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Original Article

Effect of oral vitamin D analogs on mortality and cardiovascular outcomes among adults with chronic kidney disease: a meta-analysis

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Abstract

Background. Vitamin D deficiency is highly prevalent in patients with chronic kidney disease (CKD) and has been associated with all-cause and cardiovascular mortality in observational studies. However, evidence from randomized controlled trials (RCTs) supporting vitamin D supplementation is lacking. We sought to assess whether vitamin D supplementation alters the relative risk (RR) of all-cause and cardiovascular mortality, as well as serious adverse cardiovascular events, in patients with CKD, compared with placebo.

Methods. PubMed/MEDLINE, EMBASE, Cochrane Library, and selected nephrology journals and conference proceedings were searched in October 2013. RCTs considered for inclusion were those that assessed oral vitamin D supplementation versus placebo in adults with CKD ($\leq$60 mL/min/1.73 m^2), including end-stage CKD requiring dialysis. We calculated pooled RR of mortality (all-cause and cardiovascular) and that of cardiovascular events and stratified by CKD stage, vitamin D analog and diabetes prevalence.

Results. The search identified 4246 articles, of which 13 were included. No significant treatment effect of oral vitamin D on all-cause mortality (RR: 0.84; 95% CI: 0.47, 1.52), cardiovascular mortality (RR: 0.79; 95% CI: 0.26, 2.28) or serious adverse cardiovascular events (RR: 1.20; 95% CI: 0.49, 2.99) was observed. The pooled analysis demonstrated large variation in trials with respect to dosing (0.5 ug–200 000 IU/week) and duration (3–104 weeks).

Conclusions. Current RCTs do not provide sufficient or precise evidence that vitamin D supplementation affects mortality or cardiovascular risk in CKD. While its effect on biochemical endpoints is well documented, the results demonstrate a lack of appropriate patient-level data within the CKD literature, which warrants larger trials with clinical primary outcomes related to vitamin D supplementation.

Keywords: cardiovascular outcomes; clinical trials; meta-analysis; mortality; vitamin D

Introduction

The chronic kidney disease (CKD) patient population experiences a high burden of cardiovascular mortality [1]. Moreover, those with CKD demonstrate severe vitamin D deficiency [1], which generates downstream disruptions of systemic mineral metabolism [2, 3]. Recent evidence suggests that vitamin D supplementation may provide a survival benefit with respect to cardiovascular mortality, suggesting that this benefit may be related to vitamin D metabolism [1, 3–10]. Unfortunately, this evidence is predominately derived from observational studies [6, 8, 10].

Vitamin D supplementation is a reasonably safe and simple intervention, and its impact on cardiovascular outcomes has been extensively studied in randomized controlled trials. Although a recent meta-analysis of 40 such trials reported no association between vitamin D therapy and the relative risk (RR) of cardiovascular endpoints, studies of subjects with chronic comorbidities, such as CKD, were excluded [11]. Other meta-analyses and a recent umbrella review assessing the efficacy of vitamin D therapy on mortality risk in the CKD population only included small trials that were not adequately powered to assess this clinically important outcome. Not surprisingly, the authors did not find any significant effect at the time of publication [12–15]. Since these results were published, the clinical landscape has evolved, and now a number of new nutritional and activated vitamin D analogs are available, which are being used in the

management of patients with CKD [5]. Whether specific analogs of vitamin D provide varying degrees of all-cause or cardiovascular survival benefit in the CKD population remains poorly studied.

We undertook a systematic review and meta-analysis of RCTs to investigate the effect of vitamin D therapy versus placebo on the risk of all-cause and cardiovascular-related mortality, as well as serious adverse cardiovascular events, among adults with CKD. We specifically aimed to address the following unanswered questions: (a) does oral vitamin D therapy reduce the RR of all-cause mortality, cardiovascular mortality and other serious adverse cardiovascular events, compared with placebo in patients with CKD and (b) are different vitamin D analogs associated with varying degrees of RR of all-cause mortality, cardiovascular mortality and other serious adverse cardiovascular events compared with placebo in patients with CKD?

Methods

Data sources and searches

Our literature search was conducted using PubMed/ MEDLINE (1966 to October 2013), EMBASE (1980 to October 2013), the Cochrane Collaboration Central Register of Controlled Clinical Trials, the Cochrane Database of Systematic Reviews and the Cochrane Database of Registered Clinical Trials. A search of all registered trials on ClinicalTrials.gov as well as two major nephrology journals (Journal of the American Society of Nephrology and Kidney International) and the conference proceedings and abstracts from annual American Society of Nephrology and World Congress of Nephrology meetings for inclusion of unpublished data for the systematic review was done. The bibliographies of all articles included in the full-text review were scanned for further consideration. The search was inclusive of all languages. An example of the full electronic search strategy utilized in MEDLINE is outlined in Supplemental Table S1.

Study selection criteria

Our systematic review and meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) statement [16]. Two reviewers (M.C.M. and A.J.H.) independently screened abstracts identified based on the aforementioned search strategy (Supplemental Table S1) to identify articles eligible for full-text review. Placebo-controlled randomized trials reporting on original data studying oral vitamin D (active or inactive analogs) supplementation for any stage of CKD (eGFR $\leq$ 90 mL/min/1.73 m^2) in adults ($\geq$18 years old) were considered eligible for inclusion. Trials with intravenous vitamin D interventions and subjects with kidney transplantation or previous parathyroidectomy were excluded.

Disagreements upon abstracts eligible for full-text review were discussed and finalized through mutual consensus. Eligible abstracts then underwent full-text review by M.C.M. and A.J.H. independently. Consensus was obtained between M.C.M. and A.J.H. for the final studies to be included for data extraction with input from the authors DJR, BRH and DMR. Only trials that reported mortality data, including zero events, were included in our systematic review. Articles which did not clearly define whether events occurred in the treatment or placebo arms were excluded. The authors of trials with unavailable data were contacted to determine their eligibility for inclusion in our study.

Data extraction and quality assessment

We extracted data using a predetermined template in Microsoft Excel. Information retrieved included patient demographics (age, sex, prior cardiovascular history, CKD stage, diabetic status, previous supplement use, and medication use), baseline and post-intervention physiological characteristics (serum and urinary renal and mineral metabolism parameters), vitamin D intervention (analog, dose, dose adjustments and frequency of treatment) and patient-level outcomes reported (all-cause and/or cardiovascular mortality and other serious adverse cardiovascular events). Serious adverse cardiovascular events were defined as either fatal or non-fatal MI, CHF, sudden cardiac death (SCD) and aortic dissection or as classified by the authors of each trial. Values for pre- and post-treatment variables were combined for trials that had more than one treatment group. Study quality was assessed using the Cochrane Collaboration Tool for Assessing Risk of Bias in RCTs [17]. Studies were included in the systematic review and meta-analysis regardless of the results of study quality assessment.

Data synthesis and analysis

We used a DerSimonian and Laird random-effects model to derive the pooled RRs to determine the relationship between vitamin D supplementation and all-cause mortality, cardiovascular mortality and serious adverse cardiovascular events in subjects with CKD [18]. RRs were derived from sample sizes and the event rates for death and cardiovascular events within each trial.

Stratified meta-analyses were done to determine whether the effect estimate differed by CKD stage, vitamin D analog utilized in each trial and proportion of subjects from each trial with diabetes. The CKD stage was determined by the reported mean baseline eGFR for each trial. Vitamin D analog used was defined by the form of vitamin D assigned in each trial. The average weekly dose was calculated by converting dosages to micrograms and then determined the amount of vitamin D received over a 1-week period (ug/week). The proportion of patients with diabetes in each of the trials was categorized as 0, <25, 50, 75 or 100% of subjects enrolled. Heterogeneity between the included trials was assessed using the I^2 statistic and Q statistic based on the chi-square distribution with 12 degrees of freedom. All data reported herein represent means $\pm$ SD with a P-value $\leq$ 0.05 considered significant. All statistical analysis was performed using Stata version 12.0 (Stata Corp, College Station, Texas).

Results

Literature search

We identified 4246 abstracts based on pre-specified criteria (Figure 1, Supplemental Table S1). After removal of duplicates, 107 manuscripts were identified for full-text review (agreement between the authors M.C.M. and A.J.H. was 92%; kappa 0.53; 95% CI: 0.48–0.59). After the full-text review, 96 articles were excluded. Overall, 13 RCTs were eligible for inclusion in the systematic review and meta-analysis [7, 19–30]. All 13 studies reported incidence
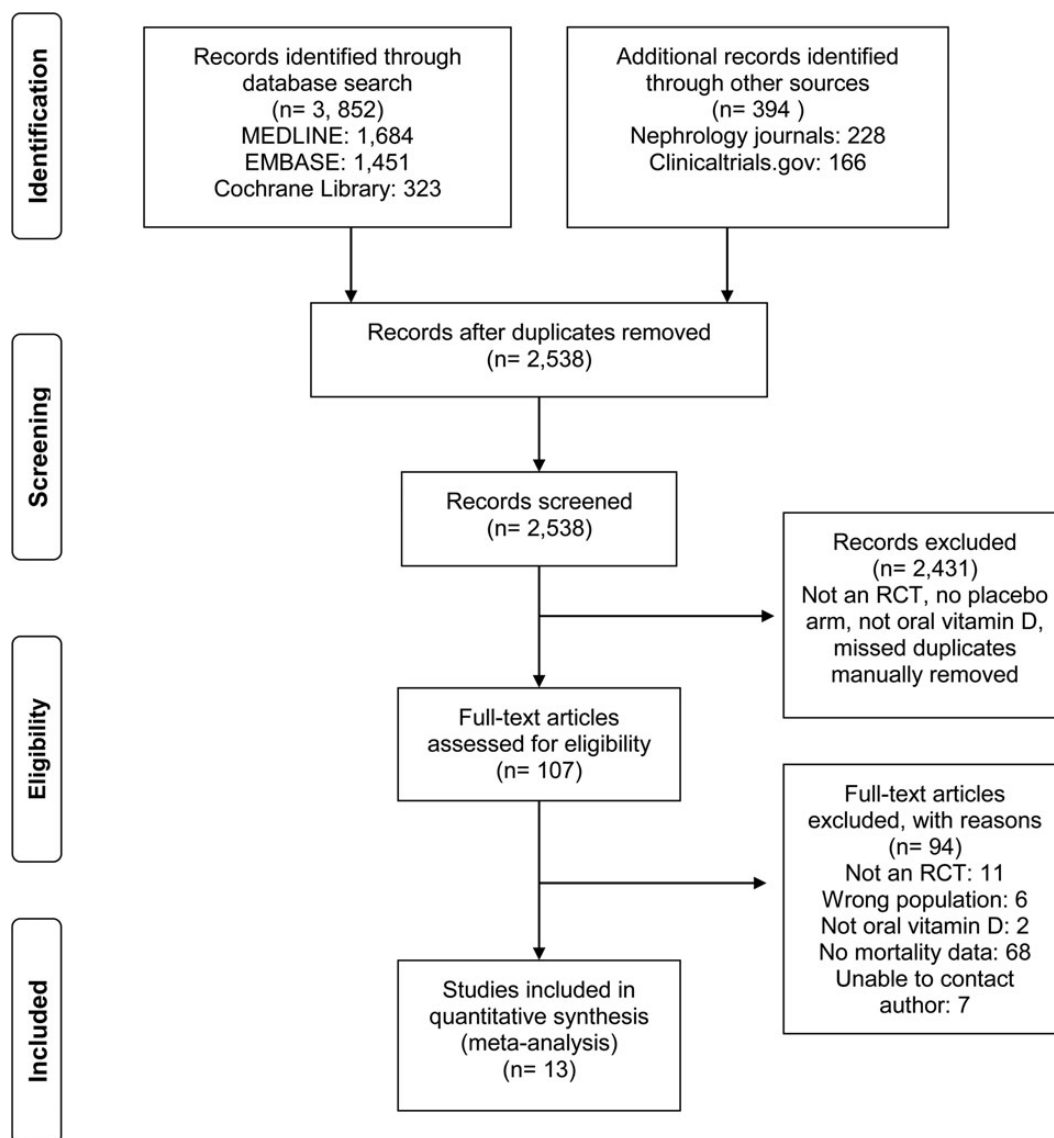
Fig. 1. PRISMA literature search and study selection.

of mortality (zero deaths or more), and 5 trials [7, 20, 22, 24, 25] specified cardiovascular mortality. All but three studies [19, 23, 30] reported the presence or absence of cardiovascular adverse events during the intervention period.

Quality assessment and publication bias

Overall, trial quality was consistent for a low-moderate risk of bias for all of the domains within and across the studies listed (Supplemental Table S2). There was a lack of clarity around the methods surrounding randomization sequence generation in 4 of the 13 trials (31%) [23, 25, 28, 29], unclear blinding methods in 2 trials (15%) [23, 29] and unclear allocation concealment protocol for 8 of the trials (46%) [20, 23–29].

Study characteristics

The subject characteristics, intervention and outcomes reported in the 13 trials are displayed in Table 1. These studies were published between 1981 and 2013 with data collected from a total of 1469 patients. Length of follow-up ranged from 3 to 104 weeks. There were a total of 41 all-cause deaths in the 13 trials, with 18 deaths in the placebo and 23 in the treatment arm. Six trials [7, 20, 22, 24–26] specified deaths related to a cardiovascular etiology, and seven [7, 20, 22, 24, 25, 29] reported non-fatal cardiovascular adverse events. None of the 13 trials listed mortality or cardiovascular event rate as an *a priori* primary or secondary outcome.

The trials included patients with CKD stage 1–5 [31], including end-stage kidney disease requiring hemodialysis (stage 5D); eGFR was reported in only six of the included trials [19–22, 25, 28, 30] and ranged from 23.0 to 61.25 mL/min/1.73 m^2 in subjects allocated to the placebo arm and from 19.7 to 62.5 mL/min/1.73 m^2 within the treatment group. Four of the 13 studies exclusively included end-stage kidney disease patients on hemodialysis with a mean dialysis vintage ranging from 45 to 70 months in the placebo arm and 22 to 60 months in the treatment arm [23, 24, 28, 30]. Baseline mean 25-hydroxy vitamin D

Table 1. Characteristics of randomized controlled trials included

Author, year	Location	Sample size		Mean age (years)		% Female		% Diabetes		CKD Stage	Intervention	Dosing regimen	Duration of Study (weeks)	Primary outcome	All-cause mortality		Cardiovascular mortality		Cardiovascular events	
		Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment						Placebo	Treatment	Placebo	Treatment	Placebo	Treatment
Alvarez, 2012 [19]	USA	24	22	63 ± 9	62 ± 11	8	9	71	82	1 and 2	Cholecalciferol	50 000 IU per week for 12 weeks followed by 50 000 IU per week for 40 weeks	52	Maintain vitamin D status, reduction in PTH	1	1	NR	NR	NR	NR
Coburn, 2004 [20]	USA	28	27	65 ± 12	64 ± 13	14	22	0	0	3 and 4	Doxercalciferol	0.5 ug twice daily, increased by 1 capsule per day at monthly intervals until PTH < 30% baseline	32	Reduction in PTH	1	0	1	0	1 MI, 1 SCD	1 CHF
Coyne, 2006 [21]	USA, Poland	113	107	62 ± 12	64 ± 13	33	32	NR	NR	3 and 4	Paricalcitol	2 ug thrice weekly, increased to 4 ug if PTH > 500 pg/mL	24	Reduction in PTH	1	2	0	0	0	1 bradycardia
de Zeeuw, 2010 [22]	USA, Europe	93	188	64 ± 11	65 ± 10	65	28	100	100	2 and 3	Paricalcitol	1.5 ug daily	24	Reduction of albuminuria	0	2	0	1	1 hypertension	1 SCD, 1 CHF
Delanaye, 2013 [23]	Belgium	21	22	73 ± 12	75 ± 9	36	25	NR	NR	5D	Cholecalciferol	25 000 IU once every 2 weeks	52	Safe increase in 25-hydroxy vitamin D	5	6	NR	NR	NR	NR
Frazao, 2000 [24]	USA	67	71	49 ± 15	55 ± 12	51	51	NR	NR	5D	Doxercalciferol	10 ug thrice weekly, adjusted by 2.5 ug increments if PTH outside target range (150–300 pg/mL)	8	Reduction in PTH	2	1	2	1	2 SCD	1 SCD
Hamdy, 1995 [25]	Europe	87	89	51 ± 16	53 ± 15	39	39	NR	NR	2 and 3	Alfacalcidol	0.25 ug daily, adjusted 0.25–1 ug per day to maintain baseline serum calcium	104	Bone histology, markers of renal bone disease	1	4	1	4	0	0
Hewitt, 2013 [26]	Australia	30	30	67 (54,72)[a]	60 (53,71)[a]	57	47	60	50	5D	Cholecalciferol	50 000 IU once per week for 8 weeks, reduced to once per month for last 16 weeks	24	Muscle strength and function	1	1	0	1	0	0
Marckmann, 2012 [27]	Denmark	27	27	68 ± 22	71 ± 19	23	27	38	31	2 and 3	Cholecalciferol	40 000 IU once per week	8	Increase in 25-hydroxy vitamin	1	0	0	0	0	0
Memmos, 1981 [28]	UK	30	27	48 ± 12	50 ± 10	37	33	NR	NR	2–5D	Alfacalcidol	0.5 ug daily	104	Bone histology markers of renal bone disease	3	3	0	0	0	0
Thadhani, 2012 [35]	USA, Australia, Europe	112	115	66 ± 12	64 ± 11	30	31	51	55	3 and 4	Paricalcitol	2 ug daily	48	Change in left ventricular mass	1	1	1	1	4 CHF, 1 aortic dissection, 2 chest pain	1 chest pain
Wang, 2013 [29]	Hong Kong	30	30	62 ± 11	61 ± 1	53	40	43	27	3	Paricalcitol	1 ug daily	52	Change in left ventricular mass	0	0	0	0	1 MI, 1 bradycardia, 1 fluid overload	0
Wasse, 2012 [30]	USA	27	25	52 ± 14	49 ± 13	37	40	52	48	5D	Cholecalciferol	200 000 IU once per week	3	Correction of vitamin D deficiency	1	2	0	0	NR	NR

[a]Interquartile range.

levels were reported in only seven studies [19, 20, 22, 23, 26, 27, 30] and ranged from 12.0 to 32.1 ng/mL in the placebo groups and 9.5 to 26.7 ng/mL in the treatment groups. Approximately 30% of subjects in each arm reported use of renin–angiotensin–aldosterone system (RAAS) inhibitors, diuretics, diabetes medications, past vitamin D supplementation and phosphate/calcium binders.

Trials randomized patients to receive placebo or cholecalciferol [19, 23, 26, 27, 30], doxecalciferol [20, 24], paracalcitol [7, 22, 29, 32] or alfacalcidol [25, 28]. The dosage and frequency of treatment across trials differed substantially, from 0.25 ug per day [25] to 200 000 IU per week [30]. Three trials followed dose adjustment protocols based on serum PTH [20, 21, 24] or calcium [25].

All-cause mortality and vitamin D supplementation

A random-effects model of the pooled RRs of all-cause mortality across the 13 trials is displayed in Figure 2. There was no evidence of a significant effect of Vitamin D supplementation compared with placebo on the risk of all-cause mortality (pooled RR: 0.84; 95% CI: 0.47, 1.52). Point estimates for each of the 13 trials display considerable overlapping of confidence intervals, all of which cross the null value of an RR of 1.0, which suggests that there is no significant effect of vitamin D treatment on all-cause mortality in CKD patients compared with placebo. Similar insignificant pooled estimates of effect were found after stratifying by clinically important variables (Figure 3).

Cardiovascular mortality, serious cardiovascular adverse events and vitamin D supplementation

There was also no significant treatment effect of vitamin D supplementation on cardiovascular mortality (six studies; pooled RR: 0.79; 95% CI: 0.26, 2.28), with no statistical heterogeneity between the studies ($X^2 = 2.69$, P = 0.748, $I^2 = 0.0\%$) (Figure 2). In addition, no significant increase or decrease in the risk of serious adverse cardiovascular events was demonstrated with oral vitamin D supplementation (six studies; pooled RR: 1.20; 95% CI: 0.49, 2.99).

Discussion

To our knowledge, this is the first meta-analysis evaluating the effects of vitamin D supplementation compared with placebo in decreasing the risk of overall all-cause mortality, cardiovascular mortality and serious adverse cardiovascular events in individuals with CKD. The key findings from our meta-analysis are consistent with previous reviews in this area and suggest that there is no quantifiable treatment effect of vitamin D on RR of mortality or cardiovascular outcomes compared with placebo. However, the trials evaluating vitamin D therapy continue to examine physiologic primary outcomes and are not adequately designed to assess the risk of mortality or cardiovascular-related mortality and cardiovascular adverse events.
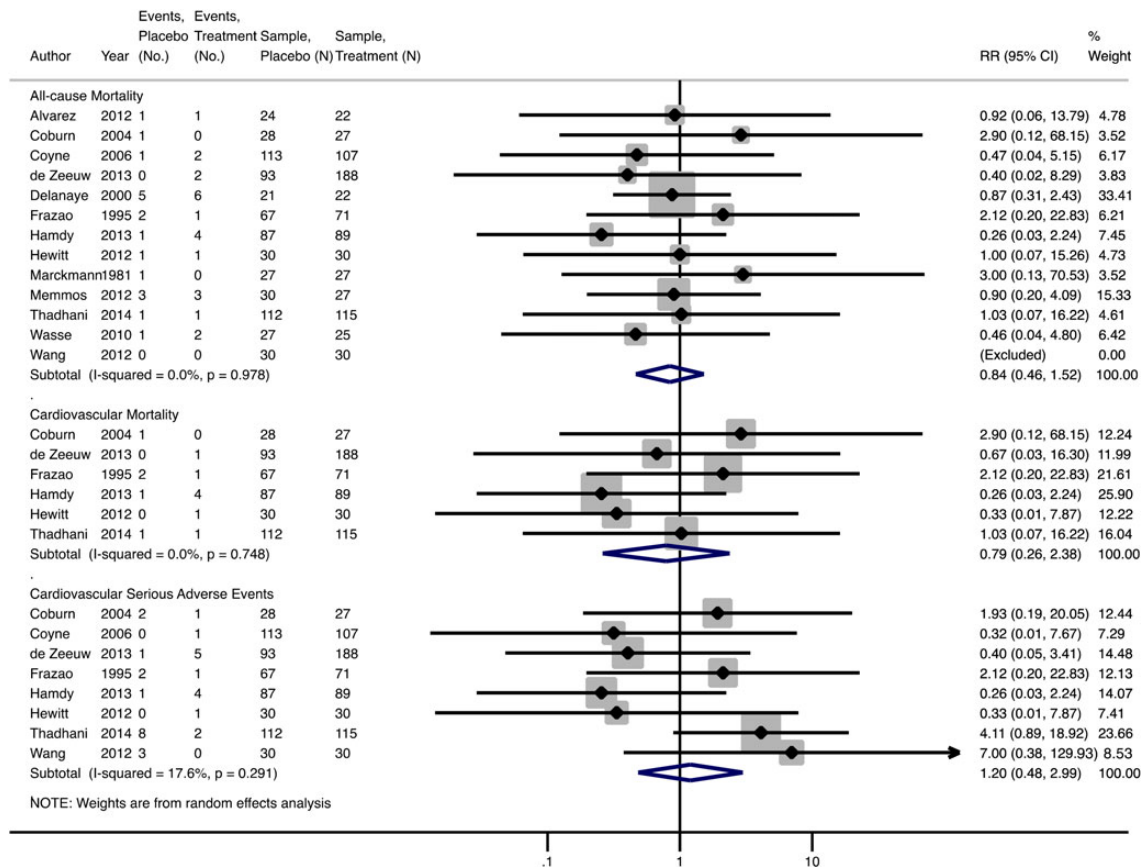
Fig. 2. Pooled relative risk of all-cause mortality, cardiovascular mortality and serious adverse cardiovascular events in relation to vitamin D supplementation.
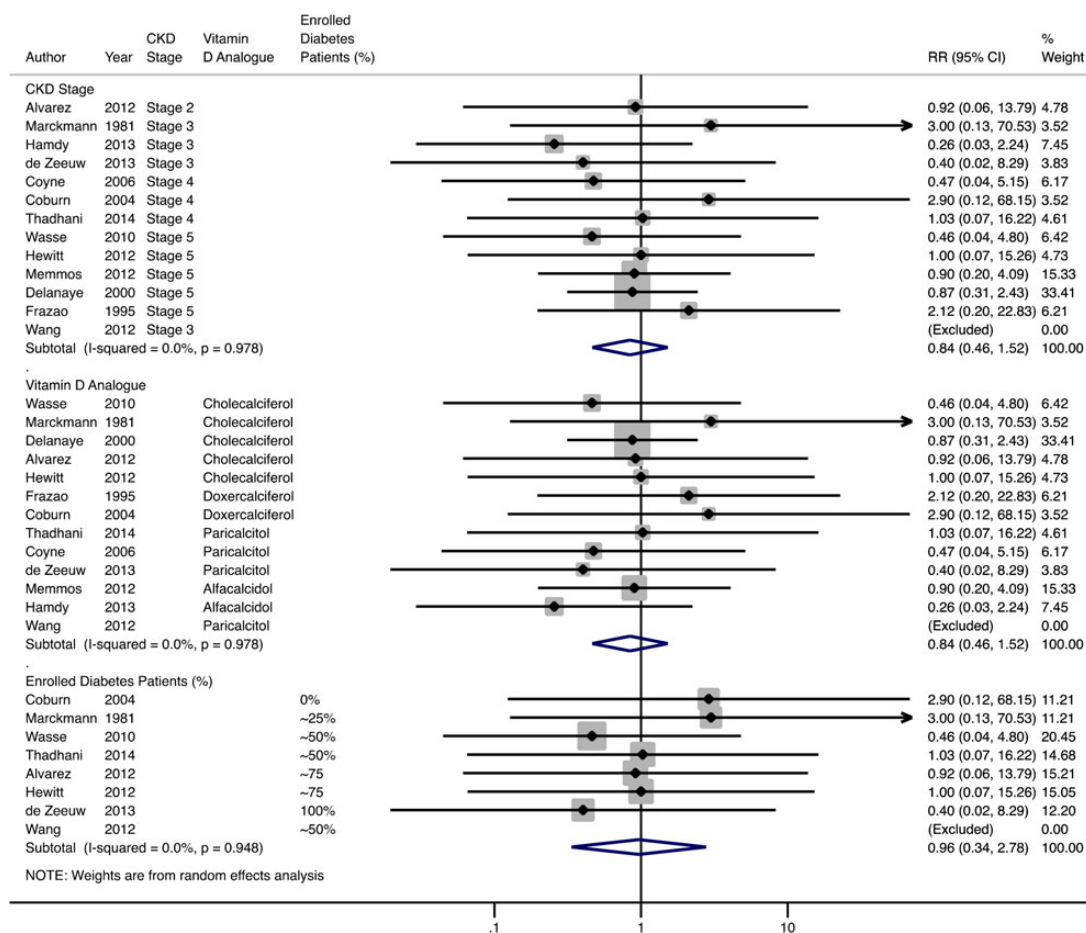
Fig. 3. Pooled relative risk of all-cause mortality in relation to vitamin D supplementation, stratified by CKD stage, vitamin D analog and proportion of diabetic subjects enrolled.

Cardiovascular mortality is arguably the most clinically important outcome for persons living with CKD. One quarter of deaths in the CKD population are reported as fatal cardiovascular events [2]. Vitamin D deficiency may play a role in the development and progression of cardiovascular disease, and there is great interest in determining whether vitamin D treatment can lower the risk of adverse outcomes. Patients with CKD are at high risk for low serum vitamin D for multiple reasons. A restrictive diet and overall deteriorating health also predisposes those with CKD to classical vitamin D deficiency defined by 25-hydroxyviamin D serum levels [5]. The kidneys also play a vital role in vitamin D metabolism and overall maintenance of mineral metabolism within the body. Classically, nutritional sources of vitamin D (cholecalciferol, vitamin D_3; and ergocalciferol, vitamin D_2) must undergo two enzymatic hydroxylations: (i) in the liver to 25-hydroxyvitamin D; (ii) in the kidney, the enzyme 1α-hydroxylase converts 25-hydroxy vitamin D to the biologically active form of vitamin D, 1,25-dihydroxycholecalciferol (calcitriol) or 1,25-dihydroxyergocalciferol [33, 34]. The liver hydroxylation is largely substrate driven, but the kidney's 1α-hydroxylase is very tightly regulated by hormonal components (i.e. PTH) and concentrations of calcium and phosphate ions [33, 34]. Throughout the progression of CKD, increasing loss of functional renal tissue reduces the availability and function of 1α-hydroxylase, which in turn disrupts overall vitamin D production, metabolism and hormones [35]. CKD patients also often experience exacerbated vitamin D deficiency due to additional non-physiological sources including intensive dietary restriction and lack of sun exposure due to decreased mobility [35].

Lower levels of serum vitamin D are associated with significant changes in mineral metabolism that adversely affect vascular function. Further, lower levels of vitamin D are associated with upregulation of the renin–angiotensin system (RAS) and subsequently lead to vasoconstriction and increased blood pressure, vascular stress and, ultimately, a higher degree of cardiovascular stress and workload [2, 36]. In relation to this, impaired hemodynamic control, baroreflex dysfunction and poor autonomic nervous system control have been observed in the CKD population [37, 38]. Vitamin D deficiency may increase cardiovascular risk by disrupting mineral metabolism leading to vascular calcification, increasing vascular stress by the upregulation of the renin–angiotensin system [4], and may also contribute to poor control of the cardiac autonomic nervous system, which has been shown to be associated with increased risk of SCD [38, 39].

In observational studies of patients with CKD, vitamin D deficiency has been associated with increased mortality and overall cardiovascular risk whereas vitamin D supplementation has been shown to ameliorate this association [8, 40]. A recent meta-analysis of 20 observational studies collectively supports these findings [6]. Unfortunately, clinical trials investigating similar outcomes remain very

few in number, and past analyses of RCTs with patient-level outcomes have also not been adequately powered to confirm or dispute the conclusions drawn from observational studies. Our meta-analysis is the most comprehensive and current assessment of placebo-controlled RCTs that report incidence of all-cause mortality, cardiovascular mortality and serious adverse cardiovascular events throughout an oral vitamin D intervention in CKD patients.

Limitations

Our meta-analysis is not without limitations, many arising from study-level and characteristics and quality. The inherent variation across each trials' intervention duration, frequency and treatment dose, as well as varying primary and secondary outcomes, decreases the compatibility of studies in regards to pooling and comparing data from included studies. The random-effects model of pooled RRs identified variation due to chance alone, and there was considerable overlap across individual study confidence intervals. None of the studies were designed *a priori* to capture mortality or cardiovascular event data, and thus, the event rates associated with the intervention and placebo may not reflect the true rates. The widespread clinical use of vitamin D supplements within the CKD patient population contrasts with the inconsistent trials and lack of patient-level outcome studies, which does not allow for appropriate evaluation of the impact of vitamin D supplementation on mortality or cardiovascular risk.

Conclusions

Overall, we found poor evidence of a precise and positive effect of vitamin D supplementation on all-cause mortality, cardiovascular mortality and/or serious adverse cardiovascular events compared with placebo. Stratification of trials by CKD stage, average weekly standardized vitamin D dose, proportion of diabetic subjects enrolled and vitamin D analog showed similar findings. The absence of a significant or precise result should not be interpreted as evidence that vitamin D therapy has no benefit in patients with CKD. There is evidence [15] that vitamin D effectively and safely lowers PTH and this review, along with those that preceded it, highlights that the trials to date are limited in their power and ability to appropriately evaluate more clinically meaningful outcomes. The current state of the literature is unfit to systematically quantify any effect of vitamin D therapy on these clinical outcomes.

Supplementary data

Supplementary data is available online at http://ndt. oxfordjournals.org.

Conflict of interest statement. The authors report no potential conflicts of interest. Results presented in this paper have not been published previously in whole or part.

(See related article by Morrone and Cozzolino. The beneficial impact of vitamin D treatment in CKD patients: what's next? *Clin Kidney J* (2015) 8: 38–40.)

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