Meta-Analysis

Cinacalcet Treatment Significantly Improves All-Cause and Cardiovascular Survival in Dialysis Patients: Results from a Meta-Analysis

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Keywords

Cinacalcet · All-cause mortality · Cardiovascular mortality · Dialysis

Abstract

Objective: To assess the long-term effects including all-cause mortality, cardiovascular mortality, and fracture incidence, of cinacalcet on secondary hyperparathyroidism (SHPT) in patients on dialysis. **Methods:** PubMed, Embase, and the Cochrane Central Register of Controlled Trials were searched from their inception to October 2018. Randomized controlled trials (RCTs) and cohort design prospective observational studies assessing cinacalcet for the treatment of SHPT in dialysis patients were included. Data extraction was independently completed by 2 authors who determined the methodological quality of the studies and extracted data in duplicate. Study-specific risk estimates were tested by using a fixed effects model. **Results:** A total of 14 articles with 38,219 participants were included, of which 10 RCTs with 7,471 participants and 4 prospective observational studies with 30,748 participants fulfilled the eligibility criteria. Compared with no cinacalcet, cinacalcet administration reduced all-cause mortality (relative risk [RR] 0.91, 95% CI 0.89–0.94, $p < 0.001$) and cardiovascular mortality (RR 0.92, 95% CI 0.89–0.95, $p < 0.001$), but it did not significantly reduce the incidence of fractures (RR 0.93, 95% CI 0.87–1.00, $p = 0.05$). **Conclusions:** The results of this meta-analysis indicated that the treatment of SHPT with cinacalcet may in fact reduce all-cause mortality and cardiovascular mortality among patients receiving maintenance dialysis.

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Chronic kidney disease (CKD) is increasingly common in developing and developed countries, and it has become a global public health issue [1]. CKD-mineral and bone disorder (CKD-MBD) involves abnormal serum concentrations of calcium, phosphorus, parathyroid hormone (PTH), and vitamin D. Correcting these abnormalities is important because they are associated with cardiovascular disease and mortality, which occur relatively frequently in hemodialysis patients [2].

Cinacalcet, a second-generation calcimimetic agent, is a positive allosteric modulator of the calcium-sensing receptor that increases its sensitivity to extracellular calcium by lowering the threshold for activation by extracellular calcium ions [3, 4]. This mechanism lowers PTH synthesis and secretion. Treatment with cinacalcet can reduce serum calcium, often accompanied by a reduction in serum phosphate, as shown in multiple randomized, controlled trials. Treatment with cinacalcet increases the risk of adverse events, such as hypocalcemia, nausea, vomiting, and diarrhea. Several meta-reviews have also confirmed the effects and adverse effects of cinacalcet on secondary hyperparathyroidism (SHPT) in CKD patients [5, 6]. However, hypocalcemia-induced serious adverse events were very rare.

By slowing the progression of vascular calcification mediated by hypercalcemia and hyperphosphatemia, cinacalcet might prevent death, particularly death due to cardiovascular disease [7, 8]. Some randomized controlled trials (RCTs) found that cinacalcet significantly reduced the likelihood of parathyroidectomy, fracture, and cardiovascular hospitalization; improved physical function; and diminished pain. However, the effect on all-cause and cardiovascular mortality was not demonstrated [9, 10]. RCTs with clinical outcomes are considered the gold standard for regulatory approval. However, by design, it is difficult to follow long-term clinical outcomes in RCTs [11]. RCT experiments are difficult to follow-up for enough time to observe the risk of death. Therefore, high-quality observational studies are required for clinical decision-making. Some high-quality observational studies found that all-cause and cardiovascular mortality rates were significantly lower for those treated with cinacalcet than for those that were not [12, 13]. Relevant meta-analysis results are also inconsistent. Few meta-analyses take into account the observational experiments. We performed this meta-analysis including RCTs and high-quality observational studies to provide further evidence regarding the effects of cinacalcet on clinical outcomes in hemodialysis patients.

Methods

Data Sources and Searches

We searched PubMed, Embase, and the Cochrane Library from their inception to October 2018, and we systematically identified clinical studies evaluating the effects of cinacalcet in dialysis patients. No language restriction was applied. The search strategy included terms for cinacalcet, SHPT, and hemodialysis. We also scanned the cited references of retrieved articles and all prior systemic reviews to identify any additional relevant studies.

Eligibility Criteria

We included studies that evaluated the effectiveness and safety of cinacalcet for the treatment of SHPT in dialysis patients. A published article was included if (1) it was an RCT or a case-control or cohort design prospective observational study, (2) the study evaluated the administration of cinacalcet alone or in combination with a vitamin D compound or phosphate binder versus the administration of placebo in combination with standard treatment or standard treatment alone, and (3) the end point events (all-cause or cardiovascular mortality and fracture incidence) and their corresponding hazard ratio (HR) or relative risk (RR) and its 95% CI were reported or could be calculated from data reported. If publications were duplicated or if the

Table 1. Methodological quality of cohort studies included in the meta-analysis

Cohort study	Representative-ness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factor or additional factor	Outcome assessment	Follow-up long enough form outcomes to occur ¹	Adequacy of follow-up of cohorts ²	Data analysis using energy adjusted residual model or nutrient density model	Total quality scores
Block et al. [25], 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	8
Gillespie et al. [13], 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	8
Akizawa et al. [26], 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	8

¹ A cohort study with a follow-up rate more than 75% was assigned one star. ² A cohort study with a follow-up time more than 8 years was assigned one star.

Fig. 1. Flow diagram of the study selection.

articles were from the same study population, the most recent publication was included. Excluded from this analysis were studies that were retrospective studies, those that included nondialysis patients, or those for which the HR or RR of the end point events could not be obtained.

Two authors independently screened the abstracts and full texts of all potentially eligible articles; disagreements between reviewers were resolved by a third reviewer. The risk of bias in RCTs was assessed using the Cochrane Collaboration's tool [14]. To assess the prospective observational study quality, a 9-star system based on the Newcastle-Ottawa Scale was used, in which a study was judged on 3 broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or the outcome of interest for case-control or prospective studies. A high-quality study was defined as a study that was awarded ≥ 7 stars (Table 1). Our meta-analysis of RCTs and prospective observational studies were performed according to both Preferred Reporting Items for Systematic Reviews [15] and Meta-analysis Of Observational Studies in Epidemiology recommendations [16].

Data synthesis was conducted and RevMan software (version 5.3; Cochrane Collaboration, Copenhagen, Denmark) was used for statistical analysis. To compute a summary RR with its 95% CI, we used the study-specific, most adjusted RR or HR (for all-cause mortality, cardiovascular mortality, and fracture incidence) and its 95% CI in all analyses. logHR or

Table 2. Characteristics of included studies

Study	Study design	Dialysis	Patients in cinacalcet/no-cinacalcet	Inclusion criteria	Exclusion criteria	Outcomes assessed
Block et al. [12], 2004	RCT	HD	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
Block et al. [25], 2010	prospective observational cohort	HD	5,976/19,174	Included patients were required to be aged at least 18 years on August 1, 2004 and to have survived 90 days	Patients' lack of adequate time to assess baseline characteristics	All-cause mortality, Cardiovascular mortality, Laboratory values included albumin, corrected calcium, phosphorus, PTH
Chertow et al. [9], 2012	RCT	HD	1,948/1,935	Adult conventional HD patients On HD treatment for at least 90 days PTH 300 pg/mL Ca 8.4 mg/dL Ca × P 45 m ² /dL ²	Severe unstable and/or life-threatening medical condition; History of the use of cinacalcet hospitalization, 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, cardiovascular mortality, hypocalcemia, parathyroidectomy nausea, vomiting, and change in serum PTH, Ca and P concentrations
Cunningham et al. [10], 2005	RCT	HD/PD	697/487	≥18 years old, exhibited an intact PTH level ≥300 pg/mL and an albumin corrected serum calcium ≥8.4 mg/dL, and had received hemodialysis 3 times per week for a minimum of 1–3 months or peritoneal dialysis for ≥1 month	Parathyroidectomy or myocardial infarction within 3–6 months of the start of treatment and change of vitamin D therapy within 30 days of the start of treatment, the existence of an unstable medical condition, and pregnancy or nursing	Mortality, fractures; Cardiovascular hospitalization; All-cause hospitalization, change in serum PTH, Ca and P concentrations
El-Shafey et al. [19], 2011	RCT	HD	55/27	Adult conventional HD patients On HD treatment for at least 90 days PTH ≥300; Ca ≥8.4	≤ in 3 months, unstable conditions and breastfeeding	Death, fractures, and change in serum PTH, Ca, and P concentrations
Fishbane et al. [20], 2008	RCT	HD	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	Death, change in serum PTH, Ca and P concentrations, and adverse event
Gillespie et al. [13], 2015	prospective observational cohort	HD	532/1,790	Adult conventional HD patients and being on HD treatment for at least 90 days	Renal transplantation, peritoneal dialysis or parathyroidectomised history	All-cause mortality; cardiovascular medication use; active vitamin D use; phosphate binder use; history of fractures; change in serum PTH, Ca and P concentrations
Lindberg [5], 2005	RCT	HD/PD	294/101	Adult dialysis patients	Patients with unstable conditions	Death, parathyroidectomy and change in serum PTH, Ca and P concentrations
Malluche et al. [24], 2008	RCT	HD	19/13	Adult HD patients	Received bisphosphonates or fluoride	All-cause mortality, bone turnover and change in serum PTH, Ca and P concentrations

Table 2 (continued)

Study	Study design	Dialysis	Patients in cinacalcet/no-cinacalcet	Inclusion criteria	Exclusion criteria	Outcomes assessed
Raggi et al. [21], 2011	RCT	HD	180/180	Adult conventional HD patients On HD treatment for at least 90 days PTH ≥ 300 pg/mL Ca $\times$ P ≥ 50 m ² /dL ² CAC score ≥ 30	The use of biphosphonate, statin, cinacalcet or calcium free phosphate binder in 30 days, history of revascularization, valve replacement or cardiac transplantation	All-cause mortality, cardiovascular calcification, gastrointestinal disorders, hypocalcemia, and change in serum PTH, Ca and P concentrations
Akizawa et al. [26], 2016	a 3-years prospective case-cohort and cohort study	HD	1,384/1,892	Conventional HD patients	Receiving dialysis for less than 3 months	Death due to any cause, death due to cardiovascular disease
Urena-Torres et al. [22], 2013	RCT	HD	155/154	On HD between 3 and 12 months PTH >300 pg/mL calcium ≥ 8.4 mg/dL	The use of cinacalcet PTH >800	All-cause mortality, nausea, vomiting and change in serum PTH, Ca and P concentrations
Wetmore et al. [23], 2015	RCT	HD	155/157	Adult HD patients	Parathyroidectomy in 12 weeks before the study inception	All-cause mortality, hypocalcemia and change in serum PTH, Ca and P concentrations
RCT, randomized controlled trials; PTH, parathyroid hormone.

Fig. 2. a Forest plot of all-cause mortality in the cinacalcet group versus the no-cinacalcet control group.
b Funnel plot to assess publication bias in effect estimates in all-cause mortality.

logRR and SElogHR or SElogOR needed to be entered. $SElogHR = (\log UCI - \log LCI) / 3.92$. A p value < 0.05 was considered statistically significant. We examined heterogeneity in results across studies using the Cochran Q and I^2 statistics. The null hypothesis that the studies are homogeneous was rejected if the p value for heterogeneity was < 0.10 or if I^2 was $> 50\%$ [17, 18]. We employed a funnel plot to assess publication bias and a fixed effects model (the inverse variance method) to estimate study-specific risk.

Results

Characteristics and quality of the studies. A total of 38,219 potentially relevant citations were identified and screened. Thirteen articles were retrieved or detailed, of which 10 RCTs [6, 9, 10, 12, 19–24] with 7,471 participants and 3 prospective observational studies [13, 25,

Fig. 3. a Forest plot of cardiovascular mortality in the cinacalcet group versus the no-cinacalcet control group. **b** Funnel plot to assess publication bias in effect estimates in cardiovascular mortality.

26] with 30,748 participants fulfilled the eligibility criteria and were included in the meta-analysis (Fig. 1; Table 2). All 14 trials included patients with stage 5 CKD who were under dialysis treatment.

All-cause mortality. We included 13 trials (including 38,219 participants) that either reported all-cause mortality or the all-cause mortality could be calculated from the data reported in 2 groups. Our results indicated that cinacalcet reduced all-cause mortality compared with placebo or no cinacalcet treatment in patients with SHPT caused by CKD (RR 0.91, 95% CI 0.89–0.94, $p < 0.001$) as determined using a fixed effects model ($I^2 = 0\%$, $p = 0.81$; Fig. 2a, b).

Cardiovascular mortality. Only 3 trials (including 32,309 participants) that either reported cardiovascular mortality or the all-cause mortality could be calculated from the data reported were included in our meta-analysis. The results showed that cinacalcet treatment may reduce cardiovascular mortality compared with no cinacalcet treatment in patients with SHPT caused by CKD (RR 0.92, 95% CI 0.89–0.95, $p < 0.001$) as determined using a fixed effects model ($I^2 = 49\%$, $p = 0.14$; Fig. 3a, b).

Fig. 4. a Forest plot on fracture incidence in the cinacalcet group versus the non-cinacalcet control group. **b** Funnel plot to assess publication bias in effect estimates in fracture incidence.

Fracture incidence. Four trials (including 7,471 participants) that either reported the incidence of fractures or the incidence of fractures could be calculated from the data reported were included in our meta-analysis. The results showed that cinacalcet did not significantly reduce the incidence of fractures (RR 0.93, 95% CI 0.87–1.00, $p = 0.05$) as determined using a fixed effects model ($I^2 = 7\%$, $p = 0.36$; Fig. 4a, b).

Discussion

Although there were several published meta-analyses of RCTs examining the effects of cinacalcet on CKD-MBD, cardiovascular mortality, and all-cause mortality, this is the first meta-analysis that included RCTs and high-quality prospective observational studies to evaluate the long-term treatment effects of cinacalcet on cardiovascular mortality, all-cause

mortality, and fracture incidence. To our knowledge, this meta-analysis of 10 RCTs and 3 prospective observational studies of patients receiving hemodialysis or peritoneal dialysis is the largest, with 36,283 participants, and the results are not in agreement with the results of previous meta-analyses [27, 28]. Previous meta-analyses included only RCTs. Owing to limited time and money, in most RCTs, observation indicators do not include death. Patients were observed only for several months, and there were almost no deaths. However, many meta-analyses discuss all-cause mortality and cardiovascular mortality [29–31]. We selected end-point events (all-cause or cardiovascular mortalities and fracture incidence) and their HR or RR and 95% CI as outcomes to report.

Evidence suggests that maintaining CKD-MBD-related mineral metabolic parameters within the K/DOQI target ranges is of significant clinical relevance [32]. Cinacalcet is widely used in clinical practice, and there is an obvious beneficial effect of cinacalcet on serum PTH, calcium, and phosphorus levels. However, it was not clear whether cinacalcet could reduce hospitalizations due to cardiovascular events, cardiovascular mortality, or all-cause mortality compared with standard treatment for CKD. The strength of the observational data suggests that high levels of calcium and phosphorus are associated with mortality. It is tempting to speculate that serum PTH, calcium, and phosphorus reductions may be the proximate cause of a survival benefit [33]. In addition, abnormal calcium and phosphorus levels in the blood and tissues are linked to vascular calcification, resulting in cardiovascular diseases. In addition, there was a significant negative correlation between PTH and all-cause mortality. It has been repeatedly confirmed that cinacalcet has a lowering effect on serum FGF-23, a marker of left ventricular hypertrophy and cardiovascular disease in the CKD population [34–36]. Therefore, in theory, improvement in the above indicators will help reduce cardiovascular mortality or all-cause mortality. In addition, some long-term high-quality prospective observational studies found that the prescription of cinacalcet to hemodialysis patients with SHPT who received traditional treatment (no-cinacalcet control group) was associated with significant reductions in all-cause and cardiovascular mortality. Our meta-analysis included evidence from both RCTs and observational studies on the effects of cinacalcet on all-cause and CV-related mortality, showing that cinacalcet may be associated with a decreased risk of all-cause (0.91, 95% CI 0.89–0.94) and CV-related mortality (0.92, 95% CI 0.89–0.95) among patients receiving maintenance dialysis. Because these results are observational and cannot establish a cause-and-effect relationship, they are not currently used in conventional therapy.

Bone remodeling is dependent on the dynamic balance between bone formation and bone resorption. Excessively high levels of serum PTH lead to an imbalance of these 2 processes and affect bone and mineral metabolism [37, 38]. El-Shafey et al. [19] reported that cinacalcet treatment increased the proximal femur BMD in patients with SHPT. In contrast, when SHPT was not effectively treated, there was a progressive loss of the proximal femur BMD. Cinacalcet treatment for 36 weeks not only halted bone loss but also resulted in a 2% increase in mineralized bone in the proximal femur; however, cinacalcet did not stop the bone loss in the lumbar spine. Some studies have demonstrated that cinacalcet ameliorated high bone turnover and increased femoral cortical bone mineral density and cortical bone strength [39]. These data suggest that cinacalcet may protect cortical bone in patients with SHPT. However, a positive result of reducing the incidence of fractures was not obtained from RCTs. Our meta-analysis results of improving fracture incidence are close to significant.

Previous studies including RCTs, meta-analyses, and observational studies found that the use of cinacalcet was correlated with a relatively high risk of adverse events, including hypocalcemia, nausea, vomiting, and diarrhea. Some 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. Research by Wang et al. [27] showed that the absolute risk of hypocalcemia, nausea, vomiting, and diarrhea increased

by 10.31, 13.16, 10.57, and 2.01% respectively, compared with placebo or no treatment. It is also not clear whether cinacalcet affects all-cause mortality and cardiovascular mortality. These findings limited the prescription of cinacalcet by clinicians. However, in some prospective and retrospective studies, cinacalcet-induced hypocalcemia was of short duration and usually self-limited. Importantly, hypocalcemia-induced serious adverse events were very rare [40]. Accordingly, the revised 2017 KDIGO CKD-MBD guideline states that mild and asymptomatic hypocalcemia can be tolerated in patients on dialysis, especially when associated with cinacalcet treatment, to avoid inappropriate calcium loading in adults [41]. Cinacalcet initiation was more effective in patients with more severe iPTH levels than that in patients with less severe iPTH levels. We combined the results of observational studies and RCTs and found that the treatment of SHPT in dialysis with cinacalcet therapy may reduce all-cause mortality and cardiovascular mortality. Clinicians should seriously consider the benefits and harms of cinacalcet versus standard treatment to persistently control elevated PTH levels due to CKD-MBD in dialysis.

In conclusion, our meta-analysis results showed that treatment of SHPT in maintenance dialysis patients with cinacalcet therapy may reduce all-cause mortality and cardiovascular mortality. However, further RCTs investigating the effect of cinacalcet on long-term mortality and fracture incidence are required.

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Disclosure Statement

The authors had full access to all the data in the study and had the final responsibility for the decision to submit to publication. The results presented in this paper have not been published previously in whole or part. The authors declare no conflicts of interest.

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