STATE OF THE ART REVIEWS

Cinacalcet versus standard treatment for chronic kidney disease: a systematic review and meta-analysis

Nigar Sekercioglu, Jason W. Busse, M. Fatih Sekercioglu, Arnav Agarwala, Shaun Shaikh, Luciane Cruz Lopes, Reem A. Mustafa, Gordon H. Guyatt, and Lehana Thabane

Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada; The Michael G. DeGroote Institute for Pain Research and Care, McMaster University, Hamilton, Ontario, Canada; Department of Anesthesia, McMaster University, Hamilton, Ontario, Canada; Department of Geography, Western University, London, Ontario, Canada; Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; Department of Economics, McMaster University, Hamilton, Ontario, Canada; Pharmaceutical Sciences Master Course, University of Sorocaba, UNISO, Sorocaba, Brazil; Department of Internal Medicine, University of Missouri–Kansas City, Kansas City, MO, USA; Department of Biomedical and Health Informatics, University of Missouri–Kansas City, Kansas City, MO, USA; Department of Medicine, McMaster University, Hamilton, Ontario, Canada; Department of Pediatrics and Anesthesia, McMaster University, Hamilton, Ontario, Canada; Centre for Evaluation of Medicine, St Joseph’s Healthcare—Hamilton, Hamilton, Ontario, Canada; Biostatistics Unit, Father Sean O’Sullivan Research Centre, St Joseph’s Healthcare, Hamilton, Ontario, Canada; Population Health Research Institute, Hamilton Health Sciences, Hamilton, Ontario, Canada

ABSTRACT

Background: Chronic kidney disease-mineral and bone disorders (CKD-MBD) have been associated with poor health outcomes, including diminished quality and length of life. Standard management for CKD-MBD includes phosphate restricted diet, vitamin D and phosphate binders. Persistently elevated parathyroid hormone levels may require the addition of cinacalcet hydrochloride (cinacalcet), which sensitizes calcium receptors in the parathyroid gland.

Purpose: The objective of this systematic review is to compare, in patients with CKD-MBD the effect of cinacalcet versus standard treatment on patient-important outcomes, including parathyroidectomy, fractures, hospitalizations due to cardiovascular events, cardiovascular mortality, all-cause mortality, and intermediate outcomes, in particular Kidney Disease Outcome Quality Initiative targets.

Methods: Data sources included MEDLINE, EMBASE, the Cochrane Register of Controlled Trials and Web of Science from 1996 to June 2015. Teams of two reviewers, independently and in duplicate, screened titles and abstracts and potentially eligible full text reports to determine eligibility, and subsequently abstracted data and assessed risk of bias in eligible trials. We calculated the effect estimates (risk ratios or mean differences) and 95% confidence intervals, as well as statistical measures of variability in results across studies using random effect models. We used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to rate quality of evidence about estimates of effect on an outcome-by-outcome basis for all outcomes. We presented our results with a GRADE summary table.

Results: Twenty-four trials including 8311 CKD patients proved eligible. The results left considerable uncertainty regarding the impact of cinacalcet on reducing fractures (relative risk [RR] 0.59, 95% confidence interval [CI] 0.13–2.60; heterogeneity: p = 0.03, I² = 78%; very low quality evidence), and indicated that cinacalcet did not reduce hospitalizations due to cardiovascular events (RR 0.93, 95% CI 0.85–1.02, moderate quality of evidence), cardiovascular mortality (RR 0.95, 95% CI 0.84–1.07; heterogeneity p = 0.61, high quality evidence) or all-cause mortality (RR 0.96, 95% CI 0.89–1.04; heterogeneity: p = 0.98, I² = 0%; moderate quality evidence). Cinacalcet reduced the need for parathyroidectomy (RR 0.30, 95% CI 0.22–0.42; heterogeneity: p = 0.70, I² = 0%; absolute effect 55 fewer per 1000 [95% CI 61 fewer to 45 fewer], high quality of evidence). The most common adverse event associated with cinacalcet therapy was gastrointestinal side effects. Cinacalcet increased nausea (RR 2.16, 95% CI 1.46–3.21, absolute effect 158 more per 1000 [95% CI 82 more to 302 more]) and vomiting (RR 2.15, 95% CI 1.66–2.80, absolute effect 63 more per 1000 [95% CI 109 more to 171 more]). Cinacalcet treatment increased the rate of hypocalcemia (RR 6.0, 95% CI 3.65–9.87; heterogeneity: p = 0.71, I² = 0%; absolute effect 20 more per 1000 [95% CI 11 more to 36 more], high quality of evidence).

Conclusions: In the hands of clinicians participating in these studies, cinacalcet decreased the rate of parathyroidectomy but had no influence on mortality. Patients and clinicians can trade off the benefit of fewer parathyroidectomies against the adverse effects.

CONTACT Nigar Sekercioglu nigars2003@yahoo.com Department of Clinical Epidemiology & Biostatistics, McMaster University, 1280 Main Street West, Hamilton, Ontario, Canada L8S 4K1

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Introduction
Chronic kidney disease-mineral and bone disorder (CKD-MBD) involves abnormal serum concentrations of calcium, phosphorus, parathyroid hormone (PTH) and vitamin D. These biochemical abnormalities lead to abnormal bone metabolism as well as cardiovascular and soft tissue calcifications. Cardiovascular calcifications have been linked to cardiovascular events and mortality, which is the leading cause of death in patients with CKD.

Persistently elevated serum PTH concentrations in those with CKD-MBD indicate the presence of secondary hyperparathyroidism (SHPT). In severe forms of the disease (serum PTH >300 pg/mL), medical management requires combination therapy: the use of vitamin D, which works through vitamin D receptors, and calcimimetic agents that work through calcium sensing receptors. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines provide weak recommendations based on moderate quality evidence in favor of surgical parathyroidectomy if PTH remains constantly above 1000 pg/mL.

Cinacalcet hydrochloride (cinacalcet) is a second generation calcimimetic agent used to sensitize calcium receptors on the parathyroid glands. This leads to decreased PTH synthesis and secretion. Cinacalcet is a positive allosteric modulator that interacts with non-calcium binding sites. Although the medication has a very wide applicability, including parathyroid cancers and primary and SHPT, cost is a major drawback that limits its utilization. The total cost of cinacalcet per patient with CKD-MBD ranges from $4000 to $23,500 per year in Canada. The cost of the unit price of the medication in the USA is $0.42 per mg. A patient who needs 100 mg cinacalcet per day would need to pay $42 dollars per day, and approximately $14,400 per year.

A consensus exists regarding the need for CKD-MBD treatment to maintain guideline recommended targets for serum PTH, calcium, and phosphorus concentrations in the presumption that meeting these targets will improve quality and quantity of life. Prior systematic reviews have suggested that cinacalcet treatment reduces the rate of parathyroidectomy and fracture; the effect on mortality has not been established. However, prior reviews have not included trials published after February 2013, searched limited databases, only included adult CKD patients, and did not assess the quality of evidence. We completed a systematic review that addresses these limitations.

The objective of this systematic review was to evaluate the impact of cinacalcet treatment in patients with CKD-MBD and uncontrolled SHPT on patient-important outcomes, including parathyroidectomy, fractures, hospitalization due to cardiovascular events, cardiovascular mortality, all-cause mortality, and intermediate outcomes—specifically, whether patients achieved Kidney Disease Outcome Quality Initiative (K/DOQI) targets.

We hypothesized that reduction in PTH levels may be associated with regression of left ventricular hypertrophy and consequently lowers cardiovascular events, cardiovascular calcifications and mortality. We also addressed the effect of cinacalcet for achieving PTH targets.

Methods
Data sources and search strategy
We searched MEDLINE, EMBASE, the Cochrane Register of Controlled Trials, and web of Science from 1996 until June 2015 without language restrictions. We used controlled vocabulary and text words to search all databases (Supplemental Table S1 available online at http://informahealthcare.com/doi/suppl/10.3109/0886022X.2016.1172468). We searched for conference abstracts from 2003 to 2014 presented at recent annual meetings of the American Society of Nephrology, National Kidney Foundation (from 2006 to 2014: conference abstracts are provided from 2006 onwards) and European Renal Association-European Dialysis and Transplant Association and International Society of Nephrology. We scanned the bibliographies of all prior systematic reviews and meta-analyses as well as all eligible primary studies for additional relevant articles.

Eligibility criteria
We included studies, which enrolled patients with CKD stages 3–5. We limited the studies included in this review to randomized controlled trials (RCTs) evaluating the effectiveness and safety of cinacalcet for the treatment of secondary HPT. We explored the effectiveness of cinacalcet treatment on the following outcomes: parathyroidectomy, fractures, hospitalization due to cardiovascular events, cardiovascular mortality, all-cause mortality, PTH levels (any measure), serum calcium concentrations (mg/dL or mmol/L), serum phosphorus concentrations (mg/dL or mmol/L) and calcium x phosphorus product (mg2/dL2). We also collected data regarding cinacalcet related adverse events, such as
hypocalcemia, nausea, and vomiting. We did not employ any restrictions for patient age. We excluded studies with a primary objective of optimal dosing or economic evaluation of cinacalcet treatment.

**Study selection**

Teams of two investigators independently screened each unique title and abstract identified in our literature search. If either reviewer identified a citation as potentially relevant, we obtained the full text of the article. Two reviewers independently determined the eligibility of all studies that underwent full text evaluation.

We measured the inter-rater agreement for full text eligibility and assessment of risk of bias using the kappa statistic. Values of kappa between 0.40 and 0.59 reflect fair agreement, between 0.60 and 0.74 reflect good agreement and ≥0.75 reflects excellent agreement. Disagreements were resolved through discussion between reviewers or through adjudication with a third party if necessary.

One of our eligibility criteria was having CKD stages 3–5. CKD is described as kidney damage caused by structural or functional abnormalities that persist for at least 3 months. We employed estimated glomerular filtration rate (eGFR) to define CKD from a functional perspective and included those with an eGFR below 60 mL/min/1.73 m², including dialysis CKD patients (CKD stage 5D) and non-dialysis CKD patients (stages 3–5).

**Data abstraction**

Using a standardized data collection form, two reviewers abstracted the following information from each study: author, date of publication, eligibility criteria, summary of baseline characteristics of the participants, number of participants in each arm at study onset and completion, duration of the trial and treatment effects, including effectiveness and safety. We resolved disagreements by discussion.

**Quality assessment and risk of bias of included studies**

Two independent reviewers employed a modified version of the Cochrane risk for bias tool (http://distillercer.com/resources/) to assess risk of bias for all eligible trials. The assessment included the following components: adequacy of sequence generation, allocation sequence concealment, level of blinding, incomplete outcome data, loss to follow-up and stopping early for benefit or futility. Reviewers chose among response options of “definitely yes”, “probably yes”, “probably no”, and “definitely no” for each of the domains, with “definitely yes” and “probably yes” ultimately assigned low risk of bias and “definitely no” and “probably no” assigned high risk of bias. The reviewers resolved disagreements by discussion.

We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to evaluate the quality of evidence, which considers the overall risk of bias, precision, consistency, directness and publication bias, and summarized the results with a GRADE summary findings table. With respect to directness, we considered differences in population, intervention, outcomes and settings (primary vs. secondary vs. tertiary care settings). With respect to consistency, we considered statistical heterogeneity and also the visual inspection of forest plots. With respect to precision, we assessed the optimal information size (OIS; the number of patients generated by a conventional sample size calculation for a single trial) and the width of the 95% CIs. For the purposes of calculating the OIS we assumed, for all-cause mortality a relative risk reduction (delta) of 25%, alpha of 0.05, beta of 0.20, and median baseline risk from the largest cohort study of 0.3. We assessed selective reporting in terms of failure to report planned outcomes by comparing published protocols with the manuscripts (when available) as well as methods and results sections of the manuscript.

After considering these reasons for rating down, the overall quality of evidence in estimates of effect for each outcome was reported as follows: “high” quality of evidence (we are very confident that the true effect lies close to that of the estimate of the effect); “moderate” quality of evidence (we are moderately confident in the effect estimate and the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different); “low” quality of evidence (our confidence in the effect estimate is limited and the true effect may be substantially different from the estimate of the effect); and “very low” quality of evidence (we have very little confidence in the effect estimate and the true effect is likely to be substantially different from the estimate of effect).

**Data synthesis and statistical analysis: measures of treatment effect**

We used contrast-level summary data to perform pairwise meta-analysis based on normal models. We reported descriptive statistics as proportions for
categorical variables and mean or medians for continuous variables. We calculated pooled risk ratios (RRs) and the associated 95% CI for each outcome using random effects models by applying the maximum likelihood method. We also calculated absolute effects and the associated 95% CIs by multiplying pooled RRs and 95% CI by the control rate of outcomes from the RCT at low risk of bias and with the largest sample size.21 All analyses were performed using Stata (StataCorp. 2013, Stata Statistical Software: Release 13, StataCorp LP, College Station, TX).

Dealing with missing participant data for dichotomous outcomes: sensitivity analyses

We employed a complete-case analysis for our primary analysis and planned to conduct sensitivity analyses to address the robustness of our findings with respect to missing data. We planned to use plausible worst-case scenario for missing trial-level data.

Assessment of heterogeneity and dealing with heterogeneity

We formally assessed heterogeneity using Cochran’s Q test, chi-square test of homogeneity and the I² statistic for which 0–40% may be unimportant heterogeneity, 30–60% moderate, 50–90% substantial, and 75–100% considerable heterogeneity.22 For cardiovascular mortality, we employed random effects meta-regression and included mean age, the mean baseline serum PTH concentration, trial duration and stages of CKD (dialysis vs. non-dialysis) in our univariate linear models. For all-cause mortality, we employed random effects meta-regression and included trial duration and stages of CKD (dialysis vs. non-dialysis) in our univariate linear models.

Assessment of publication bias

In order to identify publication bias, we employed a funnel plot of the log risk ratio of the treatment effect against its precision for each outcome.23 Publication bias is considered unlikely unless the effect measure is asymmetically distributed around the pooled effect.23 We also employed Begg’s and Mazumdar’s rank correlation test as well as Egger’s regression to address small study effects and quantify publication bias.24 These tests employ the rank or actual value of effect sizes and their precisions.24

Figure 1. Risk of bias graph in included studies of cinacalcet plus standard treatment versus placebo or no standard treatment in patients with chronic kidney disease.
| Study name/first author, year | Number of patients in the cinacalcet arm/number of patients in the control arm | Inclusion criteria | Exclusion criteria | Outcomes assessed | Duration of the trial |
|-----------------------------|--------------------------------------------------------------------------------|-------------------|-------------------|-------------------|----------------------|
| Goodman et al., 2000        | 35/16/5                                                                        | Adult conventional HD patients; PTH 300–1200               | Abnormal liver enzymes and unstable conditions | All-cause mortality, cardiovascular mortality, nausea, hypocalcemia, change in serum PTH, Ca and P concentrations | 24 days |
| Goodman et al., 2002        | 20/20                                                                          | Adult conventional HD patients On HD treatment for at least 90 days | Abnormal liver enzymes and unstable conditions | All-cause mortality, cardiovascular mortality, nausea, vomiting, hypocalcemia and change in serum PTH, Ca and P concentrations | 15 days |
| Lindberg et al., 2003       | 38/39                                                                          | Adult conventional HD patients iPTH ≥300pg/mL              | Patients with unstable conditions | Nausea, dyspnea, hypocalcemia and change in serum PTH, Ca and P concentrations | 18 weeks |
| Quarles et al., 2003        | 36/35                                                                          | Adult conventional HD patients iPTH ≥300pg/mL; Ca ≥8.8 mg/dL and <11; CaXP <0.70 m2/dL | Being on HD treatment less than 90 days | Vomiting and change in serum PTH, Ca and P concentrations | 18 weeks |
| Block et al., 2004          | 371/370                                                                       | Adult conventional HD patients and being on HD treatment for at least 90 days | Unstable conditions | All-cause mortality, nausea, hypocalcemia, hypotension and change in serum PTH, Ca and P concentrations | 26 weeks |
| Harris et al., 2004         | 17/6                                                                           | Serum calcium ≥8.4 mg/dL or phosphorus ≥3.0 mg/dL          | Not specified | Nausea, vomiting and change in serum PTH, Ca and P concentrations | 7 days |
| Charytan et al., 2005       | 27/27                                                                          | eGFR is 15–50 mL/min/1.73 m²                                | Unstable conditions | All-cause mortality, cardiovascular mortality (cardiac failure, MI) nausea, hypocalcemia, diarrhea and change in serum PTH, Ca and P concentrations | 18 weeks |
| Lindberg et al., 2005       | 294/101                                                                        | Adult dialysis patients                                     | Patients with unstable conditions | All-cause mortality, parathyroidectomy and change in serum PTH, Ca and P concentrations | 27 weeks |
| Lien et al., 2005           | 8/6                                                                            | Stage 4 and stage 5D CKD patients                           | Not specified | Bone density and change in serum PTH, Ca and P concentrations | 26 weeks |
| Fishbane et al., 2008       | 87/86                                                                          | Adult conventional HD patients; on HD treatment for at least 90 days; the use of active vitamin D | The use of cinacalcet, pregnancy and being on breastfeeding | All-cause mortality, parathyroidectomy, nausea, vomiting, hypocalcemia, change in serum PTH, Ca and P concentrations | 33 weeks |
| Akiba et al., 2008          | 91/30                                                                          | Adult HD patients with iPTH ≥300pg/mL                       | Unstable conditions | All-cause mortality, cardiovascular mortality, change in serum PTH, Ca, and P concentrations | 5 weeks |
| Fukagawa et al., 2008       | 72/71                                                                          | Adult conventional HD patients for at least 16 weeks        | Parathyroidectomy within 24 weeks prior to the treatment and abnormal liver enzymes | Nausea, vomiting, hypocalcemia and change in serum PTH, Ca and P concentrations | 14 weeks |
| Malluche et al., 2008       | 19/13                                                                          | Adult HD patients Received bisphosphonates or fluoride     | All-cause mortality, bone turnover and change in serum PTH, Ca and P concentrations | All-cause mortality, cardiovascular mortality (all deaths, no description), hypocalcemia, nausea, vomiting and change in serum PTH, Ca and P concentrations | 53 weeks |
| Messa et al., 2008          | 368/184                                                                        | Adult, dialysis treatment at least 1 month                  | Unstable medical conditions, breastfeeding and participated in other calcitriol trials | All-cause mortality, cardiovascular mortality (MI and sudden cardiac death), nausea, hypocalcemia, vomiting, change in serum PTH, Ca and P concentrations | 23 weeks |
| Chonchol et al., 2009       | 302/102                                                                        | Stages 3–4 CKD Kidney transplantation, pregnancy and unstable conditions | All-cause mortality, cardiovascular mortality (all deaths, no description), hypocalcemia, nausea, vomiting and change in serum PTH, Ca and P concentrations | All-cause mortality, cardiovascular mortality (all deaths, no description), hypocalcemia, nausea, vomiting and change in serum PTH, Ca and P concentrations | 32 weeks |
| Study name/first author, year | Number of patients in the cinacalcet arm/number of patients in the control arm | Inclusion criteria | Exclusion criteria | Outcomes assessed | Duration of the trial |
|-------------------------------|---------------------------------------------------------------------------------|-------------------|-------------------|-------------------|-----------------------|
| Raggi et al., 2011<sup>13</sup> | 180/180 Adult conventional HD patients On HD treatment for at least 90 days PTH $\geq$300 pg/mL Ca $\geq$8.4 mg/dL CaXP $\geq$50 m$^2$/dL<sup>2</sup> CAC score $\geq$30 | The use of bisphosphonate, statin, cinacalcet or calcium free phosphate binder in 30 days, history of revascularization, valv replacement or cardiac transplantation | All-cause mortality, cardiovascular calcification, gastrointestinal disorders, hypercalcemia and change in serum PTH, Ca and P concentrations. | 52 weeks |
| El-Shafey et al., 2011<sup>41</sup> | 55/27 Adult conventional HD patients On HD treatment for at least 90 days PTH $\geq$300 Ca $\geq$8.4 | MI in 3 months, unstable conditions and breastfeeding | All-cause mortality, fractures, parathyroidectomy, nausea, vomiting, hypercalcemia, and change in serum PTH, Ca, and P concentrations | 36 weeks |
| Ketteler et al., 2012<sup>49</sup> | 134/134 Adult conventional HD patients PTH 300–800 Ca 8.4–10 P $\leq$6.5 | Allergic reaction and previous parathyroidectomy | All-cause mortality, cardiovascular mortality (cardiac arrest and MI), change in serum PTH, Ca, and P concentrations, hypercalcemia, hypercalcinemia, vomiting and nausea. | 28 weeks |
| EVOLVE, 2012<sup>21</sup> | 1948/1935 Adult conventional HD patients On HD treatment for at least 90 days PTH $>800$ calcium $\geq$8.4 mg/dL CaXP $\geq$45 m$^2$/dL<sup>2</sup> | Severe unstable and/or life-threatening medical condition History of the use of cinacalcet, hospitalization (due to acute coronary syndrome, heart failure, stroke or peripheral vascular disease), seizure or parathyroidectomy within 12 weeks Those who were pregnant, on breastfeeding, allergic to cinacalcet or unable to give informed consent | All-cause mortality, fractures, nonfatal cardiovascular event (myocardial infarction, unstable angina, heart failure and peripheral vascular event (lower extremity revascularization and non-traumatic amputation), cardiovascular mortality (MI, heart failure, stroke, pulmonary embolism, CV procedure and sudden cardiac death), hypercalcemia, parathyroidectomy nausea, vomiting, and change in serum PTH, Ca and P concentrations | 4 years |
| Sezer et al., 2012<sup>52</sup> | 61/31 Adult HD patients | Not specified. | Change in serum PTH, Ca and P concentrations | 52 weeks |
| Kim et al., 2013<sup>45</sup> | 33/33 Adult PD patients | Unstable conditions | All-cause mortality, cardiovascular mortality, hypercalcemia, adverse events (nausea, vomiting) and change in serum PTH, Ca and P concentrations | 16 weeks |
| Urena-Torres et al., 2013<sup>44</sup> | 155/154 On HD between 3 and 12 months PTH $>300$ pg/mL calcium $\geq$8.4 mg/dL | The use of cinacalcet PTH $>800$ | All-cause mortality, nausea, vomiting and change in serum PTH, Ca and P concentrations | 52 weeks |
| Bell et al., 2015<sup>50</sup> | 40/38 Adult HD patients who were on HD at least 6 months | Unstable conditions | All-cause mortality, adverse events (nausea, vomiting) and change in serum PTH, Ca and P concentrations | 4 weeks |
| Wetmore et al., 2015<sup>48</sup> | 155/157 Adult HD patients Parathyroidectomy in 12 weeks before the study inception | All-cause mortality, hypercalcemia and change in serum PTH, Ca and P concentrations | 52 weeks |

Notes: Ca: calcium; eGFR: estimated glomerular filtration rate; HD: hemodialysis; P: phosphorus; PD: peritoneal dialysis; PTH: parathyroid hormone.
Results

Trial identification

Our search yielded 579 citations, of which 30 were retrieved for full review and 24 RCTs enrolling 8311 patients were eligible for our review (Figure 1). Agreement for full text eligibility was excellent (kappa = 0.80). We assessed selective reporting in all included studies methods and results sections of the manuscript.

Trial and total population characteristics

Table 1 presents the characteristics of the 24 eligible studies. In 3 of the 24 studies non-dialysis patients were included. All studies excluded patients with unstable conditions, and enrolled patients with uncontrolled SHPT. Risk of bias was low in most studies across components, including allocation concealment and blinding of participants and personnel, which was adequately reported in about 75% of the trials (Figures 1 and 2).
Figure 4. Pooled risk ratio of fracture with cinacalcet plus standard treatment versus placebo or no standard treatment.

Figure 5. Pooled risk ratio of hospitalization with cinacalcet plus standard treatment versus placebo or no standard treatment.
Outcomes assessment

Parathyroidectomy

High quality evidence from four trials found a large effect of cinacalcet for preventing parathyroidectomy (RR 0.30, 95% CI 0.22–0.42; heterogeneity: $p = 0.70$, $I^2 = 0\%$) (Figure 3). The point estimate of the absolute effect is 55 fewer events in 1000 over the period of 1 year (CI 61 fewer to 45 fewer, Table 2).

Fractures and hospitalization due to cardiovascular events

Very low quality evidence from two trials with 3965 participants and 500 events left the impact of cinacalcet on fractures uncertain (RR 0.59, 95% CI 0.13–2.60; heterogeneity: $I^2 = 77\%$, very low quality evidence) (Figure 4). The evidence was rated down due to inconsistency, indirectness and imprecision. One large trial (EVOLVE trial) reported no effect of cinacalcet on hospitalization due to cardiovascular events (RR 0.93, 95% CI 0.85–1.02, moderate quality of evidence) (Figure 5).

Cardiovascular mortality

High quality evidence from nine studies showed 382 versus 399 deaths due to cardiac causes in the cinacalcet and control arms, respectively (RR 0.95, 95% CI 0.84–1.07; heterogeneity: $p = 0.61$, $I^2 = 0\%$) (Figure 6). Cardiovascular mortality may be associated with 5 fewer cardiac deaths in 1000 patients treated with cinacalcet (CI 26 fewer to 16 more, Table 2). Mean age, the mean baseline serum PTH concentration, trial duration, and the percentage of patients receiving dialysis were not associated with magnitude of effect in our univariable linear models (Supplemental Table S2 available online at http://informahealthcare.com/doi/suppl/10.3109/0886022X.2016.1172468).

All-cause mortality

There were 766 deaths in the cinacalcet arm versus 775 deaths in the control arm of 18 studies that reported this outcome (RR 0.96, 95% CI 0.89–1.04; heterogeneity: $p = 0.98$, $I^2 = 0\%$; moderate quality of evidence about effects because of inconsistency and publication bias, Table 2) (Figure 7). We also evaluated heterogeneity using the L’abbe and Galbraith plots both of which did not indicate heterogeneity (Figures 8 and 9, respectively). The vertical distance of ±2 above or below the regression through the origin line included all trials in the Galbraith plot (Figure 9).

![Figure 6](http://informahealthcare.com/doi/suppl/10.3109/0886022X.2016.1172468)

Figure 6. Pooled risk ratio of cardiovascular mortality with cinacalcet plus standard treatment versus placebo or no standard treatment.
Table 2. GRADE assessment of quality of evidence about effectiveness of cinacalcet plus standard treatment versus placebo or no standard treatment in patients with chronic kidney disease.

| Quality assessment | Effect estimates |
|--------------------|------------------|
| No of studies with one or more event with the outcome/number of participants/number of events | Risk of bias | Consistency | Directness | Precision | Publication bias | Relative effect using random effect models (95% CI) | Absolute effect per 1000 treated (95% CI) | Control risk | Quality of evidence |
| All-cause mortality | 18/7078/1541 | No serious limitations | No serious limitations | No serious limitations | No serious limitations | Serious limitations\(^a\) | RR 0.96 (0.89–1.04) | 16 fewer per 1000 (44 fewer to 16 more) | 404 per 1000 | Moderate |
| Cardiovascular mortality | 8/4694/781 | No serious limitations | No serious limitations | No serious limitations | No serious limitations | | RR 0.97 (0.86–1.09) | 7 fewer per 1000 (31 fewer to 20 more) | 220 per 1000 | High |
| Parathyroidectomy | 4/4225/203 | No serious limitations | No serious limitations | No serious limitations | No serious limitations | | RR 0.30 (0.22–0.42) | 55 fewer per 1000 (61 fewer to 45 fewer) | 78 per 1000 | High |
| Hypocalcaemia | 14/6285/175 | No serious limitations | No serious limitations | No serious limitations | No serious limitations | | RR 6 (3.65–9.87) | 20 more per 1000 (11 more to 36 more) | 4 per 1000 | High |
| Fractures | 2/3965/500 | No serious limitations | Serious limitations\(^b\) | Serious limitations | No serious limitations | | RR 0.59 (0.13–2.60) | 5 fewer per 1000 (11 fewer to 19 more) | 12 per 10000 | Very low |
| Nausea | 11/2404/554 | No serious limitations | Serious limitations\(^b\) | No serious limitations | No serious limitations | | RR 2.16 (1.6–3.21) | 138 more per 1000 (82 more to 302 more) | 137 per 1000 | Moderate |
| Vomiting | 9/2439/405 | No serious limitations | No serious limitations | No serious limitations | No serious limitations | | RR 2.15 (1.66–2.8) | 63 more per 1000 (109 more to 171 more) | 95 per 1000 | High |

Notes: CI: confidence interval; GRADE: Grades of Recommendation, Assessment, Development and Evaluation; RD: risk difference; RR: risk ratio.
\(^a\)Serious limitations due to publication bias, which was assessed by a funnel plot and Mazumdar’s rank correlation test and Egger’s regression. See text for other potential sources of bias in individual studies.
\(^b\)Serious limitations due to the significant amount of between study variation.
We needed a total sample size of 1200 for all-cause mortality to meet the OIS, which was met. We achieved both targets in our study. We rated down quality of evidence to moderate for a publication bias (Table 2) ($p$ values for the Mazumdar’s rank correlation test = 0.04; and $p$ values for Egger’s regression = 0.06). Visual inspection of the funnel plot also indicated that small studies favored cinacalcet (Figure 10). Trial duration and the percentage of patients receiving dialysis were not associated with magnitude of effect in our univariable linear models (Supplemental Table S3 available online at http://informahealthcare.com/doi/suppl/10.3109/0886022X.2016.1172468).

**Hypocalcemia**

There were 164 cases of hypocalcemia in the cinacalcet arm versus 11 in the control arm of 14 studies (RR 6.0, 95% CI 3.65–9.87; heterogeneity: $p = 0.71$, $I^2 = 0\%$) (95% CI around absolute difference 11 more to 36 more per 1000, high quality of evidence, Table 2, Figure 11).
Nausea
Cinacalcet increased the risk of nausea (RR 2.16, 95% CI 1.46–3.21; heterogeneity: \( p = 0.001, \, \hat{I}^2 = 64\% \)). There were 425 nausea in the cinacalcet arm versus 129 nausea in the control arm of 11 studies (158 more cases, 95% CI 82 more to 302 more, moderate quality of evidence due to unexplained heterogeneity, Table 2, Figure 12).

Vomiting
There were 314 reported cases of vomiting in the cinacalcet arm versus 91 in the control arm of the nine studies (RR 2.15, 95% CI 1.66–2.80; heterogeneity: \( p = 0.032, \, \hat{I}^2 = 14\% \), high quality of evidence). Cinacalcet may have an effect on vomiting (CI 63 more to 171 more, Table 2, Figure 13).

End of treatment serum PTH, Ca and P concentrations
Moderate quality evidence from 21 trials found a significant effect of cinacalcet for lowering serum PTH concentration (WMD \(-177\) pg/mL, 95% CI \(-227\) to \(-127\); heterogeneity: \( p = 0.001, \, \hat{I}^2 = 90\% \), Figure 14, Supplemental Table S4 available online at http://informahealthcare.com/doi/suppl/10.3109/0886022X.2016.1172468). Moderate quality evidence found that cinacalcet lowered serum calcium (17 studies included) and calcium phosphorus product (9 studies included) (WMD \(-0.66\) mg/dL, 95% CI \(-1.07\) to \(-0.25\) for calcium; WMD \(-4.03\) mg\(^2\)/dL\(^2\), 95% CI \(-7.7\) to \(-0.34\) for calcium phosphorus product). Very low quality evidence found no effect on serum phosphorus concentration (WMD \(-0.12\) mg/dL, 95% CI \(-0.32\) to 0.07) (Figure 15) (Supplemental Table S4 available online at http://informahealthcare.com/doi/suppl/10.3109/0886022X.2016.1172468).

Sensitivity analyses
The majority of the studies reported numbers and reasons for missing data in each arm. We planned to employ sensitivity analysis for benefit outcomes showing significant effects—in this case, parathyroidectomy—using the plausible worst case scenario. Three of four studies reported no loss to follow-up. As a result, we did not perform the sensitivity analysis.

Discussion
Our systematic review found high quality evidence that cinacalcet therapy reduces the risk of parathyroidectomy (RR 0.30, 95% CI 0.22–0.42) and moderate quality of evidence for most variables (very low for phosphorus) in achieving K/DOQI targets (PTH WMD \(-177\) pg/mL, 95% CI \(-227\) to \(-127\); calcium WMD \(-0.66\) mg/dL, 95% CI \(-1.07\) to \(-0.25\); phosphorus WMD \(-0.12\) mg/dL, 95% CI \(-0.32\) to 0.07; calcium-phosphorus product WMD \(-4.03\) mg\(^2\)/dL\(^2\), 95% CI \(-7.7\) to \(-0.34\)). If our estimates of effect on outcomes of parathyroidectomy were accurate, the impact of cinacalcet would represent an important benefit (point estimates of absolute effects: 55 fewer parathyroidectomies per 1000 patients).

We found no effect on fractures, hospitalization due to cardiovascular events, cardiovascular mortality and all-cause mortality (RR 0.95, 95% CI 0.84–1.07 for cardiovascular mortality; RR 0.96, 95% CI 0.89–1.04 for all-cause mortality). The most common adverse events related to cinacalcet included gastrointestinal side effects, such as nausea and vomiting. Moreover,
Cinacalcet was associated with an increased risk for hypocalcemia. Even though our pooled estimate failed to show the mortality benefit of cinacalcet, several observational studies indicated a reduced risk of cardiovascular and all-cause mortality in those who were on cinacalcet treatment (HR = 0.78, 95% CI 0.71–0.86; HR = 0.73, 95% CI 0.68–0.78, cardiovascular and all-cause mortality, respectively) and those with well-controlled biochemical markers.25,26 A subgroup analysis (age <65 vs. ≥65) of the EVOLVE trial indicated mortality benefit of cinacalcet treatment in those who were older than 65 (HR = 0.73, 95% CI 0.62–0.86). The test of significance for the subgroup effect was not reported.27

In addition to study level findings, a recent systematic review explored the correlation between CKD-MBD biochemical markers and mortality.28 The results indicated a significant negative correlation between PTH and all-cause mortality.29 Nevertheless, the correlation between serum calcium and phosphorus concentration and mortality did not prove significant.28 We found that cinacalcet reduces PTH but has no effect on mortality. A mortality benefit seems implausible since the damage in the cardiovascular system is irreversible and progressive at this advanced stage of CKD-MBD.

Economic evaluation of cinacalcet in CKD-MBD indicated mixed results in terms of cost-effectiveness both in the US and European healthcare settings.29–32 The reduction in the cost was attributable to lower rates of parathyroidectomy, cardiovascular events and fractures in an economic evaluation from Japan.31 The effectiveness data were received from observational studies. This analysis is not valid given that our results show that cinacalcet does not change hospitalizations due to cardiovascular events and may not reduce fractures.31 In any case, access to cinacalcet care is restricted to those at the upper end of the socioeconomic spectrum unless publicly funded health care systems provide price subsidies for eligible patients.

### Figure 11. Pooled risk ratio of hypocalcemia with cinacalcet plus standard treatment versus placebo or no standard treatment.

| Study          | ES (95% CI)     | % Weight |
|----------------|-----------------|----------|
| Goodman et al  | 4.41 (0.30, 64.57) | 3.44     |
| Goodman et al  | 0.32 (0.01, 15.20) | 1.65     |
| Lindberg et al | 8.17 (0.44, 151.64) | 2.90     |
| Block et al    | 4.32 (1.57, 11.92) | 24.04    |
| Charytan et al | 9.00 (0.51, 159.43) | 3.00     |
| ACHIEVE study  | 8.89 (0.50, 157.53) | 3.00     |
| OPTIMA study   | 3.70 (1.00, 13.70) | 14.45    |
| Fugakawa et al | 8.87 (0.49, 161.75) | 2.94     |
| Chonchol et al | 6.79 (1.34, 34.54) | 9.37     |
| El-Shafey et al| 6.50 (0.38, 111.30) | 3.07     |
| EVOLVE study   | 8.89 (2.41, 32.77) | 14.54    |
| IMPACT SHPT study | 48.06 (2.95, 782.06) | 3.18     |
| CUPID study    | 1.28 (0.14, 11.57) | 5.11     |
| Wetmore et al  | 18.57 (3.64, 94.62) | 9.34     |
| Overall (I-squared = 0.0%, p = 0.718) | 6.00 (3.65, 9.87) | 100.00   |

Note: Weights are from random effects analysis.
Figure 12. Pooled risk ratio of nausea with cinacalcet plus standard treatment versus placebo or no standard treatment.

Figure 13. Pooled risk ratio of vomiting with cinacalcet plus standard treatment versus placebo or no standard treatment.
Strengths and limitations of this study

Strengths of our systematic review and meta-analysis include explicit eligibility criteria, a comprehensive search, independent duplicate assessment of eligibility, and use of the GRADE approach to assessing quality of evidence an outcome-by-outcome basis. This is the first systematic review that includes a search for both pediatric and adult CKD patient populations in the assessment of cinacalcet and addresses patient important outcomes available in the literature. Our search identified one study in the pediatric patient population, which proved ineligible since it was a dose-finding study. Limitations of our review included low quality evidence for some outcomes (Table 2).

Conclusions

Our findings did not indicate apparent benefits of cinacalcet therapy on mortality which may preclude the use of cinacalcet as the first line therapy in CKD patients with uncontrolled hyperparathyroidism. A systematic review with individual patient data may provide an avenue for subgroup analyses to verify potential benefits of cinacalcet in selected patient populations. In order to guide future work in this area, another recommendation would be a large multicenter RCT with a long trial period, for instance 2 years, by focusing on cardiovascular events, mortality and fractures.

In the interval, clinicians should seriously consider benefits and harms of standard treatment versus the use of cinacalcet to control persistently elevated PTH.
levels due to CKD-MBD. Patient values, preferences and ability to pay are other considerations in the decision-making process.

Disclosure statement
The authors declare that they have no financial or non-financial competing interests.

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