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Vitamin D Treatment and Mortality in Chronic Kidney Disease: A Systematic Review and Meta-Analysis

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Key Words
Chronic kidney disease · Vitamin D · Survival · Mortality · Cardiovascular mortality

Abstract
Background/Aims: Hypovitaminosis D has been associated with an increased cardiovascular mortality in the general population and in patients with chronic kidney disease (CKD). Still, whether prescribing vitamin D reduces the risk of mortality in renal patients remains controversial. ***Methods:*** We searched PubMed, ClinicalTrials.gov and the Cochrane Library for long-term longitudinal studies comparing vitamin D compounds (25-hydroxyvitamin D, 1,25-dihydroxyvitamin D and synthetic derivatives) to placebo or no treatment in renal patients, and which evaluated mortality, to perform a meta-analysis. Data concerning study quality, population and effect size were extracted independently by two investigators using predefined forms. ***Results:*** Fourteen observational studies (194,932 patients) met all eligibility criteria. Most studies were performed in hemodialysis patients and all used calcitriol or synthetic analogues. In a random effects meta-analysis, receiving any vitamin D therapy significantly reduced the risk of all-cause mortality (relative risk 0.73, 95% CI 0.65–0.82). The relative risk of death was 0.72 (95% CI 0.65–0.80) after 3 years of therapy and 0.67 (95% CI 0.45–0.98) after 5 years. In meta-regression, the risk reduction was shown to be greater in patients with higher parathyroid hormone serum levels ($p = 0.01$). The risk of cardiovascular mortality was also significantly reduced in patients receiving any vitamin D derivative (relative risk 0.63, 95% CI 0.44–0.92). ***Conclusion:*** Therapies with 1,25-dihydroxyvitamin D and analogues are associated with reduced mortality in CKD patients, and particularly in those suffering from secondary hyperparathyroidism. These results, based on observational evidence, are supportive of prescribing vitamin D therapies to CKD patients, while respecting good practice guidelines.
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Introduction

In the general population as well as in renal patients, low vitamin D precursor levels (25-hydroxyvitamin D: 25(OH)D) are associated with increased risks of cardio-

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vascular events and death [1–3]. The active form of vitamin D, 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D$), is a hormone classically known for regulating bone and mineral homeostasis, but additional biological effects including endothelial and cardiovascular protection, immunomodulation and antitumoral activities have recently been observed [4]. In the general population, restoring 25(OH)D levels with nutritional supplementation reduced the risk of mortality [5], but it is not known whether this effect remains in patients with chronic kidney disease (CKD). Vitamin D insufficiency, defined as 25(OH)D serum levels <30 ng/ml, affects up to 75% of CKD patients and can be corrected by nutritional vitamin D [6–8]. However, the impaired $1,25(OH)_2D$ synthesis due to the reduced availability of the renal enzyme 1-α-hydroxylase could preclude biological activities. Still, an abundant body of evidence shows that treatments with vitamin D derivatives (natural or synthetic $1,25(OH)_2D$ or synthetic prohormones) ameliorate mineral and bone disorders observed in CKD and improve anemia in dialysis patients [9, 10]. A previous meta-analysis of the putative benefits of treatments with these vitamin D derivatives in renal patients demonstrated that they had a proven efficacy in reducing serum alkaline phosphatase and parathyroid hormone (PTH) levels but did not influence survival [11]. This is in contrast with the clinical impression of a favorable evolution of treated patients, which is also supported by epidemiological observations in hemodialysis patients [12, 13]. Direct and indirect effects of $1,25(OH)_2D$ on the cardiorenal system are likely to occur at early stages of the disease [14, 15], suggesting that early restoration of its activity could delay dialysis initiation or death. Because the limited number of randomized controlled trials (RCTs) estimating the effect of vitamin D therapies on survival of CKD patients led to inconclusive results in a previous analysis [11], we decided to further examine this question in a meta-analysis including RCTs as well as longitudinal observational studies. We carried out a meta-analysis to evaluate the association between the use of any kind of vitamin D therapy and the risk of all-cause and cardiovascular mortality in patients affected by CKD who were followed during an average period above 6 months.

Material and Methods

Study Search and Selection

On September 1, 2010, PubMed, ClinicalTrials.gov and the Cochrane Library were searched for articles combining terms related to vitamin D (e.g. vitamin D, cholecalciferol, calcipotriol), CKD (e.g. kidney diseases, renal replacement therapy, ESRD), and mortality or cardio-vascular outcome (e.g. mortality, survival rate, coronary risk), with no time or language restrictions. Because no results met the search criteria in the ClinicalTrials.gov database, outcome terms were removed from this search (online suppl. table S1; see www.karger.com/doi/10.1159/000346846 for all online suppl. material). Authors were contacted to retrieve full-text articles when not available otherwise. Unpublished abstracts presented during the ERA-EDTA Congress (Munich, Germany, 2010) and the ASN Renal Week (Denver, Colo., USA, 2010) and literature citations were hand searched for additional studies. Reporting methods were adapted from MOOSE and PRISMA guidelines for meta-analyses [16, 17].

Studies were included in the meta-analysis if they matched all pre-specified eligibility criteria. Articles had to be original studies comparing vitamin D use to receiving a placebo or no treatment. Additional inclusion criteria were: (1) exclusion of kidney transplant patients; (2) minimal follow-up of 6 months; (3) occurrence of at least 1 death per treatment group, and (4) sufficient data to determine the relative risk and confidence interval (CI) of all-cause or cardiovascular mortality between vitamin D-treated and vitamin D-untreated patients. Searches, study selection and data extraction were performed independently by two investigators from different institutions (F.D. and M.E.R.-O.). Discrepancies were solved by discussion until consensus.

Data Extraction and Quality Assessment

From eligible studies, two reviewers independently extracted data using piloted forms (F.D. and M.E.R.-O.). The outcomes of interest were all-cause mortality, cardiovascular mortality and 3- and 5-year all-cause mortality. From each study, relative risks and 95% CI were extracted or estimated from computed estimates such as hazard ratios or from sample sizes and death rates per group [18]. In predialysis studies, deaths occurring during predialysis and dialysis stages were considered. When results were stratified, the largest stratum was included. To evaluate study quality, information depicting trial characteristics and baseline demographic and biological characteristics of patients were extracted. Because our search resulted in observational studies only, study quality was evaluated based on study design, assessment of confounding and adequacy of statistical adjustments.

Statistical Analysis

We evaluated the effect of vitamin D therapy on mortality from any cause and from cardiovascular causes, and on the 3- and 5-year all-cause mortality. Results were expressed as relative risks (RRs), defined as the ratio of the mortality rate in patients receiving vitamin D therapy over the mortality rate of patients not receiving vitamin D. Relative risks <1 suggest a protective effect of therapy. Study-specific RRs were pooled under random-effects models using the DerSimonian-Laird approach to account for expected heterogeneity [19]. Heterogeneity was assessed using the I^2 statistic for which values >50% may indicate substantial heterogeneity. The influence of sample, treatment and methodological parameters on RRs was assessed by subgroup analyses and logarithmic mixed-effects meta-regressions. The influence of within-study differences in demographic and biological characteristics of treated and control groups was tested using the same approaches. The risk of publication bias was assessed by one-tailed Egger's test, by funnel plot and by Duval and Tweedie's trim and fill method [20, 21]. Orwin's

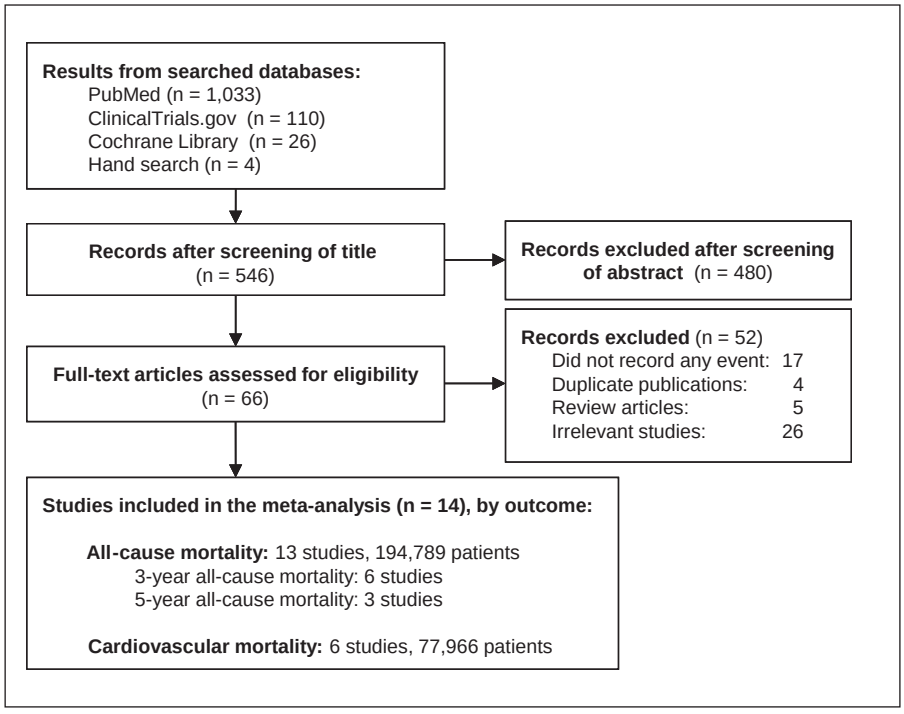

Fig. 1. Flow diagram of the selection process.

fail-safe N was calculated to estimate the number of additional non-significant studies necessary to make the pooled result of the meta-analysis reach a predefined critical value [22]. Statistical analyses were performed using Comprehensive Meta-Analysis, version 2 (Biostat Inc., Englewood, N.J., USA) and SAS, version 9.2 (SAS Institute Inc., Cary, N.C., USA).

Results

Search Results

A total of 1,169 records were identified through electronic databases PubMed, ClinicalTrial.org and the Cochrane Library, and 4 records were identified by hand (fig. 1). After screening of titles and removal of reviews, duplicate publications and irrelevant research, there remained 546 records. Screening of abstracts led to 66 remaining records of which 52 were excluded after full-text analysis because they were reviews, publications on the same study (e.g. [23]), did not provide sufficient data on effect sizes for any studied outcome (e.g. [24, 25]) or were irrelevant to the question. Consequently, 14 records were included in the meta-analysis (table 1). They included an abstract [36] and an e-published article [26], both identified through the Renal Week Symposium 2010 abstract book. An additional publication [28] providing complementary information about the original study [27] contributed to the analysis but was considered as the same work.

Records were prospective (7 studies) or retrospective (7 studies) observational studies (table 1), and there was no blinding or randomization of patients in any studies. Overall, a total of 194,932 patients were followed over an average duration of 4.5 ± 3.6 years. When given, loss to follow-up was <12% [29, 32–34]. There were 3 studies conducted in predialysis CKD patients [29, 33, 35]. Four studies were performed in patients incident to hemodialysis [31, 37, 38, 40] and the remaining 7 studies in patients already on hemodialysis [26, 27, 30, 32, 34, 36, 39]. Administered molecules were calcitriol (natural $1,25(OH)_2D_3$), paricalcitol (synthetic $1,25(OH)_2D_3$ analogue), alfacalcidol (synthetic prohormone, $1\alpha(OH)D_3$) or doxercalciferol (synthetic prohormone, $1\alpha(OH)D_2$). No study evaluated interventions with 25(OH)D supplementation or dietary precursors. One study evaluated the effect of 'active Vitamin D' but did not specify which compounds were included [36]. Treatments were given orally or by intravenous injection; 1 study did not detail the administration route [30]. Exposure was defined as receiving any dose of a vitamin D compound during follow-up.

Baseline characteristics of patients according to treatment group were available in 11 studies and absent from

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Table 1. Characteristics of the studies included in the meta-analysis

Study	Study design			Study population					Intervention		Deaths observed n	Covariates included in the adjusted model
	country	design	duration years	sample	mean age years	diabetes %	black %	mean PTH ng/l	compounds	administration route		
Jean et al. 2011 [26]	France	Prosp. cohort ARNOS	3.5	648 prevalent HD patients	67.1	32	–	270	Alfacalcidol	Oral	–	Age, gender, hypertension, diabetes, BMI, dialysis access, stroke, peripheral vascular and cardiac disease, and hospitalization
Kalantar-Zadeh et al. 2006 [27], Lee et al. 2007 [28]	USA	Retro. cohort	2	58,058 prevalent HD patients	60.3	45	32	327	Paricalcitol	Injectable	14,529 (CV, 6,243)	Age, gender, race and ethnicity, diabetes, vintage, primary insurance, marriage status, SMR, Kt/V, dialysate calcium, time-dependent serum albumin, creatinine, HCO^{3-}, hemoglobin, ferritin, WBC and lymphocyte percentage, iron-binding capacity, PCR, BMI and EPO
Kovesdy et al. 2008 [29]	USA	Retro. cohort	4	520 male incident preHD patients (veterans)	69.8	57	23	113	Calcitriol	Oral	198	None
Marco et al. 2003 [30]	Spain	Prosp. cohort	6	143 prevalent HD patients	61.9	20	0	241	Calcitriol	–	CV, 35	None
Melamed et al. 2006 [31]	USA	Prosp. cohort CHOICE	3	1,007 incident HD and PD patients	–	55	28	160	Calcitriol	Injectable	460	Age, gender, race, diabetes, dialysis modality, smoking, BMI, comorbidities, interleukin-6, CRP, education, employment status, late referral, and time-dependent albumin and hemoglobin
Naves-Díaz et al. 2008 [32]	South America	Retro. cohort CORES	4.5	16,004 prevalent HD patients	54.8	27	–	307	Alfacalcidol or calcitriol	Oral	3,110	Age, gender, race, diabetes, dialysis vintage, Kt/V, country, vascular access, weight, albumin, creatinine, hemoglobin, and time-dependent Ca, P and PTH
Shoben et al. 2008 [33]	USA	Retro. cohort, with age- and sex-matched controls	4	1,418 incident male preHD patients	70.2	59	10	151	Calcitriol	Oral	408	Age, gender, race, eGFR, diabetes, coronary heart disease, comorbidity index; use of ACEI, ARB, statin, EPO, oral calcium, BMI, SBP, albumin, Ca, P, PTH, and number of nephrology clinic visits in the previous year
Shoji et al. 2004 [34]	Japan	Prosp. cohort	6.5	242 prevalent HD patients	55.8	30	–	8,070*	Alfacalcidol	Oral	53 (CV, 31)	Age, diabetes
Sugiura et al. 2010 [35]	Japan	Retro. cohort	16	665 incident preHD patients	67	37	–	162	Alfacalcidol	Oral	132 (CV, 63)	Age, gender, diabetes, hypertension, time of enrolment, albumin, eGFR, PTH, use of ACEI
Taniguchi et al. 2010 [36] (Abstract ASN)	Japan	Prosp. cohort	2	2,854 prevalent HD patients	–	–	–	–	VDRa	Injectable and oral	–	Age, gender, albumin, Ca, P, PTH, CRP, urea nitrogen, Kt/V, PCR, comorbidities, dialysate calcium
Teng et al. 2005 [37]	USA	Retro. cohort	2	51,030 incident HD patients	61.5	53	34	306	Calcitriol or paricalcitol	Injectable	14,796	Age, gender, race, diabetes, dialysis vintage, time of enrolment, SMR, vascular access, SBP, BMI, albumin, Ca, P, PTH, HCO^{3-}, hemoglobin, ferritin, urea reduction ratio, creatinine, WBC
Tentori et al. 2006 [38]	USA	Retro. cohort	5	14,967 incident HD patients	–	–	–	–	Calcitriol, paricalcitol or doxercalciferol	Injectable	Death rate = 17.3/100 PY	Age, gender, race, etiology, dialysis vintage, Ca, P, PTH, albumin, dialysis vintage, Kt/V, creatinine, hematocrit, SMR
Tentori et al. 2009 [39]	World	Prosp. cohort DOPPS I–III	4	38,066 prevalent HD patients	61.7	38	14	280	Calcitriol, paricalcitol or doxercalciferol	Injectable and oral	Death rate = 16/100 PY	Age, gender, race, dialysis vintage, diabetes, Kt/V, vascular access, time of enrolment, country, comorbidities, parathyroidectomy, time-dependent hemoglobin, serum albumin, Ca, P, PTH and dialysate calcium
Wolf et al. 2008 [40]	USA	Prosp. cohort ArMORR	1	9,303 incident HD patients	62.8	43	35	212	Calcitriol, paricalcitol or doxercalciferol	Injectable	1,432	Age, gender, etiology, BP, BMI, vascular access, comorbidities, SMR, urea reduction ratio

*hs-PTH. ACEI = Angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blockers; BMI = body mass index; BP = blood pressure; Ca = serum calcium level; CRP = C-reactive protein; CV = cardiovascular deaths; eGFR = estimated glomerular filtration rate; EPO = erythropoietin; HCO^{3-} = serum bicarbonate level; HD = hemodialysis; P = serum phosphate level; PCR = protein catabolic rate; preHD = predialytic CKD stages; prosp. = prospective; PTH = parathyroid hormone; PY = person-year; retro. = retrospective; SBP = systolic blood pressure; SMR = standardized mortality rate; USA = United States of America; VDRa = vitamin D receptor activator; WBC = white blood cell count.

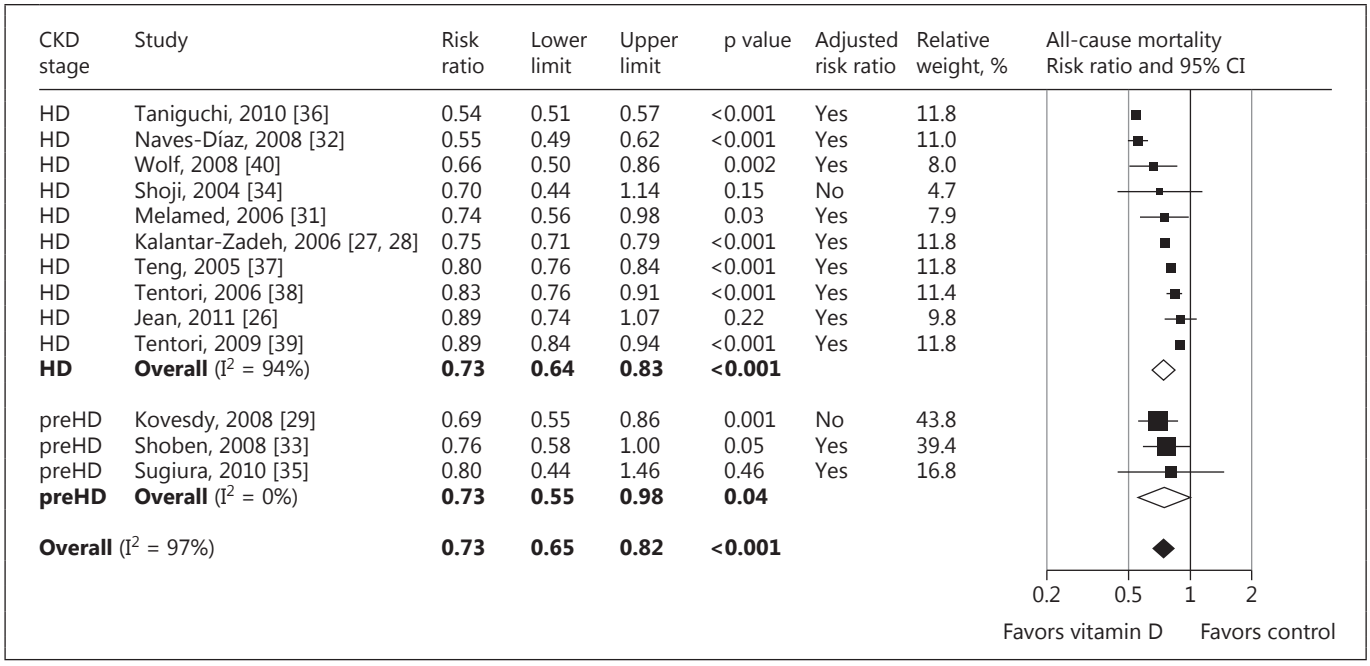

Fig. 2. Forest plots and summary estimates of all-cause mortality RRs depending on vitamin D treatment in hemodialysis patients (HD) or patients at CKD stages not requiring dialysis (preHD). RRs <1 indicate a greater chance of survival in the vitamin D therapy group as compared with the control group.

3 studies [30, 31, 36]. There were slight but consistent differences between treatment groups. Treated patients had greater baseline PTH levels (253 ± 121 vs. 159 ± 82 ng/l, p = 0.002) and serum creatinine levels (6.9 ± 3.3 vs. 6.5 ± 3.0 mg/dl, p = 0.03) and were slightly younger (62.4 ± 5.4 vs. 64.1 ± 5.3 years, p = 0.03). Four studies reported information on parathyroidectomy. At baseline, its prevalence was <9% and was not influenced by treatment group [26, 34, 38]. During follow-up, the incidence of parathyroidectomy was <0.15% [37].

Statistical adjustments were frequently applied to control for demographical, biological and therapeutic parameters and showed a large range of adjusted parameters (table 1). Based on study design, assessment of confounding and adequacy of statistical adjustments, the quality of included studies ranged from rather low to satisfactory (online suppl. table S2). The most frequently observed limitations concerned the comparability of the treated and untreated populations, and the population selection following the use of statistical models adjusting for many variables. The crude and adjusted RRs which were used in the meta-analysis are available in online suppl. table S3.

All-Cause Mortality

The association of vitamin D therapy with all-cause mortality was assessed in 13 studies [26–29, 31–40] (fig. 2). Ten studies reported a significant inverse association between receiving vitamin D and the risk of death. The pooled result showed that receiving vitamin D was significantly associated with a 27% relative risk reduction of all-cause mortality (relative risk 0.73, 95% CI 0.65–0.82). The beneficial effect was equally present among hemodialyzed patients and predialytic patients. Heterogeneity was high ($I^2 > 50\%$) in the overall meta-analysis and among studies performed in hemodialysis patients. It was absent from the subgroup of studies performed in predialysis patients ($I^2 = 0\%$). There were two study-specific estimates which did not include any adjustments [29, 34]; excluding these two crude results did not influence the results (table 2). Pooling the 11 crude RRs which were available increased the relative risk reduction to 35% (table 2).

The association between vitamin D therapy and the risk of death after 3 and 5 years of follow-up could be extracted from 6 and 3 studies, respectively (fig. 3). Most estimates were crude associations derived from survival

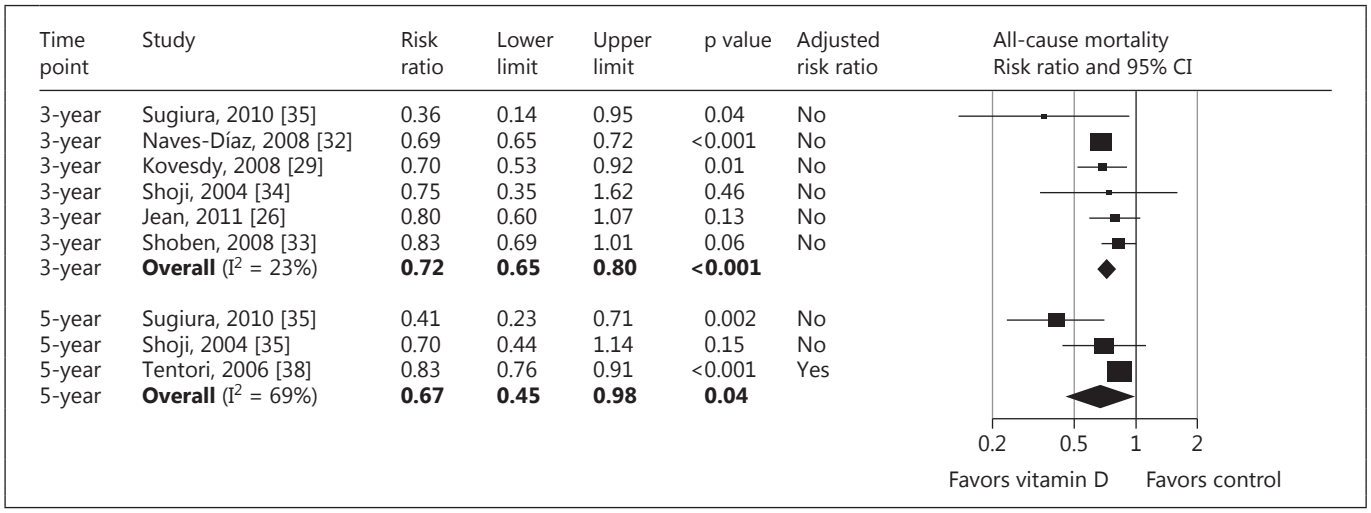

Fig. 3. Forest plots and summary estimates of all-cause mortality RRs depending on vitamin D treatment after 3 years of follow-up (3-year) or 5 years of follow-up (5-year).

Table 2. Summary estimates from random-effects meta-analyses on adjusted and unadjusted relative risks

Outcome	Studies, n	Effect size and 95% CI			p value	I^2
		RR estimate	lower limit	upper limit		
All-cause mortality						
Adjusted RR	11	0.73	0.64	0.83	<0.001	95%
Unadjusted RR	11	0.65	0.58	0.73	<0.001	94%
Cardiovascular mortality						
Adjusted RR	4	0.55	0.41	0.74	<0.001	63%
Unadjusted RR	4	0.53	0.27	1.06	0.069	83%

curves. After 3 years of follow-up, vitamin D therapy was significantly associated with a 28% relative risk reduction in mortality (RR 0.72, 95% CI 0.65–0.80), with a limited heterogeneity. Five years after study initiation, the association was similar (RR 0.67, 95% CI 0.45–0.98), with slightly greater heterogeneity.

Cardiovascular Mortality

The association of vitamin D therapy and cardiovascular mortality was assessed in 6 studies [27, 30, 32, 34–36] (fig. 4). Receiving vitamin D was significantly associated with a 37% relative reduction of cardiovascular mortality risk (RR 0.63, 95% CI 0.44–0.92). Two studies reported crude associations [27, 30]. Limiting the analysis to the 4 statistically adjusted RRs, the effect of vitamin D compounds increased to a significant 45% relative risk reduction of cardiovascular mortality (RR 0.55, 95% CI 0.41–0.74) and reduced heterogeneity (table 2). Unadjusted RR led to a similar pooled effect which was no longer significant.

Heterogeneity and Publication Bias

A significant association was observed between study-specific relative risks of death and hyperparathyroidism in treated patients (p = 0.011). Compared to untreated patients, the higher the baseline PTH levels in the treated group, the stronger the relative risk reduction in mortality (fig. 5). This was modeled by mixed-effects meta-regression on the difference between average PTH levels in treatment and control groups at baseline. The intercept of the regression line was 0.92 (95% CI 0.74–1.14) and for each differential increase of 100 ng/l of PTH levels between groups, the relative risk of death significantly decreased by 16% (RR 0.84, 95% CI 0.73–0.96). None of the

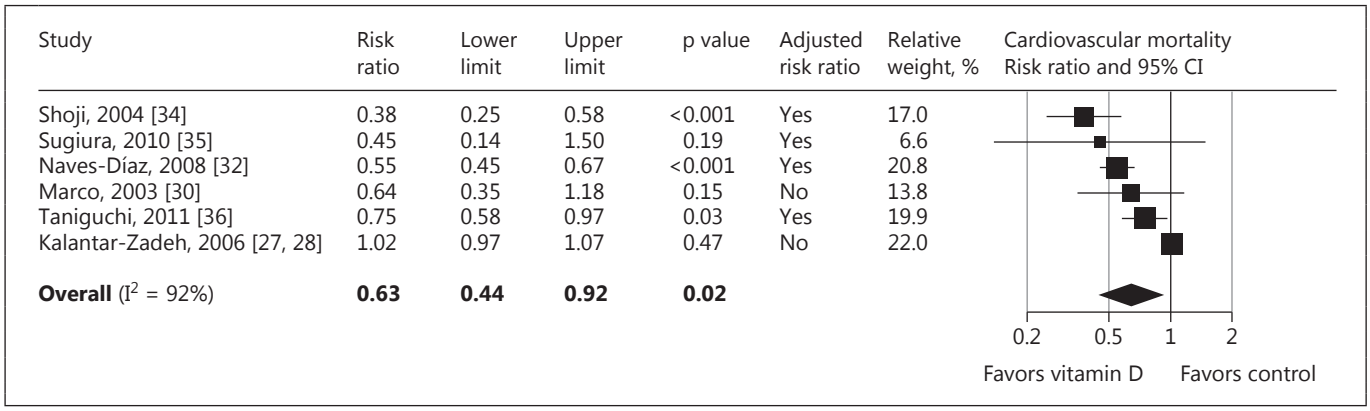

Fig. 4. Forest plot and summary estimate of cardiovascular mortality RRs depending on vitamin D treatment.

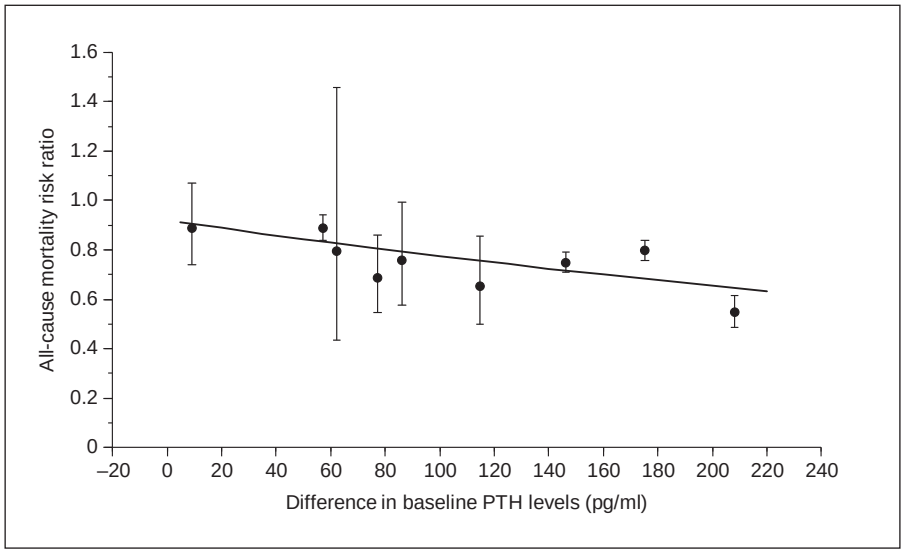

Fig. 5. Relationship between the difference in PTH levels between treatment groups and the relative risk of all-cause mortality. For each study, the difference in PTH levels was calculated at baseline, as the mean PTH level in the treated group minus the mean PTH level in the untreated group. A log linear model was fitted to the data, weighting each study by the inverse of its variance (black line). Each 100-pg/ml relative increase of PTH levels in the vitamin D group was associated with a 17% reduction of the relative mortality.

other clinical parameters which were tested (age, diabetes prevalence, albumin or creatinine levels) significantly influenced mortality RRs ($p > 0.05$).

The sample, intervention and methodological characteristics of the studies which were tested did not significantly influence results concerning all-cause mortality ($p > 0.05$, online suppl. table S4). In prevalent hemodialysis patients (6 studies) and in patients incident to hemodialysis (4 studies), the effects of vitamin D derivatives on all-cause mortality were 0.70 (95% CI 0.59–0.84) and 0.76 (95% CI 0.67–0.96), respectively. Pooled estimates from the 6 prospective studies and the 7 retrospective studies were nearly identical (0.73, 95% CI 0.60–0.88 and 0.73, 95% CI 0.61–0.87, respectively).

In one-study removed analyses, pooled estimates of all-cause mortality RR varied in a narrow range, from 0.71 (95% CI 0.63–0.81) to 0.76 (95% CI 0.70–0.82), showing the limited influence of single studies on the overall estimate (online suppl. table S5). Egger's test showed no evidence of publication bias of studies on all-cause mortality RR ($p = 0.45$). This was consistent with the symmetrical shape of the funnel plot (online suppl. fig. S1). Adding the virtually missing study from the trim and fill method did not influence pooled results. Finally, according to Orwin's fail-safe N, it would take 26 null studies to add to find an overall effect equal to a 10% relative risk reduction, signifying that unpublished non-significant studies would affect our results in a limited manner.

Discussion

Our meta-analysis found a significant 27% lower mortality risk in CKD patients receiving vitamin D therapies in the form of alfacalcidol, calcitriol or analogues. The relative risk reduction was greater with longer follow-up and for deaths attributable to cardiovascular causes (37% reduction). These results support the clinical impressions of renal physicians in favor of administering these types of vitamin D derivatives to CKD patients for their expected benefits. The survival advantage was equally observed in patients at early stages of CKD and in patients undergoing dialysis and the risk reduction was greater when treated patients were more severely affected by hyperparathyroidism.

To our knowledge, only 1 previous meta-analysis on vitamin D treatments provided results on mortality in CKD and hemodialysis patients [11]. This study included exclusively RCTs and found no influence of vitamin D therapy on mortality. However, this result, contrary to the general feeling of the renal community, needs to be carefully interpreted as it may be influenced by the lack of controlled trials analyzing an effect of vitamin D derivatives in cases of severe deficiency, since in these cases a placebo administration would have been unethical [41]. Furthermore, this estimation was based on a small number of RCTs which did not study mortality as the main objective. Altogether, these trials observed a limited number of deaths (16 deaths) occurring in 509 patients [11, 42, 43]. Our selection criteria included a minimal follow-up of 6 months to ensure sufficient time for the drug effect to occur and the outcome to be observed. Furthermore, they were settled to identify studies focusing on the association between any type of vitamin D therapy and mortality or cardiovascular diseases, in order to gather appropriately estimated results on the outcomes of interest. These stringent selection criteria failed to retain RCTs, as no RCT fulfilled them, but permitted the inclusion of 14 relevant epidemiological studies, including several large ones, observing altogether a very large number of cases (>35,155 deaths) in a total population of 194,932 patients with CKD or undergoing dialysis. The present work is, therefore, the first meta-analysis conducted to specifically estimate the treatment effect of any type of vitamin D derivative on the hard outcomes that are all-cause and cardiovascular mortality in CKD.

Overall, the majority of patients included in our analysis were clinically representative of stage 5 CKD patients, and they benefited from vitamin D therapy when they received it. However, a greater effect was observed in vitamin D-deficient patients [26, 36]. The high prevalence of vitamin D insufficiency and deficiency in CKD patients at early and final stages [7] suggests that many patients could benefit from nutritionally or medically restoring vitamin D activity. We showed that patients with greater alterations of bone and mineral homeostasis as indicated by increased serum PTH levels benefited even more from the therapy. This is interesting as serum PTH has been independently associated with increased mortality [23, 27, 44]. One could think that in our analyses treated patients, who generally had greater baseline PTH levels than untreated patients, would be at increased risk of dying. However, the proven effect of $1,25(OH)_2D$ on reducing hyperparathyroidism [45] did not only reduce a supposedly increased relative risk due to elevated PTH levels to 1, but reduced the RRs to values <1, suggesting the existence of PTH-independent biological activities of $1,25(OH)_2D$. The latter effects could also be responsible for the observed 8% risk reduction after vitamin D therapy which was present, although not statistically significant, when treated and untreated patients had similar baseline PTH levels.

In epidemiological studies, the dose-response pattern of vitamin D derivatives tended to show reduced benefits at the greater doses [27, 32]. When the mean daily intake of calcitriol or alfacalcidol exceeded 1 μg, therapies were no longer associated with survival benefits [32]. At inappropriately high doses of calcitriol or analogues, adverse effects such as hypercalcemia could overcome its protective effects. Alternatively, it could also be that the high doses were still insufficient for patients with greatly elevated PTH levels. This hypothesis is supported by the dose-response effect which appears after adjusting doses to PTH levels, showing that receiving higher doses reduced the risk of mortality to a greater extent [23]. Patients receiving greater doses are probably combined into a heterogeneous group in which both situations occur. Monitoring changes in 25(OH)D and $1,25(OH)_2D$ serum levels after vitamin D therapy could have helped understanding the physiopathological ways involved in the risk reduction, but requiring this information would have been an excessively restrictive selection criteria. Confirming our expectations, a recent analysis failed to retrieve studies on vitamin D supplementation evaluating both mortality and changes in 25(OH)D serum levels in CKD patients [8].

One limitation of the present work could be the large heterogeneity which was observed across the different study results on mortality. Because we hypothesized a clinical heterogeneity between different CKD stages, a

stratified analysis was performed according to the use of renal replacement therapy. Interestingly, heterogeneity was absent across results from non-dialyzed patients. Furthermore, therapy significantly reduced mortality to the same extent in dialyzed or in non-dialyzed patients. The fact that results were consistent independently of heterogeneity is comforting and legitimates their interpretation. Another possible limitation of our work is the inclusion of epidemiological evidence, which is prone to be affected by bias and unmeasured confounding, which would therefore remain in our meta-analysis. However, it is unlikely that the observed effect was solely due to survival bias as results remained similar after stratification for incident and prevalent populations. Confounding by indication might have occurred as we found small but systematic differences in clinical characteristics between treated and control groups which were consistent with indications for receiving vitamin D derivatives (elevated serum PTH and creatinine levels). To estimate the effect of therapy with vitamin D derivatives, independently of other patient characteristics, we used adjusted relative risks in the meta-analysis as recommended [46]. Overadjustment, which occurs after adjusting for a covariate involved in the causal pathway of the studied effect, might have been present at the study level. Still, it generally tends to underestimate the effect [47]. Disparities in concomitant medications might also have been a source of confounding. Since their introduction in 2004, calcimimetics have been used alone or in association with vitamin D derivatives in order to reduce serum PTH and calcium levels. However, the follow-up periods of most of the included studies were anterior to this date. It is therefore unlikely that calcimimetics were responsible for the observed effects. Furthermore, a recent trial suggests no direct effect of calcimimetics on survival [48].

One-study removed analysis, Egger's tests, Orwin's fail-safe N and the funnel plot showed a low risk of publication bias. However, we cannot exclude the possibility that non-significant results were not reported, in particular in the context of pharmacoepidemiology where conflicts of interest are likely to be present. Relationships with the industry were present in 8 of the included studies in the form of industrial partnership or funding, and exhaustiveness of disclosure cannot be assured. We are aware that our results are unlikely to be identically reproduced in an RCT. However, they clearly show a significant association between the use of vitamin D derivatives and a lower death risk in CKD patients.

A recent placebo-controlled RCT on paricalcitol was performed in >200 mild to moderate CKD patients [49]. Receiving paricalcitol did not improve intermediate cardiac endpoints, but was associated with fewer cardiovascular-related hospitalizations. Unfortunately for our question, no deaths occurred during a follow-up lasting over 1 year. While results from well-designed randomized clinical trials addressing the effect of vitamin D compounds on 25(OH)D status and mortality or dialysis initiation are awaited, available epidemiological evidence consistently showed that patients receiving vitamin D treatments were at lower risk of mortality. Our results are supportive of prescribing vitamin D derivatives to CKD patients, as widely accepted in the clinical community. This is particularly adapted to those patients with elevated PTH levels, provided that good practice is respected. The side effects of vitamin D derivatives should be assessed and prevented. In this regard, clinicians should adapt their practice with respect to serum calcium and phosphate levels to comply with the guidelines for bone and mineral metabolism in CKD and avoid hypercalcemia and hyperphosphatemia.

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