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Original Article

ORIGINAL ARTICLE

Active vitamin D increases the risk of hypercalcaemia in non-dialysis chronic kidney disease patients with secondary hyperparathyroidism: a systematic review and meta-analysis

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ABSTRACT

Background. This study evaluates the effects of active (1α-hydroxylated) vitamin D (AVD) therapy on hypercalcaemia in patients with non-dialysis chronic kidney disease (ND-CKD) and secondary hyperparathyroidism (SHPT).

Methods. A systematic search of the PubMed, Embase and Cochrane Library databases (up to 14 May 2020) was performed to identify randomized, placebo-controlled trials of single-agent, oral AVD therapies in adults with ND-CKD and SHPT. Only studies with ≥30 participants per arm and ≥6 weeks in duration were eligible. The outcome of interest was the number of subjects with an episode of hypercalcaemia. A meta-analysis of eligible studies was conducted using Comprehensive Meta-Analysis software (version 3.0).

Results. Six studies (five evaluating paricalcitol, one evaluating alfacalcidol) involving 799 patients were identified. Treatment durations ranged from 16 weeks to 2 years. The weekly doses of paricalcitol administered were 7 (three studies) and 14 μg (two studies); the weekly dose of alfacalcidol was 1.75–7.0 μg. Across all studies, rates of hypercalcaemia were 1.1–43.3% with AVD versus 0–3.4% with placebo. Meta-analysis of the six studies showed that AVD was associated with a 6.6-fold greater probability of hypercalcaemia versus placebo (odds ratio: 6.63, 95% confidence interval: 2.37, 18.55; $P < 0.001$). Two separate sensitivity analyses (one excluded a study identified as having a high risk of bias; the second excluded two studies that accounted for a large proportion of observed hypercalcaemia events) indicated the primary meta-analysis findings were robust.

Conclusions. Compared with placebo, AVD significantly increased the risk of hypercalcaemia among ND-CKD patients with SHPT.

Keywords: alfacalcidol, calcium, kidney failure, parathyroid hormone, paricalcitol, randomized-controlled trials, SHPT, vitamin D deficiency

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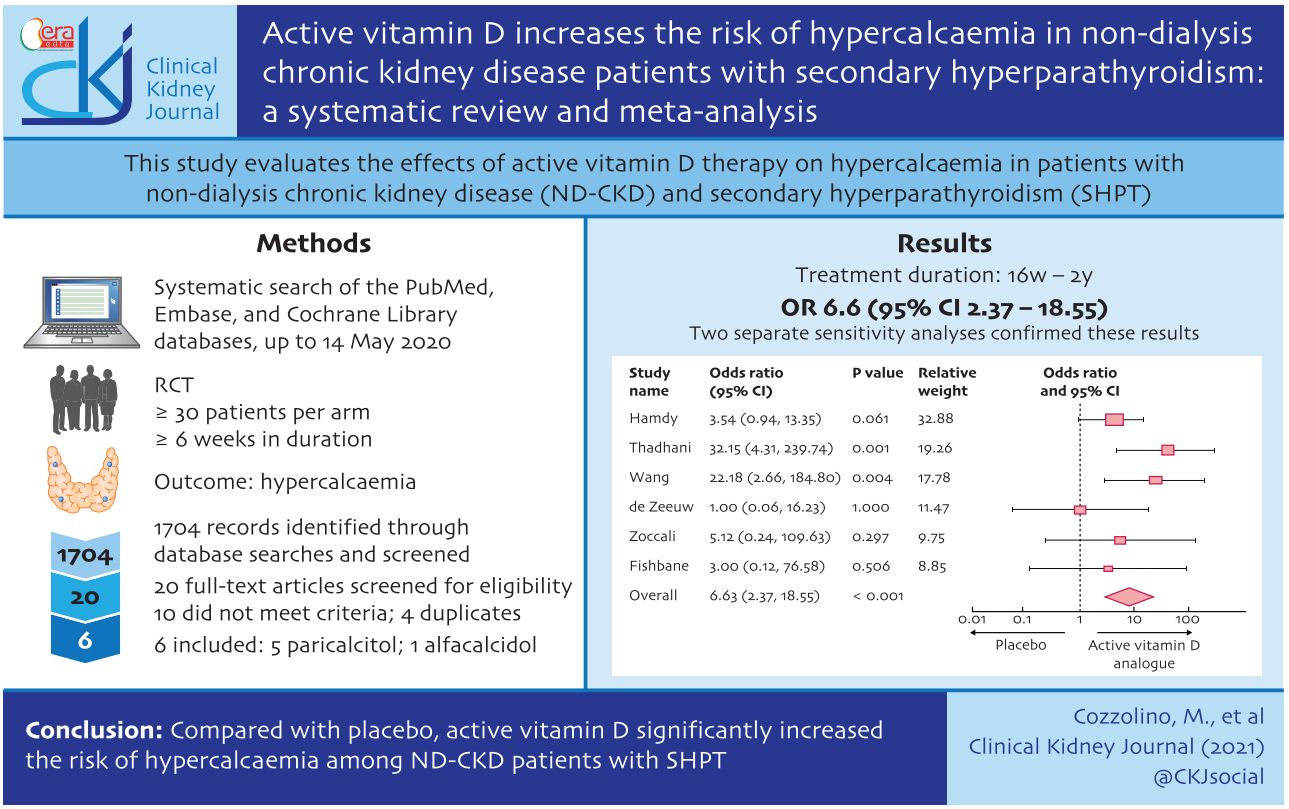
GRAPHICAL ABSTRACT



INTRODUCTION

Secondary hyperparathyroidism (SHPT), characterized by the excessive secretion of parathyroid hormone (PTH) by the parathyroid glands, is a frequent complication in patients with chronic kidney disease (CKD) [1, 2]. The prevalence and severity of SHPT increase with worsening kidney function, and it affects 40–82% of individuals with Stage 3 and 4 CKD [2]. SHPT is a key component of CKD-mineral bone disorder (CKD-MBD) [3], and sustained elevations in serum PTH can lead to bone disease and vascular and valvular calcification, increasing the risk of fractures, cardiovascular disease and mortality [2, 3].

The pathogenesis of SHPT is complex and involves several factors, including hypocalcaemia, phosphate retention and associated increases in serum fibroblast growth factor 23 (FGF23) and vitamin D insufficiency [3]. Vitamin D [25-hydroxyvitamin D (25D)] insufficiency is prevalent in patients with CKD and plays a major role in the development of SHPT [2]. 25D is converted into the active form of vitamin D [1,25-dihydroxyvitamin (1,25D)] by the cytochrome P450 enzyme, 1-alpha-hydroxylase (CYP27B1), in the kidney and other tissues [2]. Hence, low serum 25D concentrations contribute to reduced 1,25D levels by providing less substrate for conversion. 1,25D levels also progressively decrease as kidney function declines due to reduced renal CYP27B1 expression [1, 2]. Increases in FGF23 also worsen SHPT by reducing 1,25D production in the kidney through inhibition of CYP27B1 expression, and inducing the expression of another cytochrome enzyme, 24-hydroxylase (CYP24A1), which catalyses the deactivation of 1,25D [1, 4]. 1,25D reduces plasma PTH levels through its interactions with the vitamin D receptor in the parathyroid glands, and concomitantly increases the intestinal absorption of calcium. Consequently, decreased serum 1,25D levels lead to reductions in serum calcium and excessive PTH secretion.

One approach for the management of SHPT in CKD patients is treatment with calcitriol and active (1α-hydroxylated) vitamin D (AVD) analogues. Randomized-controlled trials (RCTs) have demonstrated that AVD therapies are effective for the suppression of PTH levels in patients with non-dialysis CKD (ND-CKD) and SHPT [5–7]. However, these studies have also shown that AVD frequently raises serum calcium levels, increasing the risk of these patients developing hypercalcaemia [5–7]. For this reason, the 2017 Kidney Diseases: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Diagnosis, Evaluation, Prevention and Treatment of CKD-MBD [3] does not suggest the routine use of calcitriol and AVD for the treatment of SHPT in ND-CKD patients. This suggestion was primarily based on findings from two RCTs [the PRIMO (Paricalcitol Capsule Benefits in Renal Failure-Induced Cardiac Morbidity) [6] and OPERA (Oral Paricalcitol in Retarding Cardiac Hypertrophy, Reducing Inflammation and Atherosclerosis) [7] studies], both of which reported a significantly increased risk of hypercalcaemia with paricalcitol versus placebo in ND-CKD patients. The purpose of

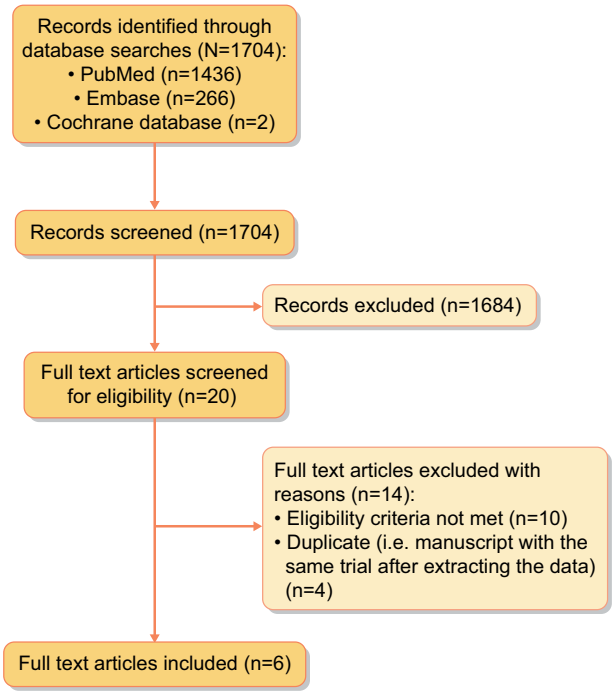


FIGURE 1: PRISMA flow diagram of the RCTs included in the meta-analysis.

this systematic literature review and meta-analysis was to evaluate all available published randomized, placebo-controlled clinical trials of AVDs in patients with ND-CKD and SHPT, in order to better determine the risk of hypercalcaemia with these agents.

MATERIALS AND METHODS

Search strategy

The systematic literature review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (http://www.prisma-statement.org/). PubMed, Embase and the Cochrane library databases were searched from inception to 14 May 2020 using the following keyword terms (alternative spellings were also considered): 'calcitriol' OR 'paricalcitol' OR 'alfacalcidol' OR '1 hydroxycholecalciferol' OR 'doxercalciferol' AND 'chronic kidney disease' OR 'kidney disease' OR 'kidney failure' OR 'kidney insufficiency' OR 'kidney function' OR 'kidney dysfunction' OR 'renal disease' OR 'renal failure' OR 'renal insufficiency' OR 'renal function' OR 'renal dysfunction'. The literature search was limited to articles reporting RCTs.

Screening and bias risk assessment of eligible studies

The results (article titles and abstracts) were independently assessed for inclusion by two reviewers. Relevant articles were selected based on predefined inclusion and exclusion criteria. Studies were included if they were randomized, double-blind, placebo-controlled trials in adults with ND-CKD and SHPT, evaluating single-agent AVD, with ≥30 participants per arm, ≥6 weeks in duration and specified the number of patients exhibiting hypercalcaemia per arm, deemed as related or possibly related to the study drug by the investigator. Single-dose studies, trials with unknown numbers of randomized patients or patients who required dialysis or renal transplant at baseline, and studies reporting pooled analyses of multiple RCTs, were excluded. If there was uncertainty about the eligibility of a study, both reviewers checked the inclusion and exclusion criteria against the full text article.

For articles that met all the inclusion criteria and none of the exclusion criteria, relevant information relating to the outcome of interest was extracted from the full article and collated for data analysis. The risk of bias of each included study was independently evaluated by both reviewers using methodology defined by the Cochrane Collaboration [8].

Outcome of interest

The outcome of interest was the number (%) of patients with hypercalcaemia deemed as related, or potentially related, to the study drug by the trial investigator.

Statistical analysis

Statistical analysis was performed using Comprehensive Meta-Analysis software version 3.0 (Biostat, Inc.). The odds ratio (OR) and its 95% confidence intervals (CIs), in addition to the combined OR and corresponding 95% CI, were calculated using only eligible studies. Heterogeneity in effect sizes across the studies was assessed using: Cochran's Q-statistic; I^2 index and Tau-squared (T^2).

RESULTS

Included studies

Overall, 1704 articles were identified by the search, of which six studies were eligible for inclusion in the meta-analysis (Figure 1). Details of these trials [6, 7, 9–12] are shown in Table 1. Five of the studies evaluated paricalcitol, while one study evaluated alfacalcidol. Overall, a total of 799 patients were involved in the studies and the number of patients per treatment arm ranged from 30 to 115. The duration of the studies ranged from 16 weeks to 2 years. The weekly doses of paricalcitol were 7 (three studies) and 14 μg (two studies), while the weekly dose in the alfacalcidol study ranged from 1.75 to 7.0 μg.

Across the six studies, events of hypercalcaemia were reported among 1.1–43.3% patients treated with AVD therapy versus 0–3.4% patients receiving placebo. The risk of bias assessment identified the study by Fishbane *et al.* [10] as having a 'high risk' of bias owing to the large proportion of randomized patients in this trial who were untreated or lost to follow-up (Table 1).

Primary analysis

The primary meta-analysis was performed on all six included studies. The results showed that patients with ND-CKD and SHPT treated with AVD were at a significantly increased risk of hypercalcaemia, compared with those treated with placebo ($P < 0.001$). There was a 6.6-fold greater probability of hypercalcaemia versus placebo (OR: 6.63; 95% CI: 2.37, 18.55) (Figure 2A).

Sensitivity analyses

Two sensitivity analyses were performed to test the robustness of the results from the primary meta-analysis of all six included studies.

One sensitivity analysis excluded the study by Fishbane *et al.* [10], which was identified as having a 'high risk' of bias. This analysis found that treatment with AVD was associated with a

Table 1. Overview of the RCTs included in the meta-analysis

Study	AVD (weekly dose, μg)	Study duration	Definition of hypercalcaemia	Baseline iPTH l evels (ng/L)[b]		Patients, *n*		Patients experiencing hypercalcaemia (%)		High risk of bias identified
				AVD	Placebo	AVD	Placebo	AVD	Placebo	
Hamdy [9]	1-Alfacalcidol (1.75–7.0)	2 years	Two consecutive Ca^{2+} values >2.63 mmol/L	97 ± 150	60 ± 43	89	87	11.2	3.4	No
Zoccali [12]	Paricalcitol (14)	16 weeks	Serum Ca^{2+} >2.75 mmol/L	102 (81–146)	102 (85–154)	45	44	4.4	0	No
Wang [7]	Paricalcitol (7)	52 weeks	Serum Ca^{2+} value >2.55 mmol/L	156 (108–235)	129 (121–176)	30	30	43.3	3.3	No
Thadhani [6]	Paricalcitol (14)	48 weeks	Two consecutive Ca^{2+} values >2.62 mmol/L	100 (66–174)	106 (71–153.5)	115	112	22.6	0.9	No
de Zeeuw [11]	Paricalcitol (7)	32.6 weeks	Two consecutive Ca^{2+} values >2.62 mmol/L	66 (48–120)	75 (46–114)	93	93	1.1	1.1	No
Fishbane[a] [10]	Paricalcitol (7)	6 months	Not specified	72.5 ± 43.7	72.7 ± 48.5	31	30	3.2	0	Yes

[a]One article identified with a high risk of bias. [b]Values displayed are mean ± standard deviations or median (interquartile range). AVD, active vitamin D; iPTH, intact parathyroid hormone.

7.2-fold greater probability of hypercalcaemia versus placebo (OR: 7.22; 95% CI: 2.21, 23.60; P = 0.001) (Figure 2B).

Evaluation of heterogeneity in effect sizes across all studies showed the two trials by Thadhani *et al.* [6] (PRIMO) and Wang *et al.* [7] (OPERA) accounted for a large proportion of the observed number of hypercalcaemia episodes. Therefore, a sensitivity analysis excluding these two RCTs was also performed. The results of this analysis showed the risk of hypercalcaemia was 3.0-fold greater in patients receiving AVD analogues versus placebo (OR: 3.03; 95% CI: 1.06, 8.71; P = 0.039) (Figure 2C).

DISCUSSION

This meta-analysis showed that, compared with placebo, treatment with AVD therapy significantly increased the risk of hypercalcaemia among ND-CKD patients with elevated PTH. The overall ORs from each meta-analysis ranged from 3.03 to 7.22 in favour of treatment with placebo. Overall, these findings support the current KDIGO clinical guideline suggestions [3] that AVD therapy should not be used for the routine treatment of SHPT in this patient population due to the greater risk of hypercalcaemia.

The two RCTs that formed the basis of these KDIGO guideline suggestions [3] relating to the use of AVD therapy in ND-CKD (PRIMO [6] and OPERA [7]) were included in this meta-analysis. It is important to note that the primary objective of these studies was to evaluate the efficacy of paricalcitol for treatment of left ventricular hypertrophy (LVH) in ND-CKD patients, rather than to specifically assess its PTH-lowering effects. Nonetheless, both trials enrolled patients with mild SHPT and demonstrated that paricalcitol provided effective reductions in PTH, but with a significantly higher rate of hypercalcaemia versus placebo [6, 7]. The findings from these studies led the KDIGO guidelines to suggest that routine use of AVD therapy should be avoided in patients with ND-CKD, and reserved only for severe and progressive SHPT [3]. It is also noteworthy that high doses of paricalcitol were used for the treatment of LVH in PRIMO and OPERA (up to 2 μg/day) [6, 7], and that lower doses may be administered for control of SHPT in clinical practice. Consequently, the risk of treatment-related hypercalcaemia with paricalcitol may be lower in the real-world setting. However, it is unclear whether lower doses of paricalcitol would still provide similarly effective levels of PTH suppression. Overall, the PRIMO and OPERA studies provided 287/799 (36%) of patients included from the six studies and contributed 41.55% of the relative weight to the primary analysis (Figure 2A). However, a sensitivity analysis excluding these two studies still showed an OR above 1.0 (3.03) in favour of placebo. Although they did not favour placebo as greatly as PRIMO and OPERA, none of the other four RCTs included in the meta-analysis had an OR below 1.0, supporting the outcome of the primary meta-analysis.

The relative impact of treatment-related hypercalcaemia on the PTH-lowering clinical benefits of AVD therapy remains to be determined. Nevertheless, the ability to reduce PTH levels without an accompanying increase in serum calcium is desirable given that uncontrolled PTH levels and increased serum calcium are both associated with worse clinical outcomes [13–21]. Observational studies show that elevated PTH levels are associated with an increased risk of cardiovascular disease, bone disease and mortality in ND-CKD patients [13, 16, 18–20], while prolonged SHPT may lead to parathyroid gland hyperplasia and eventually require parathyroidectomy [1, 22]. Similarly, numerous studies have reported a link between higher serum calcium and an increased risk of cardiovascular events and mortality in CKD patients [14, 15, 17, 21], and consequently the KDIGO guidelines suggest that hypercalcaemia should be avoided in adults with CKD G3a–G5D [3].

It should be noted that the use of calcium-based phosphate binders or calcium supplements was permitted in some of the trials included in our meta-analysis [7, 9]. Therefore, it is possible that the concomitant use of these agents together with AVD therapy may have contributed toward some of the recorded hypercalcaemia events in these studies.

The results of the present study are consistent with a prior meta-analysis by Li *et al.* [5], which showed that treatment with AVD (paricalcitol) was associated with an increased risk of

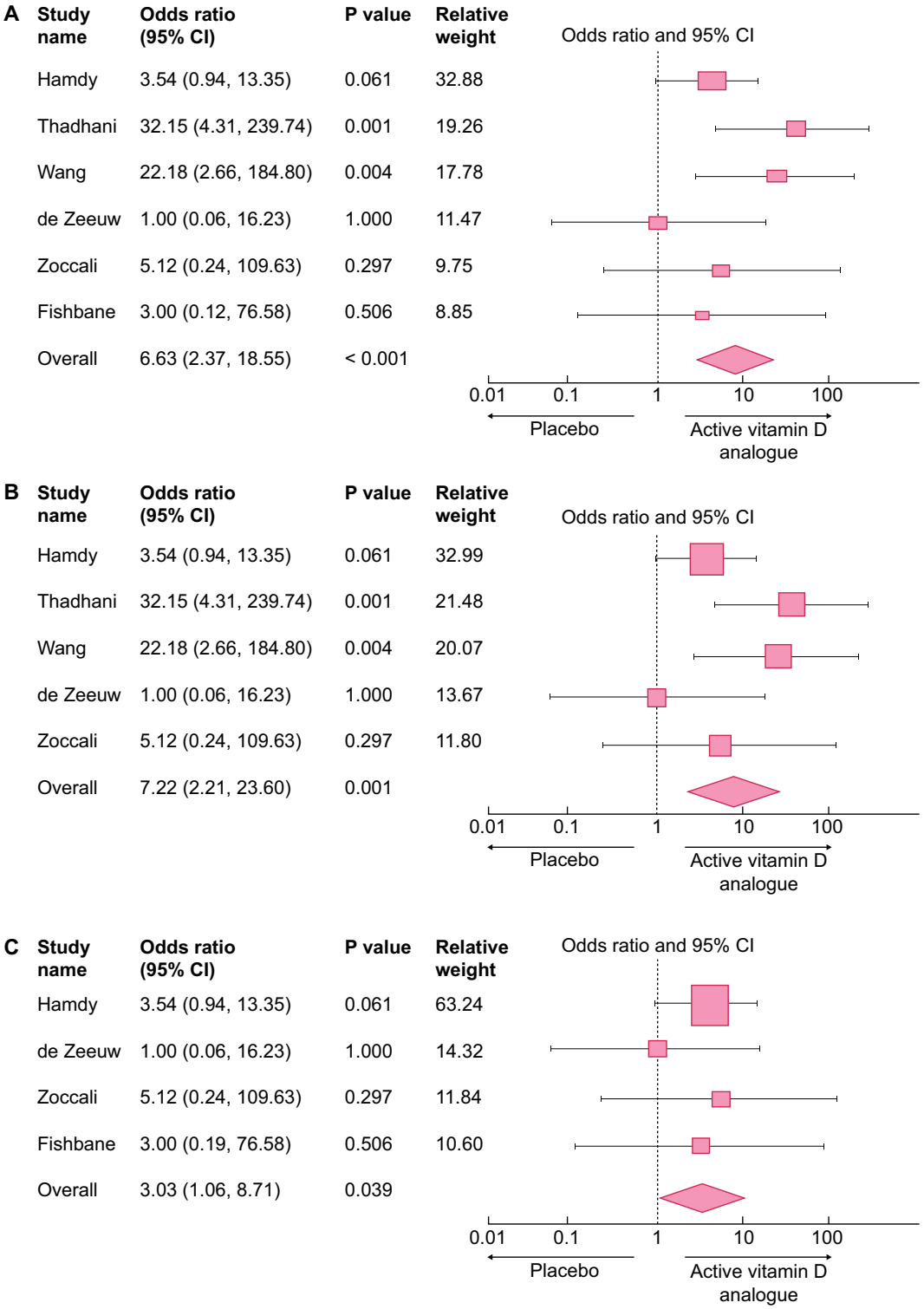


FIGURE 2: Forest plots showing significantly greater risk of hypercalcaemia[a] with AVD analogues versus placebo for (A) primary analysis ($n = 6$ studies), (B) sensitivity analysis ($n = 5$ studies)[a] and (C) sensitivity analysis ($n = 4$ studies).
[a]Sensitivity analysis excluded the study by Fishbane *et al.* [10], which was identified as having a 'high risk' of bias during the bias assessment. [b]Sensitivity analysis excluded two studies [6, 7], which accounted for a large proportion of the observed number of hypercalcaemia events.

hypercalcaemia versus placebo in ND-CKD (risk ratio 7.85; 95% CI: 2.92, 21.10). Their analysis was performed using data from four RCTs [6, 7, 10, 11], all four of which were also included in the present analysis.

This systemic literature review aimed to capture all relevant published RCTs evaluating the effects of AVD versus placebo on hypercalcaemia in patients with ND-CKD and SHPT. However, it is important to note that a study reporting the results of three

pivotal placebo-controlled trials of paricalcitol was not included in our study [23]. This was because it was a pooled analysis of the three studies and did not report the necessary parameters from the individual trials to allow their inclusion in this study. The incidence of hypercalcaemia observed with paricalcitol in these pooled trials (2%) [23] was lower in comparison with the other studies of paricalcitol included in the present meta-analysis [6, 7, 10–12]. Had these trials been analyzed separately and therefore been eligible for inclusion in the present analysis, the magnitude of overall effect size favouring placebo would likely have been lower.

The present meta-analysis had a number of limitations, including the small number of studies, the heterogeneity of the study designs and the lack of control for confounding factors. Future analyses of real-world data may help overcome a number of these limitations because this could enable a larger and broader population to be evaluated.

In conclusion, this systematic review and meta-analysis showed that AVD significantly increases the risk of hypercalcaemia among ND-CKD patients with SHPT. These observations highlight the urgent need for new treatments for SHPT in patients with ND-CKD that effectively reduce PTH levels, while avoiding undesired elevations in serum calcium.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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AUTHORS' CONTRIBUTIONS

P.A.C. and L.B. devised the concept and design for the study. L.B. performed the data collation and statistical analysis. All authors contributed towards the interpretation of the data, manuscript development and revising it critically for intellectual content, and finally, read and approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

M.C. has received research grants from AbbVie, Shire, Baxter and Keryx, as well as speaker's honoraria for the participation in scientific meetings from Amgen, Shire, AbbVie, Vifor Pharma and Baxter. L.B. and P.A.C. are employees of Vifor Pharma Ltd. Some of the data reported in this article were previously presented at a scientific congress [24]. An overview of the key results from this poster was also reported in the following abstract summary article: Addressing unmet needs in the treatment of hyperparathyroidism in patients with non-dialysis chronic kidney disease [*EMJ Nephrol* 2020; 8 (Suppl 3): 2–10].

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