Research Article

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Effects of calcimimetics on long-term outcomes in dialysis patients: literature review and Bayesian meta-analysis

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Aim: Randomized controlled trials (RCTs) with clinical outcomes are considered the gold standard for regulatory approval. However, by design they are only able to answer a small number of clinical questions. Other high-quality studies are required for clinical decision-making. The EVOLVE was the largest RCT, evaluating the effects of cinacalcet on clinical outcomes among adult patients receiving maintenance dialysis suffering from secondary hyperparathyroidism. While the EVOLVE trial did not reach its primary end point, imbalance in subjects' age at randomization and discontinuation rates are two of the reasons that the lack of mortality benefit is in question. We undertook a systematic literature review and Bayesian meta-analysis combining randomized and observational studies on the estimated effects of the oral calcimimetic cinacalcet on clinical outcomes including all-cause mortality, cardiovascular-related mortality, hospitalization for cardiovascular events, fracture and parathyroidectomy among patients on maintenance dialysis. **Methods:** Data sources included MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials databases. RCTs and observational studies were included. Data extraction was completed by two authors independently and in duplicate determined the methodological quality of the studies and extracted data. **Results:** Of 564 unique citations identified, 16 studies were included: six observational studies and ten RCTs. Four high-quality studies (two observational and two RCTs) were deemed suitable for meta-analysis. Results indicated a statistically significant reduction in the risk of death associated with cinacalcet (hazard ratio: 0.83; 95% credible interval: 0.78–0.89).**Conclusion:** The results of this meta-analysis indicate that treatment of secondary hyperparathyroidism with calcimimetic therapy may in fact reduce mortality among patients receiving maintenance dialysis. This finding provides justification for a well-designed and adequately powered randomized trial to definitively address the question.

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Keywords: all-cause mortality • cardiovascular mortality • chronic kidney disease • cinacalcet • dialysis • secondary hyperparathyroidism

Cinacalcet (Sensipar®/Mimpara®, Amgen Inc., CA, USA) is an oral calcimimetic agent available since 2004 for the reduction of parathyroid hormone (PTH) in patients with secondary hyperparathyroidism (sHPT) on maintenance dialysis [1,2]. Randomized controlled trials (RCTs) have established that cinacalcet lowers serum concentrations of PTH, calcium and phosphate relative to placebo [3–8]. Four randomized trials found that cinacalcet significantly reduced the likelihood of parathyroidectomy, fracture and cardiovascular (CV) hospitalization, improved self-reported physical function and diminished pain [9]. To examine the effect on long-term outcomes, the EVOLVE trial tested cinacalcet versus placebo in 3883 patients with moderate-to-severe sHPT on a composite end point including mortality, myocardial infarction, hospitalization for unstable angina, heart failure or peripheral vascular

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Table 1. Summary of included studies.

Study (year)	Study location (year)	Study design/data source	Dialysis	Total follow-up time (years)	n	Ref.
RCTs						
Chertow *et al.* (2012)	International (2006–2008)	Double-blind	HD	5.3	3883	[10]
Cunningham *et al.* (2005)†	International	Double-blind	HD and PD	1.1	1184	[9]
Messa *et al.* (2008)	Europe	Open-label	HD and PD	0.4	552	[25]
Malluche *et al.* (2008)	USA and Europe (2001–2003)	Double-blind	HD	1.0	48	[26]
Raggi *et al.* (2011)	International	Open-label	HD	1.0	360	[27]
El-Shafey *et al.* (2011)	Middle East (2009–2010)	Open-label	HD	0.7	82	[28]
Fishbane *et al.* (2008)	–	Open-label	HD	0.5	173	[29]
Urena-Torres *et al.* (2013)	International (2009–2011)	Open-label	iHD	1.1	309	[30]
Kim *et al.* (2013)	Korea (2010–2012)	Open-label	PD	0.3	66	[31]
Ketteler *et al.* (2012)	USA and Russia	Open-label	HD	0.5	272	[32]
Observational						
Block *et al.* (2010)	USA (2004–2006)	Prospective‡/DaVita database	pHD	2.2	19,186	[33]
Schumock *et al.* (2011)	USA (2001–2007)	Retrospective/MCCE	HD	1.4	2704	[34]
Abouchacra *et al.* (2014)	UAE (2012–2013)	Retrospective/hospital	HD	2.0	71	[35]
Friedl *et al.* (2013)	Austria (2004–2009)	Retrospective§/ADTR	pHD and pPD	7.0	8225	[36]
Gillespie *et al.* (2015)	Europe (2007–2009)	Prospective¶/ARO	iHD	5.8	2322	[37]
Akizawa *et al.* (2012)	Japan	Prospective#/MBD-5D	HD	3.0	8229	[38]

†Pooled analysis of four RCTs: published by Quarles *et al.* (2003) [24], Lindberg *et al.* (2003) [4], Block *et al.* (2004) [3] and Lindberg *et al.* (2005) [5]. Those four studies did not make study selection as none of them reported the outcomes of interest.
‡Data from DaVita database.
§Data from the Austrian Dialysis and Transplant Registry.
¶Data from the Analyzing data, Recognizing excellence and Optimizing outcomes-CKD Research Initiative.
#Study is a planned analysis of the Mineral and Bone Disorders Outcomes Study for Japanese CKD stage-5D.
ADTR: Austrian dialysis and transplant registry; ARO: Analyzing data, Recognizing excellence, and Optimizing outcomes; CKD: Chronic kidney disease; HD: Hemodialysis; iHD: Incident HD; MBD-5D: Mineral and Bone Disorders Outcomes Study for Japanese CKD stage-5D; MCCE: MarketScan commercial claims and encounter; PD: Peritoneal dialysis; pHD: Prevalent HD; pPD: Prevalent PD; RCT: Randomized-controlled trial.

event [10]. The EVOLVE trial's prespecified primary analysis, an unadjusted intention-to-treat (ITT) comparison, showed the relative hazard of the composite end point in the cinacalcet group versus the placebo group of 0.93 (95% CI: 0.85–1.02; p = 0.11). The EVOLVE investigators concluded that *"cinacalcet did not significantly reduce the risk of death or major CV events in patients with moderate-to-severe sHPT who were undergoing dialysis."*

However, there are reasons to suspect that the finding is not conclusive. First, after adjustment for baseline characteristics, the relative hazard for the primary composite end point was 0.88 (95% CI: 0.79–0.97; p = 0.008), in other words, statistically significant. Second, there was a high degree of crossover: more than one in five patients randomized to placebo was treated with cinacalcet. Third, approximately one in seven patients underwent parathyroidectomy, reducing intergroup differences in PTH control and biasing the estimate of treatment effect toward the null [10]. As a result, analyses adjusted for baseline characteristics showed a nominally significant benefit of cinacalcet on the primary composite end point and on mortality. Fourth, in a prespecified subgroup analysis based on an age threshold of 65 years, adjusted analyses indicated that among older patients, the adjusted relative hazard for mortality was 0.68 (95% CI: 0.51–0.81) and for the composite CV end point was 0.70 (95% CI: 0.60–0.81) [11].

To examine the totality of the evidence regarding the estimated effect of cinacalcet plus standard of care compared with standard of care, we conducted a systematic literature review and meta-analysis of published RCTs and observational studies that included relevant clinical outcomes (all-cause mortality, CV-related mortality, hospitalization for CV events, fracture and parathyroidectomy) among patients receiving maintenance dialysis with sHPT.

Methods

Data source

We performed electronic database searches in MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify English language articles published from database inception until 3rd April

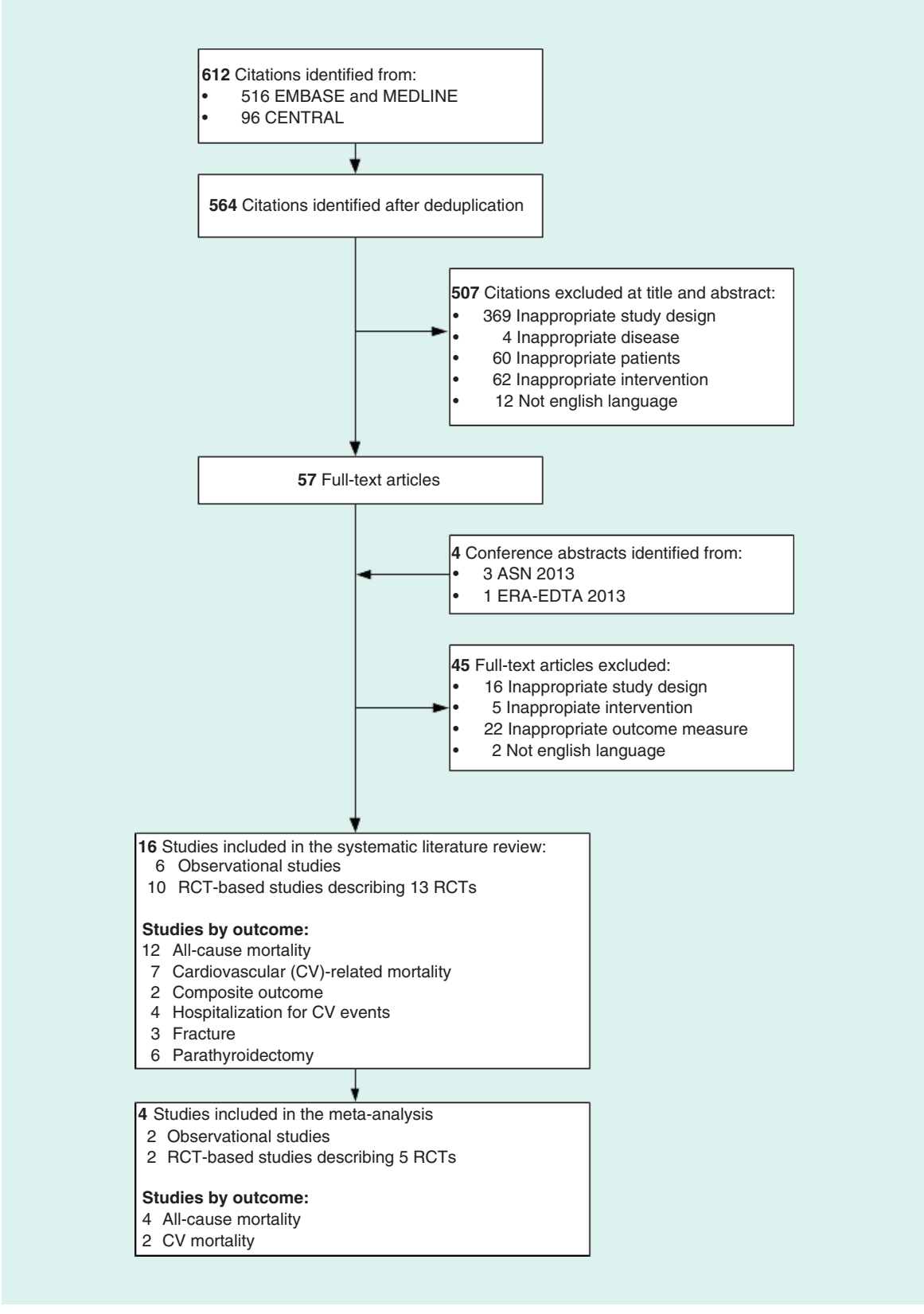

Figure 1. Flow diagram for study selection. Note: Searches conducted from database inception until 3 April 2014 for EMBASE and MEDLINE, and 10 April 2014 for CENTRAL.
RCT: Randomized-controlled trial.

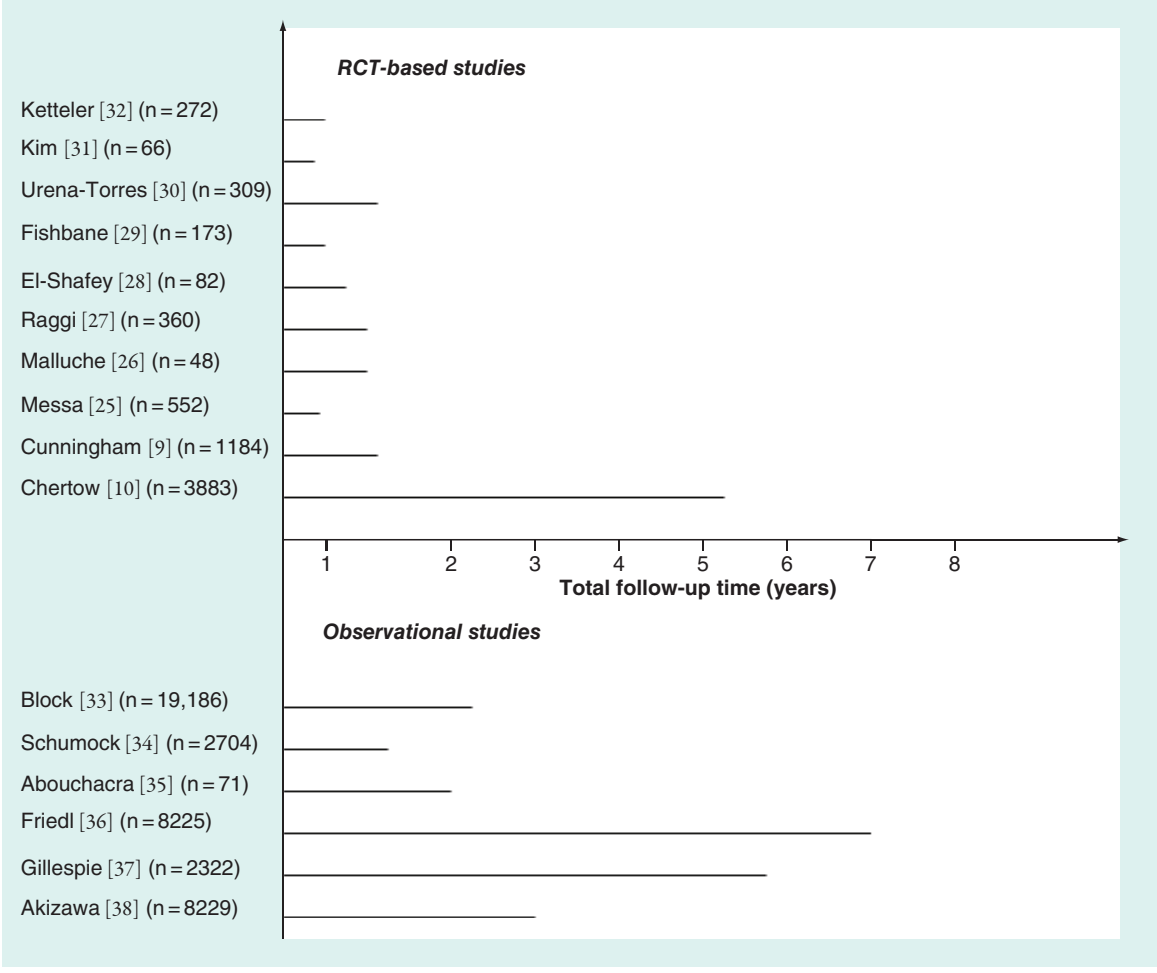

Figure 2. Duration (in years) of studies identified by the systematic literature review.

2014 (search date in MEDLINE and EMBASE) and until 10th April 2014 (search date in CENTRAL) to identify relevant articles. Abstracts from the 2012 and 2013 American Society of Nephrology and the European Renal Association and European Dialysis and Transplant Association conferences were also included. The search strategy is provided in the Supplementary Material.

Inclusion & exclusion criteria & study selection

Included studies were RCTs or observational studies that reported on relevant clinical outcomes in adult patients receiving maintenance dialysis (including hemodialysis and peritoneal dialysis). Therapies of interest included cinacalcet (with or without other concomitant therapies), vitamin D sterols, phosphate binders or both. Studies were excluded if the comparator was placebo alone.

Two authors independently screened the abstracts and full texts of all potentially eligible articles; disagreements between reviewers were resolved by a third reviewer. Both the Preferred Reporting Items for Systematic Reviews and Meta-analyses and Meta-analysis Of Observational Studies in Epidemiology checklists for the conduct of systematic literature review and meta-analysis were followed [12,13].

Data extraction & quality assessment

Two authors independently extracted data for study descriptors, baseline patient characteristics, dialysis type and vintage, characteristics of treatment, treatment discontinuation and clinical outcomes. A third author resolved any discrepancies. The authors of the original manuscripts were contacted for additional information as needed. Risk of bias in RCTs was assessed using the Cochrane Collaboration's tool [14]; and the quality of observational studies

Table 2. Baseline characteristics of patients for studies included in the meta-analysis.

Variable	Chertow		Cunningham		Block		Gillespie	
	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Noncinacalcet	Cinacalcet	Noncinacalcet
n	1948	1935	697	487	5976	13,210	532	1790
Age (year):								
– Median	55.0	54.0	–	–	–	–	67	67
– IQR (min, max)	35.0–74.0	35.0–73.0	–	–	–	–	–	–
– Mean	54.4	54.4	53.0	54.7	59.2	65.0	–	–
– SD	14.4	14.4	14.2	14.6	–	–	–	–
– Proportion of male (%)	58.5	60.3	61	63	51.8	54.6	59.0	58.9
Dialysis vintage (months):								
– Median	45.4	45.1	–	–	–	–	–	–
– IQR (min, max)	8.5–142.0	9.9–149.0	–	–	–	–	–	–
– Mean	–	–	65.8	70.1	52.8	42.0	16.3	14.6
– SD	–	–	59.9	67.1	–	–	11.7	11.3
CV comorbidities:								
– Hypertension	92.5	91.7	–	–	–	–	–	–
– Heart failure/CHF	23.1	23.6	–	–	40.6	48.9	–	–
– PVD	16.1	16.6	–	–	29.8	38.4	–	–
– MI	12.3	12.6	–	–	–	–	–	–
– CVA/ stroke/ TIA	8.3	10.0	–	–	13.3	18.8	–	–
– History of CVD	95.4	94.6	–	–	–	–	35.7	34.5
PTH (pg/ml):								
– Median	695	690	–	–	323	231	481	404
– IQR (min, max)	362–1707	363–1683			317-NR	187-NR	–	–
– Mean	–	–	731	682	–	–	–	–
– SD	–	–	531	399	–	–	–	–
Ca (mg/dl):								
– Median	9.8	9.8	–	–	–	–	9.0	8.9
– IQR (min, max)	9.0–10.7	9.0–10.7	–	–	–	–	–	–
– Mean	9.8	9.8	9.9	9.9	9.8	9.5	–	–
– SD	0.7	0.7	0.8	0.8	0.7	0.7	–	–

Ca: Calcium; CHF: Congestive heart failure; CV: Cardiovascular; CVA: Cerebrovascular attack; CVD: Cardiovascular disease; IQR: Interquartile range; MI: Myocardial infarction; NR: Not reported; PTH: Parathyroid hormone; PVD: Peripheral vascular disease; TIA: Transient ischemic attack; SD: Standard deviation.

was assessed using the Scottish Intercollegiate Guidelines Network [15]. We performed the bias assessment of each outcome using the Grading of Recommendations Assessment, Development and Evaluation guidelines (details provided in the Supplementary Material) [16].

Outcomes & effect measures

We extracted counts, rates and proportion of subjects undergoing each outcome events. We also extracted relative effect as hazard ratios with appropriate adjustments as reported in individual studies (covariate-adjusted or based on lag-censoring analyses) [1,2,17].

Data synthesis & analysis

To determine the adequacy of a meta-analysis, we assessed the heterogeneity across studies for patient characteristics and outcomes for studies that reported hazard ratios for all-cause and CV-related mortality. The hazard ratio is the preferred effect measure for synthesis for the meta-analysis because the proportional hazard assumption accommodates variable study durations. Hazard ratios had to either be reported by study authors or sufficient data

Table 3. Evidence summary from systematic literature review for all-cause mortality and cardiovascular-related mortality.

Study (year)	Reference arm	Percentage[†]		Relative risk[‡]	Hazard ratio		
		Cinacalcet	Reference	(95% CI)	Type	Value	(95% CI)
All-cause mortality – RCTs							
Chertow *et al.* (2012)	Placebo	36.1	37.1	0.97 (0.90–1.06)	Unadjusted	0.94	(0.85–1.04)
					Adjusted	0.86	(0.78–0.96)
					Lag censored	0.83	(0.73–0.96)
Cunningham *et al.* (2005)	Placebo	N/R	N/R	–	Unadjusted	0.81	(0.45–1.45)
Messa *et al.* (2008)	Placebo	3	3	0.92 (0.34–2.44)	N/R		
Malluche *et al.* (2008)	Placebo	9	13	0.75 (0.14–4.05)	N/R		
Raggi *et al.* (2011)	Placebo	6.7	6.7	1.00 (0.46–2.17)	N/R		
El-Shafey *et al.* (2011)	Noncinacalcet[§]	2	3.7	0.49 (0.03–7.55)	N/R		
Fishbane *et al.* (2008)	Vitamin D sterol	2	2	0.99 (0.14–6.86)	N/R		
Kim *et al.* (2013)	Noncinacalcet	0	0	–	N/R		
Ketteler *et al.* (2012)	Paricalcitol	0[¶]	1.6	–	N/R		
	Cinacalcet oral		0				
	Paricalcitol oral		4.2				
All-cause mortality – observational							
Block *et al.* (2010)	Noncinacalcet	19.2	30.7	0.43 (0.41–0.45)	Unadjusted	0.73	(0.68–0.78)
					Adjusted	0.74	(0.67–0.83)
Abouchacra *et al.* (2014)	Noncinacalcet	9.5	10	0.95 (0.29–3.17)	N/R		
Gillespie *et al.* (2015)	Noncinacalcet	15.8	16.6	0.95 (0.76–1.19)	Unadjusted	1.03	(0.78–1.35)
					Lag censored	0.84	(0.60–1.18)
Akiwaza *et al.* (2012)	Noncinacalcet	N/R	N/R	–	Adjusted	0.65	(0.52–0.81)
CV-related mortality – RCTs							
Chertow *et al.* (2012)	Placebo	19.4	20.2	0.96 (0.84–1.09)	Unadjusted	0.92	(0.80–1.07)
Messa *et al.* (2008)	Placebo	0.8	1.1	0.75 (0.13–4.45)	N/R		
Ketteler *et al.* (2012)	Paricalcitol	0[¶]	1.6	–	N/R		
	Cinacalcet oral		0				
	Paricalcitol oral		1.4				
CV-related mortality – observational							
Block *et al.* (2010)	Noncinacalcet	8.8	13.4	0.66 (0.60–0.72)	Unadjusted	0.78	(0.71–0.86)
					Adjusted	0.76	(0.66–0.86)
Abouchacra *et al.* (2014)	Noncinacalcet[#]	4.8	5	0.95 (0.17–5.45)	N/R		
Friedl *et al.* (2013)	Noncinacalcet	N/R	N/R	–	Unadjusted	0.76[††]	–
Akizawa *et al.* (2012)	Noncinacalcet	N/R	N/R	–	Adjusted	0.68	(0.48–0.98)

Note: Unadjusted rates were reported by Cunningham *et al.* to be 5.2 per 100 patient year in the cinacalcet arm versus 7.4 per 100 patient year in the placebo arm. Block *et al.* reported rates of 17.6 (95% CI: 16.6–18.6) per 100 patient year in the cinacalcet arm versus 23.0 (22.4–23.6) per 100 patient year in the placebo arm. Chertow *et al.* adjusted for age, sex, race, BMI, vintage, blood pressure, medical history, vitamin D, phosphate binders, CV medication and laboratory information (including calcium, phosphorus, and PTH among many others). Block *et al.* adjusted for age, sex, race, dialysis duration, BMI, primary cause of renal failure, co-morbidities, hospital days, vascular access and laboratory information (including calcium, phosphorus and PTH among many others). Akizawa *et al.* adjusted for calcium, phosphorus, PTH, VDRA, phosphate binder, albumin, BMI, age, sex, vintage, primary renal disease, CV morbidity and number of non-CV co-morbidities).

[†]Either reported or estimated from count of events.

[‡]Crude relative risks were calculated from data reported.

[§]Conventional therapy.

[¶]Cinacalcet intravenous.

[#]On vitamin D or analogs.

[††]Calculated relative risk at end of study using Kaplan–Meier curves was estimated to be approximately 0.76 from a figure.

CV: Cardiovascular; n: Number of patients who had the event; N: Number of patients in analysis; N/R: Not reported; PTH: Parathyroid hormone; RCT: Randomized controlled trial; VDRA: Vitamin D receptor activator.

Table 4. Risk of bias of the ten randomized controlled trial-based studies (12 randomized controlled trials) included in the systematic literature review.

Study (year)	Selection bias		Performance bias	Detection bias	Attrition bias	Analysis by ITT	Reporting bias	Other potential threats to validity	
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed		Selective outcome reporting	Imbalance in baseline characteristics	Intervention (misclassification of exposure, other)
Chertow *et al.* (2012)	Low	Low	Low	Low	Low	Low	Low	High	High
Cunningham *et al.* (2005)	–	–	–	–	–	–	–	–	–
Block *et al.* (2004)†	Low	Low	Low	Low	Unclear	Low	Low	Low	Low
Lindberg *et al.* (2003)†	Low	Low	Low	Low	Low	High	High	Low	Low
Lindberg *et al.* (2005)†	Low	Low	Low	Low	Low	High	High	Low	Low
Quarles *et al.* (2003)†	Low	Low	Low	Low	Low	High	High	Low	Unclear
Messa *et al.* (2008)	Unclear	Unclear	High	Low	Low	Unclear	Low	Low	High
Malluche *et al.* (2008)	Low	Low	Low	Low	High	High	Low	Low	Low
Raggi *et al.* (2011)	Unclear	Unclear	High	Low	Low	High	High	Unclear	Low
El-Shafey *et al.* (2011)	Unclear	Unclear	High	Low	High	High	Low	Low	Unclear
Fishbane *et al.* (2008)	Unclear	Unclear	High	Low	Low	Low	Low	Low	Unclear
Urena-Torres *et al.* (2013)	Low	Low	High	Low	Low	Low	Low	Low	Unclear
Kim *et al.* (2013)	Unclear	Unclear	High	Low	High	High	Unclear	Low	High
Ketteler *et al.* (2012)	Unclear	Unclear	High	Low	High	Low	Low	High	Low
Total low risk	6	6	5	12	7	5	8	9	5
Total unclear risk	6	6	0	0	1	1	1	1	4
Total high risk	0	0	7	0	4	6	3	2	3

An unclear risk was occasionally given due to a lack of reporting rather than due to a poorly conducted trial.
†RCTs by Block *et al.*, Lindberg *et al.* (2003), Lindberg *et al.* (2005) and Quarles *et al.* were included in the pooled analysis reported by Cunningham *et al.* Although the authors of the individual RCT studies did not report sequence generation and allocation concealment, Cunningham *et al.* stated that a computer-generated randomization system was used.
ITT: Intent-to-treat; RCT: Randomized-controlled trial.

Table 5. Risk of bias of the six observational studies included in the systematic literature review.

Study (year)	Internal validity				Overall assessment of study
	Selection of subjects	Assessment of outcomes	Confounding	Statistical analysis	
Block *et al.* (2004)	Low	Low	Low	Low	High quality
Schumock *et al.* (2011)	High	Low	High	Low	Acceptable
Abouchacra *et al.* (2014)	High	Unclear	High	Low	Acceptable
Friedl *et al.* (2013)	Low	Unclear	Low	Low	High quality
Gillespie *et al.* (2015)	High	Low	Low	Low	High quality
Akizawa *et al.* (2012)	Unclear	Unclear	Unclear	Unclear	Unknown

An unclear risk was occasionally given due to a lack of reporting rather than due to a poorly conducted trial.

Table 6. Grade assessment of the entire body of evidence included in the meta-analysis, in other words, observational studies and randomized-controlled trials.

Number of studies/study type	Quality assessment				Summary of findings			
	Limitations	Indirectness	Inconsistency	Imprecision	No. of patients		Relative effect	Quality of body of evidence (GRADE)
					Cinacalcet	Noncinacalcet	Unadjusted HR (95% CI)	
All-cause mortality – unadjusted hazard ratios								
Two RCTs	Some	None	None	Some	2645	2422	0.87 (0.71, 1.06)	Moderate
Two OBS	None	None	Some	Some	5976	13,120	–	–
Quality	+1	0	-1	-1	NA	NA	NA	–
CV-related mortality – unadjusted hazard ratios								
One RCT	Some	None	None	Some	1948	1935	0.84 (0.71, 0.99)	Moderate
One OBS	None	None	None	Some	5976	13,120	–	–
Quality	-1	0	0	-1	NA	NA	NA	–

CV: Cardiovascular; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HR: Hazard ratio; NA: Not applicable; OBS: Observational study; RCT: Randomized-controlled trial.

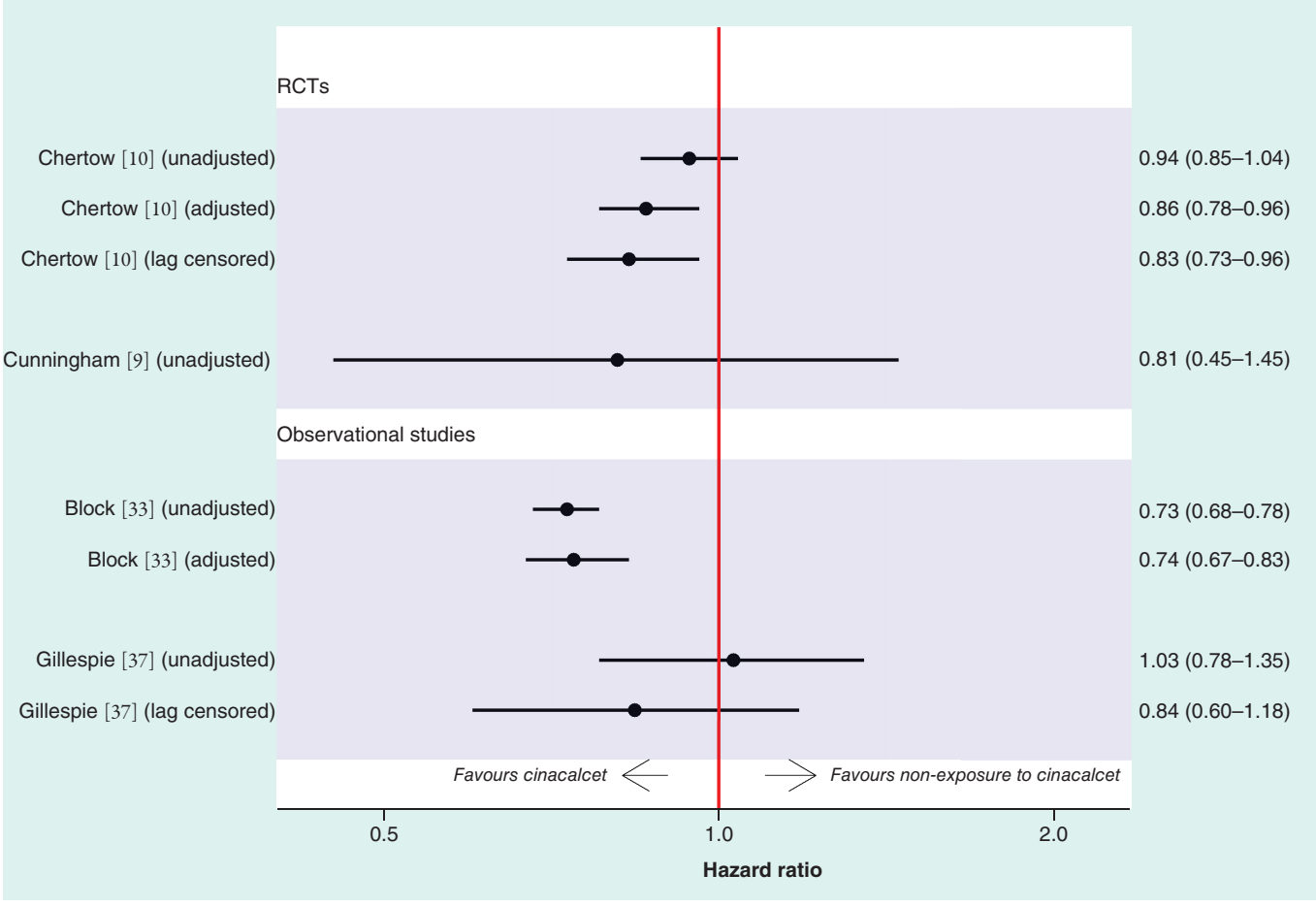

Figure 3. Evidence base for all-cause mortality.
RCT: Randomized-controlled trial.

reported to allow their calculation [18]. Kaplan–Meier curves were visually inspected to verify that the proportional hazard assumption was not violated.

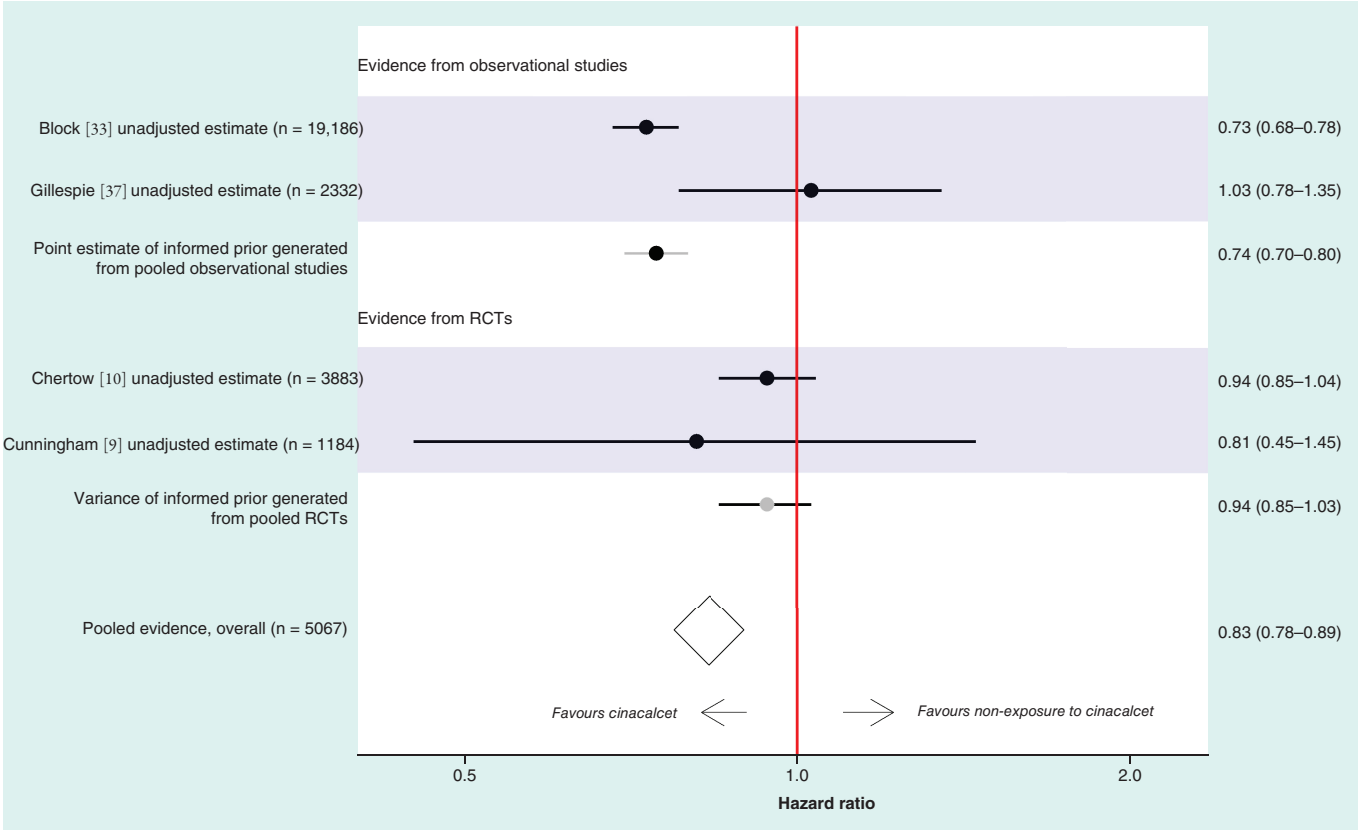

Figure 4. Bayesian meta-analysis of all-cause mortality evidence and evidence synthesis. Note: Prior belief of relative treatment effect was informed from point estimate obtained from the meta-analysis of observational studies, and variance obtained from the meta-analysis of randomized-controlled trials (black markers).
RCT: Randomized-controlled trial.

We reviewed published models for pooling evidence from both RCT and observational studies [19–21], and employed Sutton *et al.*'s approach [19] to allow evidence from observational studies to inform the prior belief on the relative treatment effect when pooling estimates from RCTs with Bayesian meta-analysis techniques.

The meta-analysis conducted here used an 'equivalent prior' on the relative treatment effect where both observational and RCT evidences were given equal weighting to inform the prior belief with respect to the relative treatment effect. The prior distribution of treatment effect was normally distributed, centered about the mean derived from meta-analyzed observational evidence, with variance informed from the meta-analyzed RCT evidence. The analysis was conducted using both a fixed and random effects framework. The fixed effect model was selected over the random effects model if any of the following conditions were met: it offered better model fit, based on the Deviance Information Criterion [22], and the posterior distribution of the between-studies variance was not updated from the prior distribution.

The meta-analysis was executed using Markov chain Monte Carlo techniques, using the interactive Windows version of Bayesian Inference using Gibbs Sampling Statistical Package [23]. We used unadjusted hazard ratios for our base-case analysis because those estimates were the most conservative with respect to the magnitude of the effect of cinacalcet on all-cause mortality. Two sensitivity analyses were conducted using hazard ratios from adjusted ITT and lag-censoring (i.e., discontinuation-adjusted) analyses, respectively, where available.

Results

Selection of studies

We identified 19 studies that met the eligibility criteria [3–5,10,24–38]; one article [9] reported *post hoc*-pooled analysis of one Phase II [24] and three Phase III RCTs [3–5], to simplify reporting, we refer to this as a single study (Figure 1).

Table 7. Meta-analysis results for base-case and sensitivity analyses, for outcome of all-cause mortality.

Analysis	Evidence	Random effects model				Fixed effect model		
		HR	(95% CI)	Between-study SD prior: uniform (0, 5)	DIC	HR	(95% CI)	DIC
Base – case analysis; using unadjusted HRs								
1	RCTs, informed prior of treatment effect	0.89	(0.23–3.36)	0.96 (0.02, 4.08)	-1.225	0.83	(0.78–0.89)	1.728
2	RCTs only	0.89	(0.05–16.43)	1.28 (0.02, 4.56)		0.94	(0.85–1.03)	
3	Observational studies only	0.86	(0.04–20.45)	1.47 (0.09, 4.62)		0.74	(0.70–0.80)	
SA; using adjusted HRs where available								
4	RCTs, informed prior of treatment effect	0.81	(0.21–3.02)	0.93 (0.02, 4.04)	-0.709	0.78	(0.71–0.86)	-2.256
5	RCTs only	0.82	(0.04–15.36)	1.26 (0.02, 4.55)		0.83	(0.73–0.95)	
6	Observational studies only	0.77	(0.05–13.18)	1.18 (0.02, 4.51)		0.73	(0.69–0.78)	
SA; using lag-censoring HRs where available								
7	RCTs, informed prior of treatment effect	0.85	(0.22–3.20)	0.93 (0.02, 4.06)	-1.234	0.81	(0.76–0.88)	-2.591
8	RCTs only	0.84	(0.05–15.69)	1.26 (0.02, 4.55)		0.86	(0.77–0.95)	
9	Observational studies only	0.86	(0.04–19.79)	1.44 (0.07, 4.61)		0.77	(0.70–0.85)	

DIC: Deviance information criterion; HR: Hazard ratio; RCT: Randomized clinical trial; SA: Sensitivity analysis; SD: Standard deviation.

All included studies investigated cinacalcet as add-on to standard therapy (i.e., vitamin D sterols, phosphate binders or both) compared with standard therapy alone.

Characteristics of studies included

Detailed study characteristics and study durations are described in Table 1 and Figure 2, respectively.

Mean age at study entry ranged from 48 to 67 years and mean dialysis vintage ranged from 7 to 79 months. The severity of sHPT as indicated by serum PTH (median: 231–695 pg/ml) and calcium concentrations (median: 8.9–9.8 mg/dl) varied across studies, as did the proportion and type of CV comorbidities. Baseline characteristics for the subset of studies included in the meta-analysis are provided in Table 2.

Outcomes of studies included in systematic literature review

The count or proportion of deaths from any cause, or the hazard ratio between study arms, was reported in 13 studies (Table 3). The underlying absolute event rate varied substantially across studies, which was associated with duration of follow-up (i.e., fewer deaths reported in shorter duration studies); however, in comparing the risk of death between study arms, the direction of association was consistently toward a protective effect of cinacalcet (one study reported a null effect with a point estimate of 1.00). In three studies – one RCT and two observational studies – investigators reported a significant effect size; however, in several cases this effect size was from a sensitivity analysis rather than a primary outcome.

Similar results were observed in the seven studies reporting on CV-related mortality (Table 3): the directions of effect estimates consistently indicated a protective effect of cinacalcet, although the findings were statistically significant in only two of the six studies reporting this outcome.

Two studies reported evidence for the composite outcome of all-cause mortality or CV event. In both studies, the effect estimate indicated a significant beneficial effect of cinacalcet relative to standard of care: the hazard ratio was 0.67 (95% CI: 0.52–0.85) in one (observational) study, [38] and 0.88 (95% CI: 0.79–0.97) in the adjusted analysis of the EVOLVE RCT (of note: in the unadjusted analysis of the EVOLVE study, the hazard ratio was not significantly different from 1.0) [10].

The relative risk of CV events was reported in three studies, and one other study looked at the risk of hospitalization for CV events. In the pooled analysis of RCTs by Cunningham *et al.*, the risk of hospitalization for CV events

was significantly lower in the cinacalcet arm compared with the standard of care arm (unadjusted hazard ratio: 0.61; 95% CI: 0.43–0.86) [9]. Similarly, there were significantly fewer CV events in the cinacalcet arm than in the control cohort in the retrospective observational study by Abouchacra *et al.* (33.3 vs 67.5%, p = 0.001) [35]. In the EVOLVE RCT, cinacalcet resulted in a nominally significant beneficial effect over standard of care for heart failure [10]. For myocardial infarction, unstable angina and peripheral vascular events (other nonfatal components of the primary composite end point), results suggested a protective effect of cinacalcet (hazard ratios ranging from 0.82 to 0.97); however, none reached statistical significance [10]. The RCT by Keteller *et al.* reported higher rates of serious CV events in the noncinacalcet arms (3.1% in the cinacalcet/IV vitamin D and 1.4% in the cinacalcet/oral vitamin D stratums vs 9.7% in the paricalcitol/IV vitamin D and 8.3% in the paricalcitol/oral vitamin D stratums) [32].

In the three studies reporting on fracture, the risk was generally lower in RCT arms involving cinacalcet. In the pooled trials reported by Cunningham *et al.*, this finding was statistically significant with a hazard ratio of 0.46 (95% CI: 0.22–0.95) [9]. In EVOLVE, an analysis adjusted for baseline characteristics showed a significant reduction among cinacalcet users; the hazard ratio was 0.83 (95% CI: 0.72–0.98) [39]. El-Shafey *et al.* reported a lower rate of lower extremity fractures in patients randomized to cinacalcet compared with standard of care (3.8 vs 19.2%, respectively) [28].

The direction of association for the outcome of parathyroidectomy tended toward a lower risk in the cinacalcet arm in five of the six studies reporting this outcome; the finding was statistically significant in the two studies that reported a p-value. In contrast, in the analysis of administrative claims data, Schumock *et al.* reported an increased risk of parathyroidectomy associated with cinacalcet compared with paricalcitol (adjusted hazard ratio = 0.21 for paricalcitol vs cinacalcet; $p < 0.001$), perhaps related to the severity of sHPT [34].

The results of the quality assessment of RCTs, observational studies and meta-analyses are provided (Tables 4–6, respectively).

Bayesian meta-analysis of all-cause mortality

Four studies (two based on RCTs [9,10] and two observational [33,37]) reported hazard ratios as the measure of effect and thus were suitable for inclusion in the meta-analysis. Tests of heterogeneity indicated that studies could validly be combined in meta-analysis. In the remaining studies, outcomes were reported as counts, proportions or rates, and did not provide the requisite data for the calculation of hazard ratios.

Unadjusted and adjusted estimates from the contributing RCTs and observational studies are presented in Figure 3 as well as an estimate based on a lag-censoring analysis reported by Chertow *et al.* [10]. All estimates were either statistically significant in favor of a reduced hazard associated with cinacalcet, or not significantly different versus standard of care.

The estimated hazard ratio from the base-case meta-analysis was 0.83 (0.78, 0.89), indicative of a statistically significant reduction in the risk of death associated with cinacalcet compared with standard therapy. The contributing evidence is fully described in Figure 4, including the pooled estimates generated from RCTs alone and from the observational studies alone, as well as the evidence that was borrowed from each to inform the prior belief of treatment effect. The estimate from the base-case model was consistent with those obtained through sensitivity analyses (Table 7) including: the random effects models (a fixed effect model was selected in the base case, as there were not sufficient data to estimate the between-study variance under the random effects model); scenarios where adjusted and hazard ratios based on lag-censoring analyses were used when available (Table 7, analyses 4 and 7).

Bayesian meta-analysis of CV-related mortality

There was only one RCT and one observational study available for inclusion in the CV-related mortality meta-analysis. The meta-analysis was run using these two studies: the estimate from the single RCT by Chertow *et al.* [10] was updated through a prior distribution of the treatment effect informed by evidence from the observational study by Block *et al.* [33]. The resulting hazard ratio from the fixed effect model was 0.91 with CI (0.79–1.05), indicating a nonsignificant protective effect of cinacalcet on CV-related mortality.

Bayesian meta-analysis of other outcomes

There was insufficient evidence to conduct meta-analyses on the composite outcome of all-cause mortality and CV events, or on the outcomes of hospitalization for CV events, fracture or parathyroidectomy.

Discussion

This is the first systematic literature review and quantitative synthesis that includes evidence from both RCTs and observational studies on the effects of cinacalcet on all-cause and CV-related mortality, hospitalization for CV events, fracture and parathyroidectomy, among patients with sHPT-receiving maintenance dialysis. The findings of our study provide additional evidence that cinacalcet may be associated with a lower risk of mortality among patients receiving maintenance dialysis.

By design, each of the RCTs of cinacalcet was insufficient to detect differences in clinical outcomes; however, by pooling results from several study types, the power to estimate the hazard ratio within the initial time window was increased. To reduce the risk of bias, investigators of the observational studies employed strategies for adjusting for known confounders and the observational studies that were included into the meta-analysis were assessed as having low risk of confounding bias, and overall high quality [33,37]. Thus, coupling these high-quality observational studies with the pooled power from the individual RCTs provided the strongest possible evidence base upon which to assess the effects of cinacalcet on clinical outcomes.

The benefits and risks of cinacalcet therapy in adults with end-stage renal disease (ESRD) have been previously meta-analyzed [40,41]. However, only randomized studies have been included. For all-cause mortality, Palmer *et al.* [40] reported a relative risk of 0.97 (0.89, 1.05); Zhang *et al.* [41] reported an odds ratio of 0.86 (0.46, 1.60), each of which is consistent with the findings of our study. Many of the studies included in the meta-analyses by Palmer *et al.* and Zang *et al.* could not be included in our meta-analysis, because they did not report hazard ratios, which were our selected outcomes.

This study has several strengths. First, we adopted a state-of-the-art and rigorous approach to assess the quality of the evidence and the feasibility of combining observational and RCT evidence in a meta-analysis. The systematic literature review identified all published evidence for the outcomes of interest in a well-defined adult patient population (i.e., patients with ESRD receiving maintenance dialysis). Second, the meta-analysis was conducted using appropriate statistical techniques that allowed for the incorporation of all available evidence to inform an estimate of the effect of cinacalcet, compared with standard of care, in reducing all-cause and CV-related mortality for individuals with ESRD who are on maintenance dialysis. We selected unadjusted hazard ratios for the base-case analysis to adopt a conservative approach to the estimate of effect as adjusted estimates from included studies tended to show a stronger treatment effect. We reported the impact of this choice in sensitivity analyses. Additionally, to reduce variability arising from different study durations, we included the hazard ratio as the preferred measure of effect. While there are methodologies that allow for combining count and hazard ratio statistics [42], we chose not to combine the two types of evidence here. Hazard ratios are ideally suited to describe the prolongation in time-to-event [18], which is the relevant effect for cinacalcet; while a binary measure would imply assessing the effect of cinacalcet with regard to prevention of death. However, few studies reported the outcomes as hazard ratios, which in turn, limited our ability to: conduct a more robust statistical analysis directly incorporating evidence from observational studies in the meta-analysis [19] rather than via a prior distribution; estimate the between-study variance, under a random effects model; and explore sources of heterogeneity through covariate adjustment [21].

The main limitation lies in the evidence base itself. Randomized trials of this question have provided lessons about future trials of patients on dialysis on end points, analytic strategies including the need to account for effect modification, power and sample size after accounting for crossover, nonadherence and cointerventions, and interpretation of the findings [43].

We synthesized all available evidence on the effect of cinacalcet on all-cause and CV-related mortality; however, due to the limited reporting of outcomes on the hazard ratio scale, we were only able to incorporate 4 out of the 16 studies into a quantitative estimate of the estimated effect of cinacalcet and overall mortality, and only two studies into an estimate for CV-related mortality. While the identified evidence suggests that cinacalcet does provide a protective effect, more studies (or more data from the existing studies) are needed to reach a statistically significant result from a quantitative synthesis, under a random effect model, which we considered, *a priori,* a more appropriate model.

Conclusion

The results of this meta-analysis indicate that treatment of sHPT with calcimimetic therapy may in fact reduce mortality among patients receiving maintenance dialysis. This finding provides justification for a well-designed and adequately powered randomized trial to definitively address the question.

Summary points

- Traditional meta-analyses of clinical evidence include only randomized controlled trials (RCTs) for the summary measures.
- Key limitations of RCTs include a threat to external validity and, often, lack of power to demonstrate effects on hard outcomes such as hospitalizations and mortality; well-designed observational studies can help address these limitations.
- Including evidence from well-designed observational studies can help overcome the limitations of traditional meta-analyses to provide more robust estimates of effect in real-world populations.
- This study aimed to quantitatively summarize studies of the real-world effects of a calcimimetic therapy on clinical outcomes among patients on dialysis including RCTs and observational studies using the Bayesian approach.
- The combined estimate of effect suggests potential survival improvement associated with calcimimetic therapy.
- When limited data are available from RCTs, a thoughtful evidence synthesis from trials and well-designed observational studies can aid in medical decision-making.

Author's contributions

All the authors contributed to manuscript writing, critical revision and final review of the manuscript. ME Bensink, GA Block, GM Chertow, ML Trotman, K Cooper and V Belozeroff contributed to the conception and design of the study. G Lozano-Ortega, S Goring, H Bennett and AR Levy contributed to the conception and design of the study, development of the search strategy and data extraction forms, and study selection process. N Waser contributed to the development of the search strategy and data extraction forms, and study selection process.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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