningham 2004a

Methods	Study duration: 72 weeks
Participants	**Inclusion criteria** Haemodialysis patients, iPTH ≥ 300 pg/mL Number included: 1,184 (697 treatment group, 487 control group)
Interventions	**Treatment group** Cinacalcet (dose not stated) (iPTH, 250 pg/mL) **Control group** Placebo
Outcomes	
Notes	Five trials, possible duplicate of previous study (yet to be confirmed)

de Francisco 2004

Methods	Study duration: not stated
Participants	**Inclusion criteria** Haemodialysis (iPTH ≥ 300 pg/mL) Number included: 311 (139 treatment group, 150 control group)
Interventions	**Treatment group** Cinacalcet 30-180 mg/d (iPTH ≤ 250 pg/mL) **Control group** Placebo
Outcomes	
Notes	Possible duplicate of previous study (yet to be confirmed)

Fournier 2004

Methods	Study duration: not stated
Participants	**Inclusion criteria**

Fournier 2004 *(Continued)*

	RRT, iPTH ≥ 300 pg/mL Number included: not stated
Interventions	**Treatment group** Cinacalcet 30-180 mg/d (iPTH ≤ 250 pg/mL) **Control group** Placebo
Outcomes	
Notes	Three trials, possible duplicate of previous publication (yet to be confirmed)

Frazao 2004

Methods	Study duration: not stated
Participants	**Inclusion criteria** RRT, iPTH ≥ 300 pg/mL Number included: 1,136 (556 treatment group, 471 control group)
Interventions	**Treatment group** Cincalcet > 180 mg/d (iPTH ≤ 250 pg/mL) **Control group** Placebo
Outcomes	
Notes	Analysis of 3 trials, unconfirmed if RCTs, possible duplicate of a previous publication (yet to be confirmed)

Goodman 2003

Methods	Study duration: 24 weeks
Participants	**Inclusion criteria** Haemodialysis and peritoneal dialysis < 12 months (iPTH ≥ 300 pg/mL) Number included: 121
Interventions	**Treatment group** Cincalcet 30-80 mg/d **Control group** Placebo

Goodman 2003 *(Continued)*

Outcomes	
Notes	Analysis of 3 tirals unconfirmed if RCTs

Martin 2003

Methods	Study duration:26 weeks
Participants	**Inclusion criteria** Haemodialysis (iPTH ≥ 300 pg/mL) Number included: 410 (205 treatment group, 205 control group)
Interventions	**Treatment group** Cincalcet (dose not stated) (iPTH ≤ 250 pg/mL) **Control group** Placebo
Outcomes	
Notes	Possible duplicate publication of previous publication (yet to be confirmed)

Quarles 2003

Methods	Study duration: 24 weeks
Participants	**Inclusion criteria** Haemodialysis and peritoneal dialysis (iPTH ≥ 300 pg/mL) Number included: 1,136 (665 treatment group, 471 control group)
Interventions	**Treatment group** Cincalcet (dose not stated) **Control group** Placebo
Outcomes	
Notes	Three trials, possible duplicate of previous publication (yet to be confirmed)

Sterrett 2004

Methods	Study duration: 48 weeks
Participants	**Inclusion criteria**

Sterrett 2004 *(Continued)*	
	Haemodialysis (iPTH ≥ 300 pg/mL) Number included: 210 (99 treatment group, 111 control group)
Interventions	**Treatment group** Cincalcet (dose not stated) **Control group** Placebo
Outcomes	
Notes	Two trials, possible duplicate of a previous publication (yet to be confirmed)

Characteristics of ongoing studies *[ordered by study ID]*

CONTROL 2004

Trial name or title	CONTROL
Methods	
Participants	N = 76 K/DOQI iPTH target 150-300 pg/mL CaxP outside K/DOQI range
Interventions	TREATMENT Cinacalcet (30-180 mg/d) target iPTH 150-300 pg/mL CONTROL Placebo
Outcomes	
Starting date	
Contact information	
Notes	Study duration 8 weeks Data unpublished and preliminary data NA

TARGET 2004

Trial name or title	TARGET
Methods	
Participants	N = 424 Mild/moderate SHPT; iPTH 300-800 pg/mL
Interventions	TREATMENT Cinacalcet (dose NA)

TARGET 2004 *(Continued)*

	CONTROL Placebo
Outcomes	
Starting date	
Contact information	
Notes	Study duration 8-14 weeks Data unpublished and preliminary data NA

NA = not available

DATA AND ANALYSES

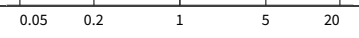
Comparison 1. Calcimimetics versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	5	1285	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.30, 1.88]
2 30% or more decrease in mean PTH level	4	1284	Risk Ratio (M-H, Random, 95% CI)	4.49 [3.04, 6.64]
3 Fractures	0	0	Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Hypocalcaemia	4	868	Risk Ratio (M-H, Random, 95% CI)	2.89 [0.71, 11.73]
5 Nausea	5	1263	Risk Ratio (M-H, Random, 95% CI)	1.40 [1.00, 1.95]
6 Vomiting	2	1136	Risk Ratio (M-H, Random, 95% CI)	1.89 [1.47, 2.43]
7 Dyspnoea	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8 Asthenia, muscle weakness or paraesthesia	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.1 Asthenia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 Muscle weakness or paraesthesia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9 Hypotension	2	1136	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.36, 0.79]
10 Upper respiratory tract infection	2	1136	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.34, 2.18]
11 Parathyroidectomy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12 Headache	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
13 Abdominal pain	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
14 Diarrhoea	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15 Mixed uraemic osteodystrophy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
16 Bone histomorphometry	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17 PTH (pg/mL)	4	1276	Mean Difference (IV, Random, 95% CI)	-290.79 [-360.23, -221.34]
18 Calcium (mg/dL)	3	1201	Mean Difference (IV, Random, 95% CI)	-0.77 [-0.93, -0.60]
19 Phosphorus (mg/dL)	3	1195	Mean Difference (IV, Random, 95% CI)	-0.29 [-0.50, -0.08]
20 Calcium x phosphorus	3	1194	Mean Difference (IV, Random, 95% CI)	-7.90 [-10.25, -5.54]

Analysis 1.1. Comparison 1 Calcimimetics versus placebo/no treatment, Outcome 1 All-cause mortality.

Study or subgroup	Calcimimetic	Placebo/no treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Block 2004a	6/371	7/370		72.95%	0.85[0.29,2.52]
Goodman 2000	0/16	0/4			Not estimable
Goodman 2002	0/40	0/12			Not estimable
Lindberg 2003	0/38	0/39			Not estimable
Lindberg 2005	3/294	2/101		27.05%	0.52[0.09,3.04]
Total (95% CI)	**759**	**526**		**100%**	**0.75[0.3,1.88]**
Total events: 9 (Calcimimetic), 9 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.23, df=1(P=0.63); I^2=0%					
Test for overall effect: Z=0.62(P=0.53)					

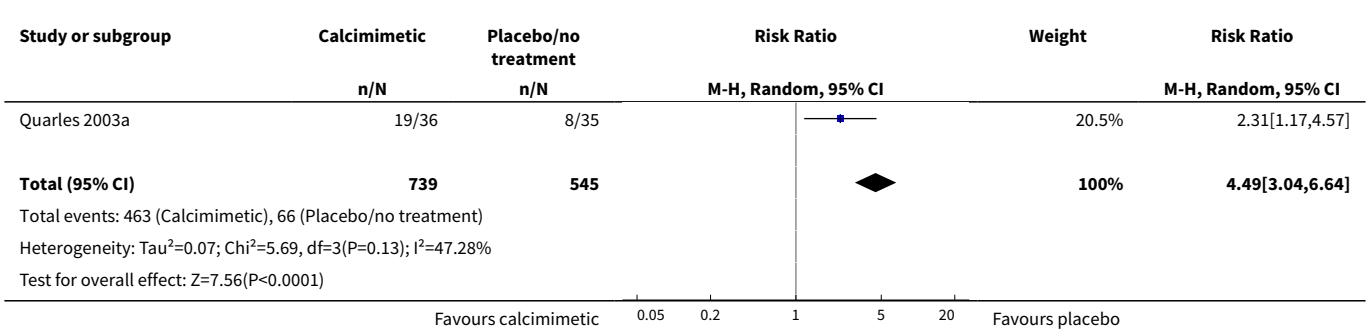


Favours calcimimetic — Favours placebo

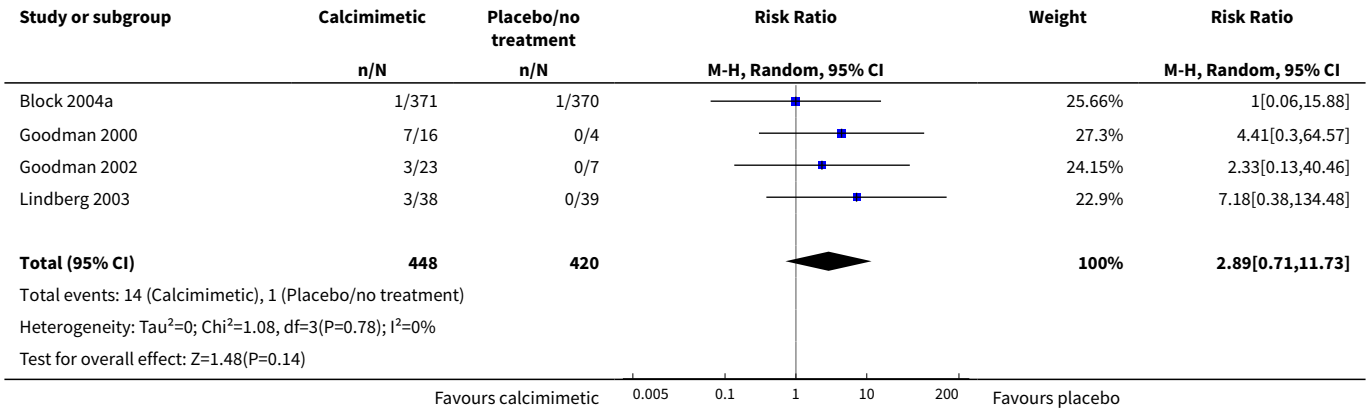
Analysis 1.2. Comparison 1 Calcimimetics versus placebo/ no treatment, Outcome 2 30% or more decrease in mean PTH level.

Study or subgroup	Calcimimetic	Placebo/no treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Block 2004a	239/371	42/370		42.03%	5.68[4.23,7.62]
Lindberg 2003	14/38	3/39		9.31%	4.79[1.5,15.34]
Lindberg 2005	191/294	13/101		28.16%	5.05[3.02,8.44]

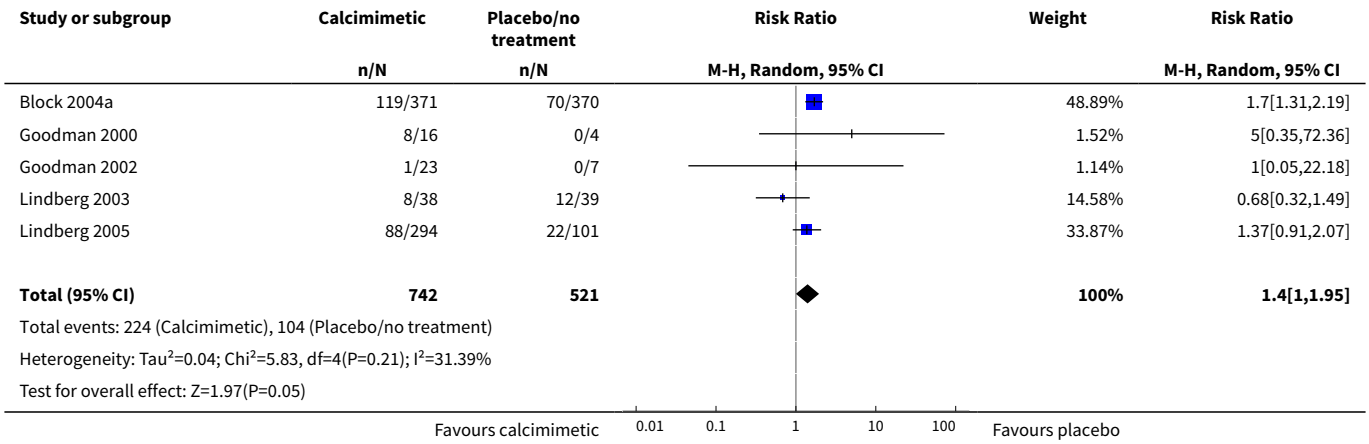
Favours calcimimetic — Favours placebo



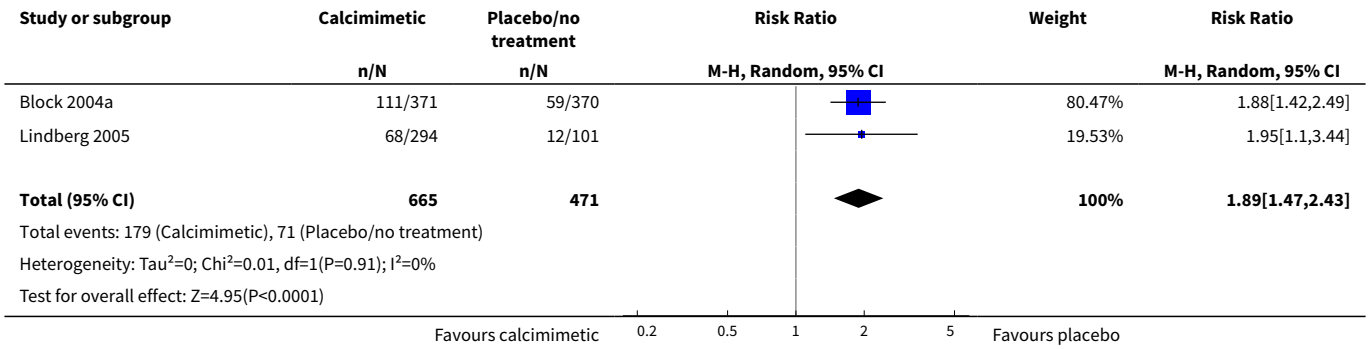
Analysis 1.4. Comparison 1 Calcimimetics versus placebo/no treatment, Outcome 4 Hypocalcaemia.



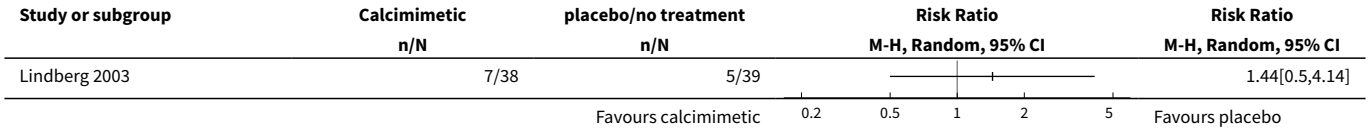
Analysis 1.5. Comparison 1 Calcimimetics versus placebo/no treatment, Outcome 5 Nausea.



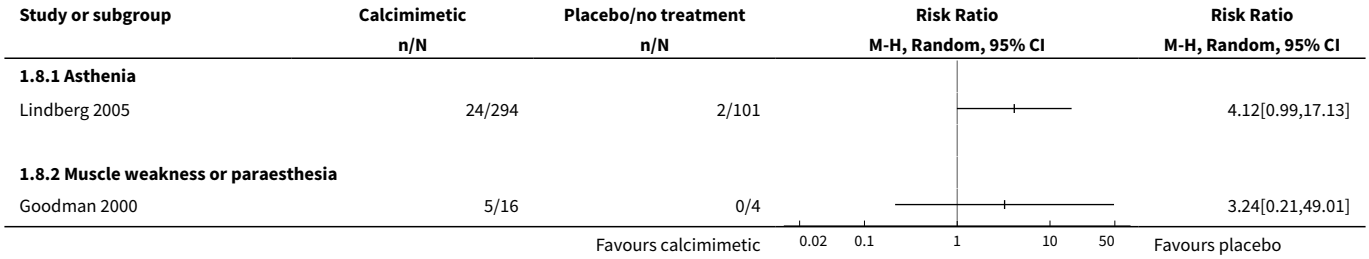
Analysis 1.6. Comparison 1 Calcimimetics versus placebo/no treatment, Outcome 6 Vomiting.



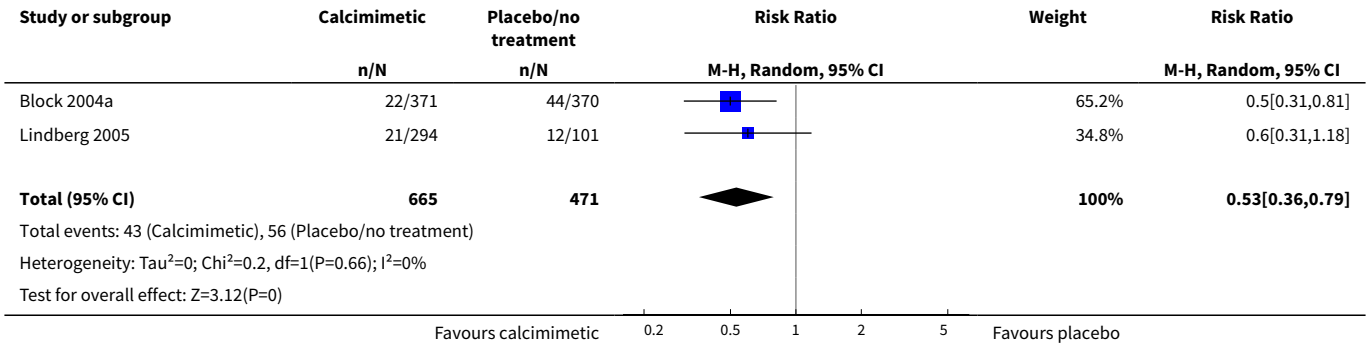
Analysis 1.7. Comparison 1 Calcimimetics versus placebo/no treatment, Outcome 7 Dyspnoea.



Analysis 1.8. Comparison 1 Calcimimetics versus placebo/no treatment, Outcome 8 Asthenia, muscle weakness or paraesthesia.

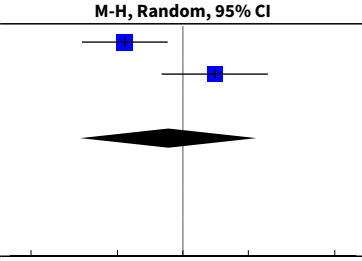


Analysis 1.9. Comparison 1 Calcimimetics versus placebo/no treatment, Outcome 9 Hypotension.



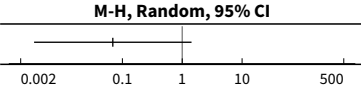
Analysis 1.10. Comparison 1 Calcimimetics versus placebo/no treatment, Outcome 10 Upper respiratory tract infection.

Study or subgroup	Calcimimetic n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Block 2004a	26/371	48/370		51.58%	0.54[0.34,0.85]
Lindberg 2005	53/294	13/101		48.42%	1.4[0.8,2.46]
Total (95% CI)	**665**	**471**		**100%**	**0.86[0.34,2.18]**
Total events: 79 (Calcimimetic), 61 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.39; Chi^2=6.65, df=1(P=0.01); I^2=84.97%					
Test for overall effect: Z=0.32(P=0.75)					



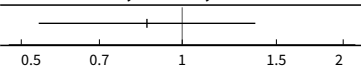
Analysis 1.11. Comparison 1 Calcimimetics versus placebo/no treatment, Outcome 11 Parathyroidectomy.

Study or subgroup	Calcimimetic n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Lindberg 2005	0/294	2/101		0.07[0,1.43]



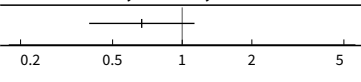
Analysis 1.12. Comparison 1 Calcimimetics versus placebo/no treatment, Outcome 12 Headache.

Study or subgroup	Calcimimetic n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Lindberg 2005	50/294	20/101		0.86[0.54,1.37]



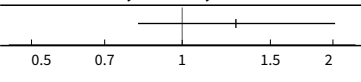
Analysis 1.13. Comparison 1 Calcimimetics versus placebo/no treatment, Outcome 13 Abdominal pain.

Study or subgroup	Calcimimetic n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Lindberg 2005	35/294	18/101		0.67[0.4,1.13]



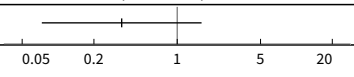
Analysis 1.14. Comparison 1 Calcimimetics versus placebo/no treatment, Outcome 14 Diarrhoea.

Study or subgroup	Calcimimetic n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Lindberg 2005	71/294	19/101		1.28[0.82,2.02]



Analysis 1.15. Comparison 1 Calcimimetics versus placebo/no treatment, Outcome 15 Mixed uraemic osteodystrophy.

Study or subgroup	Calcimimetic n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Malluche 2004a	2/19	4/13		0.34[0.07,1.6]

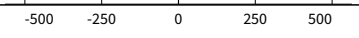


Analysis 1.17. Comparison 1 Calcimimetics versus placebo/no treatment, Outcome 17 PTH (pg/mL).

Study or subgroup	Calcimimetic N	Calcimimetic Mean(SD)	Placebo/no treatment N	Placebo/no treatment Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Block 2004a	371	374 (366)	370	693 (442.4)		53.62%	-319[-377.47,-260.53]
Lindberg 2003	38	460 (289.7)	37	701 (437.1)		14.23%	-241[-409.29,-72.71]
Lindberg 2005	294	525.5 (510.8)	101	852 (551)		23.49%	-326.5[-448.8,-204.2]
Quarles 2003a	34	451 (431.5)	31	552 (484.4)		8.66%	-101[-324.86,122.86]
Total ***	**737**		**539**			**100%**	**-290.79[-360.23,-221.34]**

Heterogeneity: Tau^2=1451.01; Chi^2=4.08, df=3(P=0.25); I^2=26.45%

Test for overall effect: Z=8.21(P<0.0001)

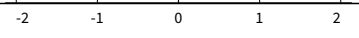


Analysis 1.18. Comparison 1 Calcimimetics versus placebo/no treatment, Outcome 18 Calcium (mg/dL).

Study or subgroup	Calcimimetic N	Calcimimetic Mean(SD)	Placebo/no treatment N	Placebo/no treatment Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Block 2004a	371	9.2 (0)	370	9.9 (0)		56.31%	-0.7[-0.7,-0.7]
Lindberg 2005	294	9.1 (1.7)	101	10.1 (1)		22.02%	-1[-1.28,-0.72]
Quarles 2003a	34	9.2 (0.6)	31	9.9 (0.6)		21.67%	-0.7[-0.98,-0.42]
Total ***	**699**		**502**			**100%**	**-0.77[-0.93,-0.6]**

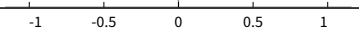
Heterogeneity: Tau^2=0.01; Chi^2=4.53, df=2(P=0.1); I^2=55.89%

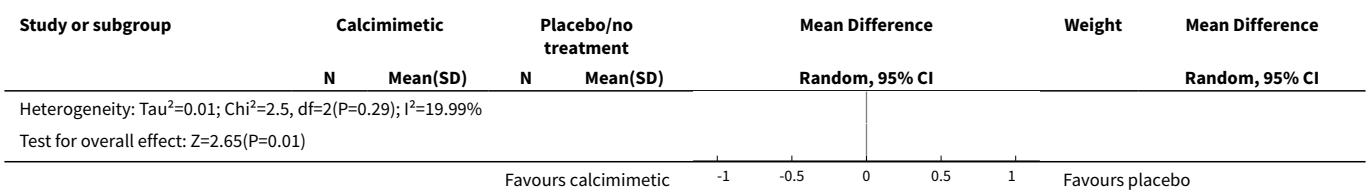
Test for overall effect: Z=9.04(P<0.0001)



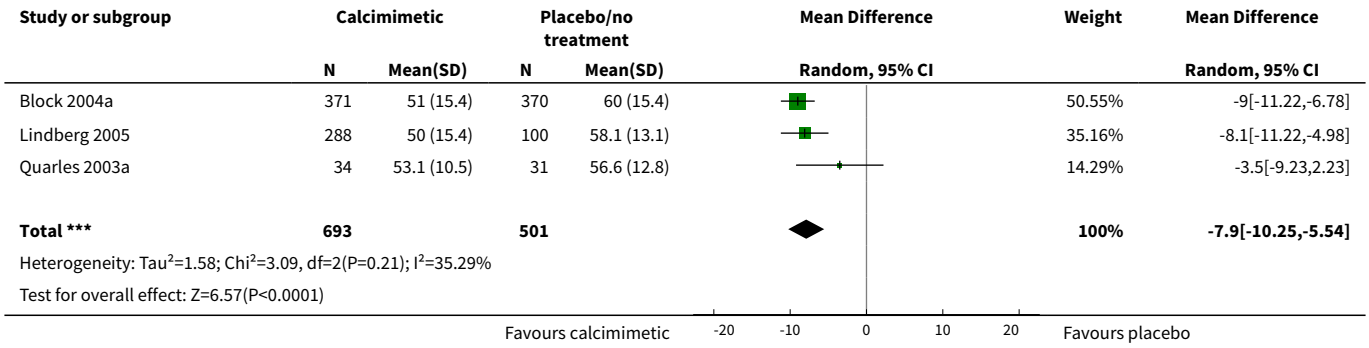
Analysis 1.19. Comparison 1 Calcimimetics versus placebo/no treatment, Outcome 19 Phosphorus (mg/dL).

Study or subgroup	Calcimimetic N	Calcimimetic Mean(SD)	Placebo/no treatment N	Placebo/no treatment Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Block 2004a	371	5.6 (1.9)	370	6 (1.9)		43.21%	-0.4[-0.68,-0.12]
Lindberg 2005	289	5.5 (1.7)	100	5.8 (1)		43.21%	-0.3[-0.58,-0.02]
Quarles 2003a	34	5.8 (1.2)	31	5.7 (1.1)		13.58%	0.1[-0.45,0.65]
Total ***	**694**		**501**			**100%**	**-0.29[-0.5,-0.08]**





Analysis 1.20. Comparison 1 Calcimimetics versus placebo/no treatment, Outcome 20 Calcium x phosphorus.



ADDITIONAL TABLES

Table 1. Electronic search strategies

Database	Search terms
CENTRAL	1. KIDNEY DISEASES single term 2. KIDNEY FAILURE single term 3. KIDNEY FAILURE CHRONIC single term 4. RENAL DIALYSIS explode all trees 5. (hemodialysis or haemodialysis) 6. dialysis 7. (capd or ccpd or apd) 8. predialysis 9. ((chronic next renal) or (chronic next kidney)) 10. (kidney next disease*) 11. (kidney next failure) 12. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11) 13. BONE DISEASES explode all trees 14. RENAL OSTEODYSTROPHY single term 15. (bone next disease*) 16. (bone* and (atroph* or formation or deform* or destruct* or necrosis or resorption or metabol* or turnover or demineral* or decalcif* or density)) 17. (osteo* or hyperparathyroid*) 18. (#13 or #14 or #15 or #16 or #17) 19. (#12 and #18) 20. calcimimetic* 21. cinacalcet 22. NAPHTHALENES single term 23. (#20 or #21 or #22) 24. (#19 and #23)

Table 1. Electronic search strategies *(Continued)*

MEDLINE	1. Kidney Diseases/ 2. Kidney Failure/ 3. Kidney Failure Chronic/ 4. exp Renal Dialysis/ 5. ((kidney$ or renal) and (dialysis or failure)).tw. 6. (hemodialysis or haemodialysis).tw. 7. (peritoneal dialysis or CAPD or CCPD or APD).tw. 8. or/1-7 9. exp Bone Diseases/ 10. bone disease$.tw. 11. (bone$ and (atroph$ or formation or deform$ or destruct$ or necrosis or resorption or metabol $ or turnover or demineral$ or decalcif$ or density)).tw. 12. (osteo$ or hyperparathyroid$).tw. 13. or/9-12 14. 8 and 13 15. Renal Osteodystrophy/ 16. 14 or 15 17. randomized controlled trial.pt. 18. controlled clinical trial.pt. 19. randomized controlled trials/ 20. random allocation/ 21. double blind method/ 22. single blind method/ 23. or/17-22 24. animals/ not (animals/ and human/) 25. 23 not 24 26. clinical trial.pt. 27. exp clinical trials/ 28. (clinic$ adj25 trial$).ti,ab. 29. cross-over studies/ 30. (crossover or cross-over or cross over).tw. 31. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. 32. placebos/ 33. placebo$.ti,ab. 34. random$.ti,ab. 35. research design/ 36. or/26-35 37. 36 not 24 38. 25 or 37 39. 16 and 38
EMBASE	1. Kidney Disease/ 2. Kidney Failure/ 3. Chronic Kidney Failure/ 4. exp hemodialysis/ 5. (hemodialysis or haemodialysis).tw. 6. dialysis.tw. 7. (CAPD or CCPD or APD).tw. 8. predialysis.tw. 9. (chronic renal or chronic kidney).tw. 10. or/1-9 11. exp Bone Disease/ 12. bone disease$.tw. 13. (bone$ and (atroph$ or formation or deform$ or destruct$ or necrosis or resorption or metabol $ or turnover or demineral$ or decalcif$ or density)).tw. 14. (osteo$ or hyperparathyroid$).tw. 15. Renal Osteodystrophy/ 16. or/11-15 17. 10 and 16 18. Calcimimetic Agent/

Table 1. Electronic search strategies *(Continued)*

19. Cinacalcet/
20. naphthalene derivative/ or naphthalene/
21. ("R-568" or "AMG 074" or "AMG 073" or "KRN 1493").tw.
22. calcimimetic$.tw.
23. cinacalcet.tw.
24. or/18-23
25. and/17,24

WHAT'S NEW

Date	Event	Description
14 January 2010	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 4, 2006
Review first published: Issue 4, 2006

Date	Event	Description
13 August 2009	Amended	Contact details updated.
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CONTRIBUTIONS OF AUTHORS

- Strippoli GFM: design, conduct, data-extraction and analysis, writing the review
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DECLARATIONS OF INTEREST

None known

INDEX TERMS

Medical Subject Headings (MeSH)

Calcimimetic Agents [adverse effects] [*therapeutic use]; Calcium [blood]; Cardiovascular Diseases [mortality]; Cause of Death; Hyperparathyroidism, Secondary [blood] [*drug therapy] [etiology]; Kidney Failure, Chronic [*complications] [therapy]; Naphthalenes [adverse effects] [*therapeutic use]; Parathyroid Hormone [blood]; Phosphorus [blood]; Randomized Controlled Trials as Topic; Renal Dialysis

MeSH check words

Humans