

Active Vitamin D Treatment for Reduction of Residual Proteinuria: A Systematic Review

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ABSTRACT

Despite renin-angiotensin-aldosterone system blockade, which retards progression of CKD by reducing proteinuria, many patients with CKD have residual proteinuria, an independent risk factor for disease progression. We aimed to address whether active vitamin D analogs reduce residual proteinuria. We systematically searched for trials published between 1950 and September of 2012 in the Medline, Embase, and Cochrane Library databases. All randomized controlled trials of vitamin D analogs in patients with CKD that reported an effect on proteinuria with sample size ≥ 50 were selected. Mean differences of proteinuria change over time and odds ratios for reaching $\geq 15\%$ proteinuria decrease from baseline to last measurement were synthesized under a random effects model. From 907 citations retrieved, six studies (four studies with paricalcitol and two studies with calcitriol) providing data for 688 patients were included in the meta-analysis. Most patients (84%) used an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker throughout the study. Active vitamin D analogs reduced proteinuria (weighted mean difference from baseline to last measurement was -16% [95% CI, -13% to -18%]) compared with controls ($+6\%$ [95% CI, 0% to $+12\%$]; $P < 0.001$). Proteinuria reduction was achieved more commonly in patients treated with an active vitamin D analog (204/390 patients) than control patients (86/298 patients; OR, 2.72 [95% CI, 1.82 to 4.07]; $P < 0.001$). Thus, active vitamin D analogs may further reduce proteinuria in CKD patients in addition to current regimens. Future studies should address whether vitamin D therapy also retards progressive renal functional decline.

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CKD is a worldwide health burden, affecting about 15% of the Western adult population.¹ CKD is associated with premature death, cardiovascular disease, infection, and cancer, and it consumes disproportionate health care resources.^{2–4} The mainstay of current CKD treatment is pharmacological blockade of the renin-angiotensin-aldosterone system (RAAS) by angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). Although these drugs may retard progression of both renal and cardiovascular disease^{5–9} partly through their capacity to reduce proteinuria,^{10,11} progression to ESRD and cardiovascular complications cannot be prevented in many CKD patients.

A recent single-level meta-analysis including over 2 million participants showed that albuminuria

is independently associated with mortality and ESRD, regardless of age.¹² The amount of residual albuminuria/proteinuria under RAAS blockade is a strong predictor of both long-term renal disease progression^{13,14} and cardiovascular complications,¹⁵

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and an absent or blunted proteinuria response to the use of RAAS blockers is an especially strong predictor.¹⁶ The efficacy of RAAS blockade intensification in an attempt to further reduce residual proteinuria is, however, limited by side effects, such as hyperkalemia and hypotension.^{17,18} Adjunctive therapies, which can offer the lowering of residual proteinuria but without these drawbacks, may improve renal and cardiovascular protection.

Studies in animal models of CKD suggested that proteinuria, renal fibrosis, and renal function loss may be reduced by treatment with an active vitamin D analog not only as monotherapy but also when given as adjunctive therapy to conventional RAAS blockade.^{19–21} In CKD patients, lower vitamin D concentrations have been associated with an increased risk of mortality,^{22,23} cardiovascular complications,²⁴ and renal disease progression.²⁵ These findings have resulted in a number of small- to medium-sized prospective randomized controlled trials (RCTs) with the use of active vitamin D analogs targeting reduction of (residual) proteinuria in CKD patients. So far, results have been inconclusive, with studies reporting significant,^{26–28} borderline significant,^{29–31} or nonsignificant^{32,33} effects. We performed a systematic review and meta-analysis of all available RCTs to address the effect of active vitamin D analogs on residual proteinuria in patients with CKD.

RESULTS

The selection process for the articles included in the meta-analysis is presented in Figure 1. From the eight RCTs with active vitamin D analogs in CKD patients in which an effect of proteinuria or albuminuria was reported, six trials had a sample size of at least 50 and hence, were considered eligible for inclusion in our meta-analysis.^{26,28–31,33} Two additional studies had a sample size below 50 and were only qualitatively adjudged.^{27,32} Characteristics of the trials are summarized in Table 1.

Of the trials included in the quantitative analysis, the median number of participants per study was 105 (first to third quartile, 54–169), and median study duration was 24 (22–48) weeks. Four of six trials were with the synthetic active vitamin D analog paricalcitol as the active treatment,^{26,29,30,33} whereas the other two trials used endogenous active vitamin D (calcitriol).^{28,31} Two studies were performed exclusively in patients with diabetic nephropathy,^{28,29} and one study was performed exclusively in patients with IgA nephropathy³¹; the other studies were in patients diagnosed with diverse underlying renal disorders. The overall weighted mean age was 61 years, and 67% of patients were men. The majority of patients (84%) used an ACE inhibitor or ARB throughout the study. For three studies, outcome data on the proportion of patients with $\geq 15\%$ proteinuria reduction were available.^{29,31,33} One study

reported on (semiquantitative) dipstick proteinuria,²⁶ and two studies reported the proportion of patients with $\geq 10\%$ or $\geq 30\%$ proteinuria reduction, respectively.^{28,30}

Quality assessment revealed that most studies described concealment of allocation or blinding of the outcome assessor.^{27,29–33} Two of six trials did not describe whether the analyses were by intention to treat.^{26,28} Across all trials, the mean Jadad score was 3.6 (maximum of 5). There was no evidence of publication bias (Supplemental Figure 1 shows a funnel plot with pseudo-95% confidence interval [pseudo-95% CI]; Egger's test, $P=0.36$).

A subanalysis of the population with albuminuria at baseline from the PRIMO trial (Paricalcitol Capsules Benefits in Renal Failure Induced Cardiac Morbidity in Subjects With Chronic Kidney Disease Stage 3/4) revealed that 62 of 115 patients in the paricalcitol group and 59 of 112 patients in the placebo group had albuminuria at baseline (Supplemental Table 1). The adjusted estimated albumin to creatinine ratio (ACR) at week 48 was lower than at baseline for the paricalcitol group, but this change did not reach statistical significance ($P=0.26$), and there was not a

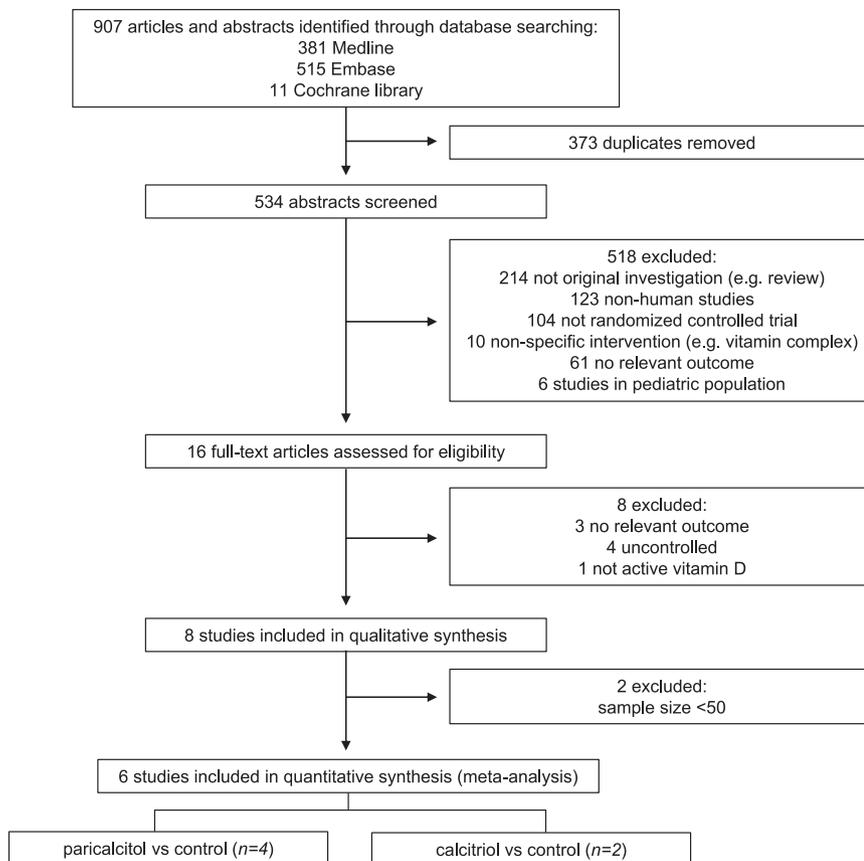


Figure 1. Flowchart of the process to identify eligible studies.

Table 1. Characteristics of all RCTs with active vitamin D analogs that had proteinuria as outcome (qualitative analysis)

Authors (yr)	Study Arms (n)	Baseline Parameters				Underlying Conditions	Follow-Up	Main Result
		ACR (mg/g)	PCR (g/g)	eGFR (ml/min per 1.73 m ²)	Diabetes Mellitus (%)			
Agarwal et al. ²⁶ (2005)	Paricalcitol (57)	N/A		24 (8)	59	68	Diverse	Dipstick proteinuria decreased in 51% of patients in paricalcitol group and 25% of patients in placebo group (P=0.004)
	Placebo (61)			23 (7)	58	70		
Alborzi et al. ²⁷ (2008)	Paricalcitol 1 μg/d (8)	72 (30–172)		48 (9)	50	100	Diverse	From baseline to last measurement, ACR increased in placebo group but decreased in both paricalcitol groups
	Paricalcitol 2 μg/d (8)	39 (18–82)		47 (13)	88	100		
Fishbane et al. ³⁰ (2009)	Placebo (8)	241 (57–1022)	2.6 (N/A)	44 (12)	75	100	Diverse	PCR placebo: +2.9%; paricalcitol: –17.6%, P=0.04
	Paricalcitol 1 μg/d (31)		2.8 (N/A)	40 (24)	65	89		
de Zeeuw et al. ²⁹ (2010)	Placebo (30)	894 (832)		35 (18)	50	93	Diabetic nephropathy	ACR from baseline to last evaluation was –3% in placebo group, –14% in 1 μg paricalcitol group, and –20% in 2 μg paricalcitol group (P=0.05)
	Paricalcitol 1 μg/d (93)	814 (761)		40 (15)	100	100		
De Boer et al. ³² (2013) ^a	Paricalcitol 2 μg/d (95)	832 (717)		42 (18)	100	100	Diverse	ACR at last evaluation was 15% lower after paricalcitol than after placebo treatment when comparing individual patients (P=0.31)
	Placebo (93)	593 (1460)		39 (17)	100	100		
Thadhani et al. ³³ (2012) ^b	Paricalcitol 2 μg/d (11)	257 (478)		39 (12)	0	73	Diverse	Adjusted mean change in log-transformed ACR at week 48 was –0.11 [95% CI, –0.35 to 0.13] in paricalcitol group and 0.10 [95% CI, –0.14 to 0.33] in placebo group (P=0.23)
	Placebo (59)	450 (156–1040)		40 (12)	58	84		
Liu et al. ³¹ (2012)	Paricalcitol 2 μg/d (62)	278 (88–980)		31 (23–39)	56	80	lgA nephropathy	24 h proteinuria from baseline to last evaluation was +21% in control group and –19% in calcitriol group (P=0.03)
	Placebo (59)	N/A ^c		83 (36)	0	100		
Krairitichai et al. ²⁸ (2012)	Calcitriol 0.5 μg 2×/wk (25)		3.73 (2.20)	78 (28)	0	100	Diabetic nephropathy	Urinary PCR decreased by 18.7% in calcitriol group and increased by 9.9% in control group (P<0.01)
	No treatment (25)		3.39 (2.10)	38 (18)	100	61		
	No treatment (45)			37 (17)	100	53		

ACR, protein to creatinine ratio (PCR), and eGFR data presented as mean (SD) or median (95% CI) depending on their distribution. N/A, not available.

^aThe original study had a crossover design. To avoid repeated inclusion, we used data from the first study period only.

^bData represent the subgroup of patients with albuminuria at baseline. Baseline data for the complete study population are available in the original publication.³³

^cNo baseline PCR/ACR data were available. The 24-hour urinary protein excretion at baseline was 1.60 g/24 h in the calcitriol-treated group and 1.29 g/24 h in the control group.

significant difference with the ACR change over time in the placebo group (overall $P=0.54$) (Supplemental Table 2). A $\geq 15\%$ reduction of ACR was reached by 23 of 49 subjects in the paricalcitol group and 17 of 53 subjects in the placebo group ($P=0.12$) (Supplemental Table 3).

In the meta-analysis considering all six studies, the weighted mean change in proteinuria from baseline to the last measurement was -16% (95% CI, -13% to -18%) in patients treated with an active vitamin D analog versus $+6\%$ [95% CI, 0% to $+12\%$] in patients receiving control treatment ($P<0.001$) (Figure 2, upper panel). Proteinuria reduction was achieved more commonly in patients treated with a vitamin D analog (204/390 patients) than control patients (86/298 patients; odds ratio, 2.72 [95% CI, 1.82 to 4.07], $P<0.001$) (Figure 2, lower panel). When only studies that had $\geq 15\%$ proteinuria reduction as an end point were considered, results remained similar (odds ratio, 2.02 [95% CI, 1.32 to 3.10], $P=0.001$).

Subgroup analyses (Figure 3) suggested that paricalcitol and calcitriol comparably reduce proteinuria. Studies using a higher dose of paricalcitol (2 $\mu\text{g/d}$) did not show a stronger reduction of proteinuria compared with studies using a lower dose (1 $\mu\text{g/d}$). The antiproteinuric effect also seemed similar in studies with only diabetic nephropathy patients compared with studies not restricted to patients with diabetic nephropathy or studies without diabetic nephropathy. The effect was not significantly different between the larger and smaller studies, and the effect was not significantly different in studies with longer compared with shorter follow-up lengths. Addition of the two very small studies (sample

size <50),^{27,32} exclusion of the study that used dipstick assessment of proteinuria,²⁶ or exclusion of the two studies with untreated controls instead of a placebo group^{28,31} did not materially change the results of the meta-analysis or the subgroup analyses. Similarly, exclusion of the study that did not have proteinuria as a primary outcome³³ did not materially change the results.

In both the continuous analysis ($I^2=0\%$, $P=0.62$) (Figure 2, upper panel) and the dichotomous analysis ($I^2=26\%$, $P=0.24$) (Figure 2, lower panel), heterogeneity was limited. We used random effects models in both analyses to account for the clinical heterogeneity.

In the two largest trials (VITAL [Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes] and PRIMO),^{29,33} a small but significant reduction of creatinine-based measures of estimated GFR (eGFR) was observed (Table 2). The overall number of patients reaching ESRD during the studies was low. In general, treatment with active vitamin D analogs was well tolerated. Adverse event rates and discontinuation rates were generally similar between active treatment and control arms. In the studies with paricalcitol, hypercalcemia was detected more frequently in study patients than controls; both studies with calcitriol reported that no patients developed hypercalcemia.

DISCUSSION

Residual proteinuria during ACE inhibitor or ARB therapy is considered an independent risk factor for progressive renal

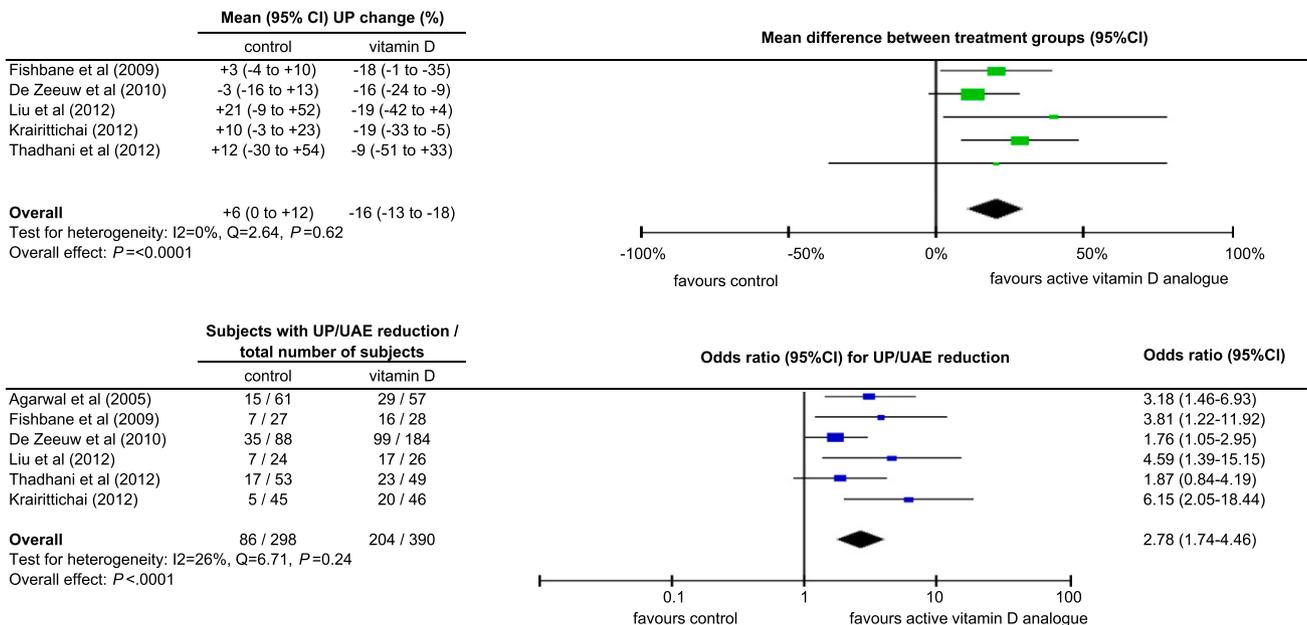


Figure 2. Effect of active vitamin D or control treatment on proteinuria in the meta-analysis. (Upper panel) Relative proteinuria change from baseline to last available measurement for all studies with available data. P value (overall effect) is for the comparison between the proteinuria change during active vitamin D treatment and the proteinuria change during control treatment. (Lower panel) Odds ratio of a relevant proteinuria reduction for active vitamin D analog versus control treatment. A relevant reduction of proteinuria was defined as a reduction of $\geq 15\%$ in proteinuria or albuminuria in most studies. UAE, urinary albumin excretion; UP, proteinuria.

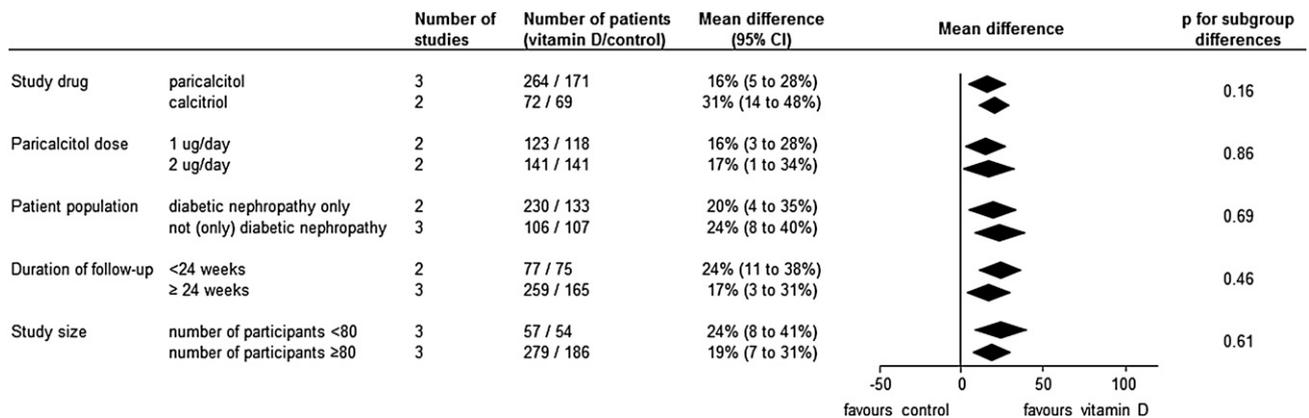


Figure 3. Subgroup analyses for the effects of vitamin D analogs on proteinuria reduction.

Table 2. eGFR change and adverse events reported in the studies

Authors (yr)	Study Arms	eGFR Change (ml/min per 1.73 m ²)	AE	SAE	Hypercalcemia	Discontinuation	ESRD	Death
Agarwal <i>et al.</i> ²⁶ (2005)	Paricalcitol mean 9.5 μg/wk	-3.0 (-3.1 to -2.9)	9/57	7/57	N/A	N/A	N/A	N/A
	Placebo	-2.5 (-2.6 to -2.4)	2/61	2/61				
Alborzi <i>et al.</i> ²⁷ (2008)	Paricalcitol 1 μg/d	-3.2 (-8.1 to -1.7)	N/A	N/A	N/A	1/8	N/A	N/A
	Paricalcitol 2 μg/d	+6.9 (-1.4 to +15.2)				0/8		
	Placebo	+5.3 (-3.1 to +13.7)				1/8		
Fishbane <i>et al.</i> ³⁰ (2009)	Paricalcitol 1 μg/d	No change within or between groups (data N/A)	7/31	2/31	1/31	3/31	N/A	N/A
	Placebo		9/30	2/30	0/30	2/30		
de Zeeuw <i>et al.</i> ²⁹ (2010)	Paricalcitol 1 μg/d	-1.2 (-3.8 to 1.4)	3/93	13/93	1/93	15/93	2/93	0/93
	Paricalcitol 2 μg/d	-7.6 (-10.1 to -5.1)	8/95	19/95	3/95	26/95	4/95	3/95
	Placebo	-0.1 (-2.6 to 2.4)	5/93	12/93	1/93	20/93	1/93	0/93
De Boer <i>et al.</i> ³² (2013)	Paricalcitol 2 μg/d	-6.3 (-13.5 to 0.9)	14/22	N/A	1/22	2/22	N/A	N/A
	Placebo	-0.2 (-6.2 to 5.9)	11/22		0/22	0/22		
Thadhani <i>et al.</i> ³³ (2012)	Paricalcitol 2 μg/d	-4.1 (-4.3 to -3.9)	92/115	17/115	26/115	27/115	6/115	0/115
	Placebo	-0.1 (-0.2 to 0.0)	87/112	11/112	1/112	21/112	1/112	0/112
Liu <i>et al.</i> ³¹ (2012)	Calcitriol 0.5 μg 2×/wk	-3.2 (-8.1 to +1.7)	7/26	1/26	0/26	4/26	N/A	N/A
	No treatment	+0.0 (-4.9 to +4.9)	9/24	0/24	0/24	3/24		
Krairittichai <i>et al.</i> ²⁸ (2012)	Calcitriol 0.5 μg 2×/wk	Baseline 37 (32–41)	4/46	N/A	0/46	5/51	N/A	N/A
	No treatment	End 36 (31–42)	6/45		0/45	3/48		
		Baseline 38 (31–42) End 37 (31–43)						

AE, adverse events; SAE, serious adverse events; N/A, not available.

function loss^{13,14} and cardiovascular complications,¹⁵ and it has, therefore, become a key target for adjunctive renoprotective therapy. The main finding of this meta-analysis of RCTs is that active vitamin D analogs (in most cases given on top of RAAS blockade) achieved a mean additional proteinuria reduction of 16%. Reduction of proteinuria was more likely to occur with active vitamin D therapy than control treatment added to standard RAAS-blocking therapy.

Post hoc analyses of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and Irbesartan Diabetic Nephropathy Trial (IDNT) studies suggest that, in diabetic nephropathy, the amount of residual

albuminuria predicts the risk of doubling of serum creatinine, ESRD, or death³⁴ as well as the risk of cardiovascular complications.¹⁵ Also, in nondiabetic kidney disease, residual albuminuria is associated with an increased risk of ESRD.¹³ In the Ramipril Efficacy in Nephropathy (REIN) study (stratum 1), treatment with an ACE inhibitor reduced proteinuria by 15% from baseline to last measurement; this reduction was accompanied by a reduced risk of reaching ESRD.³⁵ Furthermore, a recent study suggested that low dietary sodium intake could enhance the efficacy of RAAS blockade by increasing the anti-proteinuric effect from 20% to 31%; this result was accompanied by a significantly lower incidence rate of ESRD in the low

sodium group.³⁶ Whether the 16% reduction of residual proteinuria by active vitamin D analogs as observed in our analysis can actually translate into a reduced risk of renal disease progression remains to be addressed by future studies; the results of our meta-analysis will allow for more accurate trial design.

Mechanistic studies have elucidated that the vitamin D receptor can directly downregulate prorenin gene expression through interaction with its promoter region^{37,38}; vitamin D may also influence other RAAS components.³⁹ Enhanced RAAS blockade, even against the background of an ACE inhibitor or ARB, may therefore be a mechanism by which active vitamin D analogs reduce proteinuria. Inhibition of the TGF- β pathway has recently been proposed as an additional mechanism by which active vitamin D analogs could reduce renal damage.⁴⁰ The vitamin D system is, in any case, profoundly abnormal in most CKD patients, with adverse implications for skeletal health and integrity as a result of CKD-associated secondary hyperparathyroidism.^{41,42} Many CKD patients would receive some form of active vitamin D if their serum parathormone concentrations were elevated, but routine native vitamin D supplementation in these patients is not yet ubiquitous.

Our meta-analysis included a subanalysis of the population with albuminuria at baseline from the PRIMO trial. Similar to the previously published data from this trial, paricalcitol did not significantly reduce ACR. Certain differences with other studies must be pointed out. First, the main exposure used in this subanalysis was ACR from a single first morning spot urine sample compared with several averaged ACR measurements in other trials. ACR's large interindividual variability could have altered the signal to noise ratio and attenuated the effect. Second, this subanalysis has a smaller sample size compared with other studies. Third, after subgroup analysis, the benefits of randomization assumptions no longer apply.

Subgroup analysis of the meta-analysis suggested that paricalcitol and calcitriol reduced proteinuria to a similar extent, although statistical power was limited, because only two trials with calcitriol (141 participants) were available to be included in the analysis. The largest individual study with two doses of paricalcitol (1 and 2 $\mu\text{g}/\text{d}$) suggested a dose-dependent effect of vitamin D on albuminuria²⁹; this result could, however, not be confirmed when other studies with paricalcitol were considered together in our subgroup analysis. This finding might be explained by the frequent dose reductions observed in 2 $\mu\text{g}/\text{d}$ paricalcitol groups across studies incorporating its use. The antiproteinuric effect of vitamin D therapy also seemed similar in studies with only diabetic nephropathy patients compared with studies that did not contain or did not exclusively contain diabetic nephropathy patients. Findings also seemed unchanged irrespective of study size and duration of follow-up.

Although our meta-analysis was not designed primarily to address adverse events and therefore, did not contain all studies reporting safety end points, we have summarized the safety signals reported in the eight trials in our meta-analysis. Our

data are in line with a previous meta-analysis on the safety of paricalcitol.⁴³ Numbers of severe adverse events and discontinuation were similar between active treatment and control arms. Hypercalcemia was observed more frequently with paricalcitol than placebo in PRIMO.³³ In VITAL, the number of patients with hypercalcemia was very low, but the paricalcitol dose was frequently reduced in response to parathyroid (over) suppression, which may have acted to mitigate hypercalcemia. The two largest trials, PRIMO and VITAL, also reported a small but significant reduction in renal function (eGFR). Although this finding could reflect a true GFR reduction, which was seen with conventional RAAS blockade,⁴⁴ an indirect effect on renal function through alteration of creatinine metabolism, which has been reported for both paricalcitol⁴⁵ and calcitriol,⁴⁶ seems a more likely explanation. Irrespective of the cause, the reduction of eGFR associated with paricalcitol was reversible²⁹ and similar to or less than what would be expected with addition of ARB to ACE inhibitor therapy.⁴⁷ In addition, the eGFR needs to be interpreted with caution in patients with diabetes (*e.g.*, all patients in the VITAL trial), because a recent study showed poor agreement between eGFR and measured GFR.⁴⁸ Clearly, future randomized trials are needed to address the efficacy and safety of active vitamin D analogs on hard end points, such as doubling of serum creatinine, ESRD, and all-cause and cardiovascular events.

This study is the first meta-analysis to address the effect of active vitamin D analogs (synthetic or endogenous) on residual proteinuria. Strengths include a clinically relevant research question examined using a rigorous methodology. Limitations of our study include the relatively small number of studies that were suitable for inclusion, the small to medium sample sizes of most studies included, the heterogeneity among the patient populations in which the studies took place, the fact that concomitant use of over the counter vitamin D supplements could not be excluded, and the relatively short follow-up period. Despite these limitations, the antiproteinuric effect of active vitamin D analogs, mostly given on top of RAAS blockade, was consistent across all studies and significant on meta-analysis, suggesting a true effect. The definition of a 15% reduction in proteinuria as a primary outcome for our analysis was based primarily on the REIN trial (stratum 1). In this study, a 15% reduction in proteinuria by ACE inhibitor treatment was associated with a significantly reduced risk of ESRD.³⁵ However, the clinical relevance of a 15% reduction in proteinuria is not clear and may differ per individual depending on, for example, underlying type of kidney disease and baseline proteinuria level. However, there are not many interventions providing an additional 15% proteinuria reduction on top of RAAS blockade. Therefore, we consider these data promising and requiring confirmation in prospective studies on hard end points.

In conclusion, we found that active vitamin D therapy with either paricalcitol or calcitriol provides a significant reduction of proteinuria achieved against the background of RAAS blockade in most patients. Side effects were limited, although a

negative effect on eGFR was observed in the larger studies, which might be explained by an effect on creatinine metabolism or an inappropriate eGFR in studies in diabetic patients rather than an effect on true GFR. Not many other adjunctive therapies with a similar or stronger effect on residual proteinuria are available. Therefore, we advocate a prospective RCT to address whether vitamin D may actually decrease the risk of CKD progression or mortality.

CONCISE METHODS

Search Strategy

We performed a systematic review of the available literature in accordance with the PRISMA statement.⁴⁹ The literature search, data extraction, and quality assessment were performed independently by two reviewers (M.H.d.B. and D.J.A.G.). Pubmed/Medline (from 1950 to September of 2012), Embase (from 1966 to September of 2012), and the Cochrane library database (no date restriction) were searched for relevant keywords, including all spellings of vitamin D analogs and proteinuria or albuminuria (Supplemental Material shows the complete search strategy). Search results were restricted to RCTs without language restriction. When an abstract did not contain proteinuria or albuminuria data but the presence of such data were expected in the full-text paper, the full-text paper was screened as well. We manually checked the references from all identified articles to screen for additional relevant studies. If necessary, the corresponding authors of clinical trials were requested to provide additional data for the meta-analysis. All completed RCTs with a sample size of at least fifty⁵⁰ with any follow-up length that assessed the effect of active vitamin D analogs on proteinuria (or albuminuria) in adult patients with CKD were eligible for inclusion in the meta-analysis. The outcomes analyzed were the mean change (%) in proteinuria or albuminuria from baseline to last measurement and the proportion of patients who reached a proteinuria or albuminuria reduction of $\geq 15\%$.

Data Collection and Validity Assessment

The two reviewers extracted data on patient characteristics (age, sex, renal function, underlying renal conditions, and presence of diabetes mellitus), inclusion and exclusion criteria, type of active vitamin D analog, use of comedication (especially an ACE inhibitor or ARB), duration of follow-up, and BP. Given the heterogeneity of the end points across the studies (albuminuria or proteinuria, unadjusted or adjusted for creatinine excretion, and 24-hour excretion or single portion), the end point of interest for the meta-analysis was defined as the change in proteinuria or albuminuria during the study from baseline to the last available measurement. Two analyses were performed: a continuous analysis, which yielded changes in proteinuria over time for both active and control treatment, and a dichotomous analysis, where the proportion of patients with a relevant reduction of proteinuria/albuminuria, defined as a $\geq 15\%$ decrease from baseline to last measurement, was the outcome of interest. If the proportion of patients with a $\geq 15\%$ proteinuria/albuminuria reduction was not reported in the paper, the corresponding

author was contacted to request additional data. If this information was not provided but a different percentage of proteinuria reduction was reported in the paper, these data were used. The quality of the included studies was evaluated by allocation concealment and intention-to-treat analysis; blinding of investigators, participants, and outcome assessors; similarity for prognostic factors of all study groups at baseline; and completeness of follow-up. We also used the Jadad score to quantify study quality.⁵¹

PRIMO Trial

The primary aim of the PRIMO trial (clinicaltrials.gov: NCT00497146) was to determine the effects of paricalcitol on left ventricular mass over 48 weeks in patients with an eGFR of 15–60 ml/min per 1.73 m².³³ Details and primary results of the study have been previously published.³³ Patients had first morning void urine samples collected at baseline and weeks 24 and 48 after randomization; albumin and creatinine levels were measured, and ACR was calculated. All patients with at least two ACR measurements (at baseline and either 24 or 48 weeks of follow-up) and albuminuria at baseline (ACR > 30 mg/g = 3.4 mg/mmol) were included in this meta-analysis.

Statistical Analyses

For dichotomous outcome data, individual hazard ratios and 95% CIs were calculated from individual studies before data pooling. Summary odds ratios were obtained by use of a random effects model given the clinical heterogeneity of the studies. The weighted mean reduction of proteinuria in response to active treatment was calculated by the sum of each study's mean proteinuria/albuminuria difference from baseline to the last measurement multiplied by the number of patients in the active treatment arm, which was divided by the total number of participants with active treatment across all studies. The weighted mean proteinuria reduction during control treatment was calculated similarly. Heterogeneity of the studies was assessed by the I^2 and Q statistics. To investigate potential publication bias, we created a funnel plot and used the Egger test.⁵²

For reanalysis of the PRIMO study, a maximum likelihood mixed effects repeated measures model with all longitudinal observations was used to compare the change in log-transformed ACR (caused by positive skewness) between paricalcitol and placebo groups in patients with proteinuria at baseline. The models included terms for treatment, visit, and treatment by visit interaction and log-transformed baseline outcome value. Frequency values (ACR reduction $\geq 15\%$) at 48 weeks were compared using Fisher exact test. A two-sided P value < 0.05 was considered significant. Statistical analyses were performed using PASW Statistics 18 for Windows (SPSS; IBM Company, Armonk, NY), Review Manager 5.1 (Cochrane Collaboration, Oxford, United Kingdom), and SAS 9.2 (SAS Institute, Cary, NC).

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