

## Authors and Disclosures

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## From European Journal of Heart Failure

### The Vitamin D System: A Crosstalk Between the Heart and Kidney

Mario Cozzolino; Markus Ketteler; Daniel Zehnder

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## Abstract and Introduction

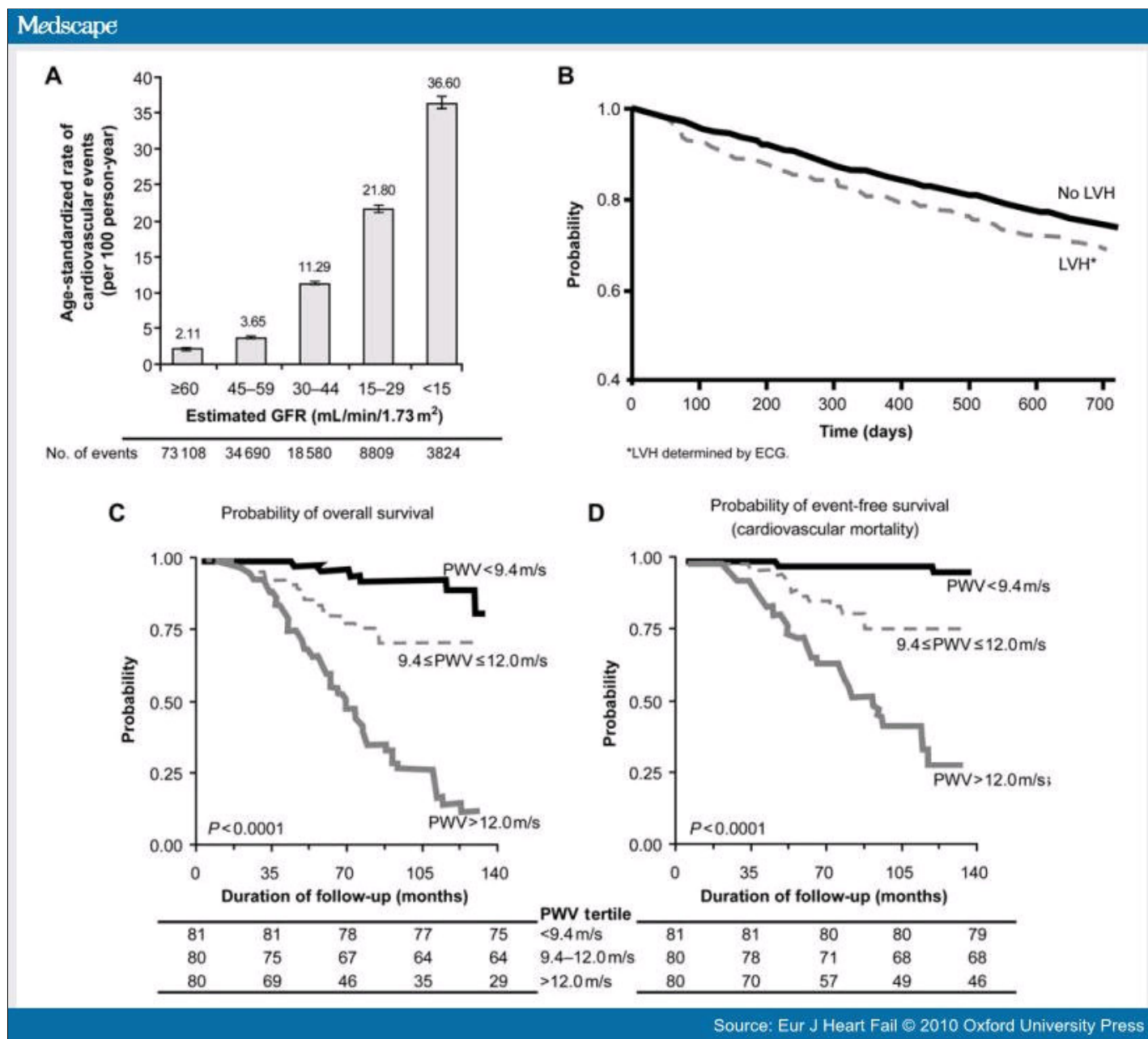
### Abstract

Chronic kidney disease (CKD) independently increases the rates of cardiovascular disease, whereas the severity of kidney disease correlates with increased cardiovascular morbidity and death. Vitamin D is modified in the liver and the kidney to its active form (1,25-dihydroxyvitamin D) by the 25-hydroxy vitamin D 1-hydroxylase enzyme (CYP27B1). The activated vitamin D brings about its actions through the vitamin D receptor (VDR). The VDRs and CYP27B1 have recently been shown to be expressed in several tissues, not directly involved in mineral homeostasis, including the cardiovascular, immune, and epithelial systems. The action of vitamin D in these tissues is implicated in the regulation of endothelial, vascular smooth muscle, and cardiac cell function, the renin-angiotensin system, inflammatory and fibrotic pathways, and immune response. Impaired VDR activation and signalling results in cellular dysfunction in several organs and biological systems, which leads to reduced bone health, an increased risk for epithelial cancers, metabolic disease, and uncontrolled inflammatory responses. Failure of cardiovascular VDR activation results in hypertension, accelerated atherosclerosis and vascular calcification, cardiac hypertrophy with vascular rarefaction and fibrosis, and progressive renal dysfunction. An emerging body of evidence has prompted attention to the relationship between CKD, mineral bone disorder (CKD-MBD), and cardiovascular disease in the new guidelines from Kidney Disease: Improving Global Outcomes. Vitamin D receptor activators, commonly used to treat CKD-MBD, and an appropriate treatment of vitamin D hormonal system failure in patients with CKD, may help to reduce cardiovascular morbidity and mortality in these patients.

### Introduction

Chronic kidney disease (CKD) results in progressive kidney dysfunction characterized by diminished glomerular filtration rate (GFR), endocrine dysfunction, soft tissue calcification, and disrupted bone and mineral metabolism.<sup>[1]</sup> Secondary hyperparathyroidism (sHPT) and vitamin D deficiency are frequently present in patients with CKD and may also contribute to disease progression and cardiovascular disease-related morbidity and mortality.<sup>[2,3]</sup> Substantial data in patients with CKD indicate that there is a close relationship between progressive renal dysfunction and cardiovascular disease and mortality.<sup>[4-7]</sup> Furthermore, mortality in patients with moderate kidney dysfunction (measured by estimated GFR) is commonly associated with cardiovascular-related events (Figure 1).<sup>[4]</sup> The prevalence of vitamin D deficiency among patients with CKD and its association with cardiovascular morbidity and mortality<sup>[2,3,8]</sup> suggests a potentially

important link between low vitamin D levels and risks for cardiovascular events in this patient population. Data from a 5-year prospective longitudinal study involving more than 27 000 patients in the USA demonstrated that, in patients with CKD (defined as estimated GFR <90 mL/min per 1.73 m<sup>2</sup> on two separate measurements at least 90 days apart), death is more likely than end-stage renal disease (ESRD) and that congestive heart failure (CHF) and coronary artery disease are more prevalent than haemodialysis in this patient population.<sup>[9]</sup> Furthermore, hypertension is cited as the second most common cause of ESRD after diabetes,<sup>[10]</sup> and arterial calcification is a complication of CKD.<sup>[5,6]</sup> In light of this emerging evidence, the relationship between CKD-related mineral bone disorder and cardiovascular disease have been a focal point of the new guidelines from Kidney Disease: Improving Global Outcomes (KDIGO).<sup>[11]</sup> Although there appears to be an obvious link between vitamin D deficiency and increased cardiovascular risk, the mechanisms involved are not well understood. This article discusses the preclinical and clinical data that explore the potential mechanisms supporting the link between vitamin D deficiency, failure of the vitamin D hormonal system, vitamin D receptor (VDR) activator therapy, and cardiovascular disease.

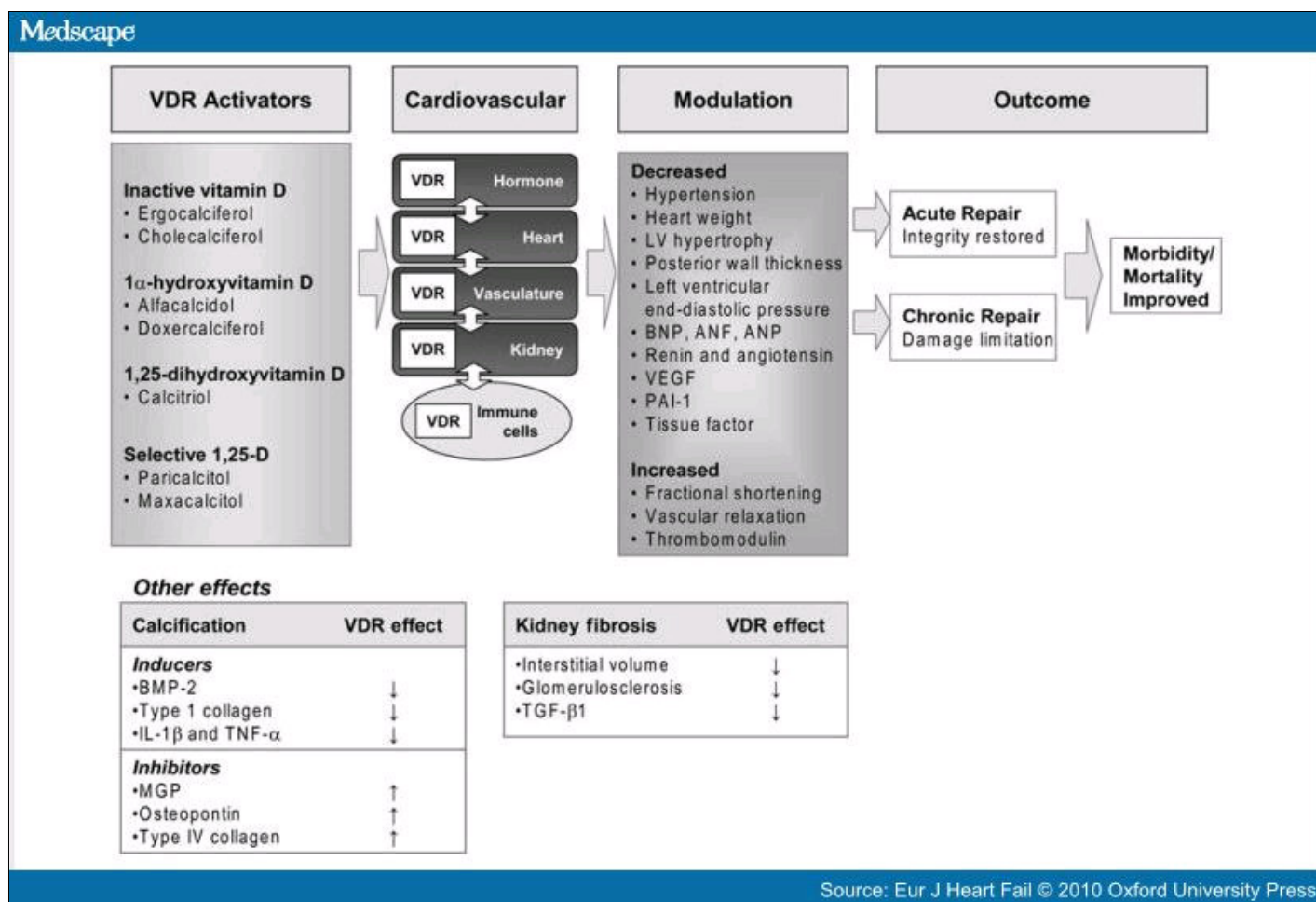


**Figure 1.** Clinical impact of eGFR, left ventricular hypertrophy, and pulse wave velocity on cardiovascular events and survival in patients with end-stage renal disease. (A) Age-standardized cardiovascular events by eGFR (reproduced with permission from Go *et*

al.<sup>4</sup> ©2004-Massachusetts Medical Society. All rights reserved). (B) Effect of left ventricular hypertrophy (determined via ECG) on survival. Kaplan–Meier survival estimates were adjusted for potential confounders (i.e. age at study start, sex, and race) by multivariate Cox regression analysis. \* $P < 0.01$  (reprinted with permission from Stack and Saran.<sup>85</sup> ©2002 with permission from Elsevier). (C) Probability of overall and (D) event-free survival by pulse wave velocity. Kaplan–Meier survival estimates were compared using the Mantel (log-rank) test and prognostic factors (i.e. age and aortic pulse wave velocity) were identified using a Cox proportional-hazards regression model (reproduced with permission from Blacher *et al.*<sup>86</sup>). ECG, electrocardiogram; eGFR, estimated glomerular filtration rate.

## Vitamin D Hormonal System

Vitamin D is obtained as an inactive substance from dietary sources (vitamin D<sub>2</sub>, ergocalciferol) and from the action of sunlight on the skin (vitamin D<sub>3</sub>, cholecalciferol), and is metabolized from the inactive form (25-hydroxyvitamin D [25-D]) to the active 1 $\alpha$ ,25-dihydroxyvitamin D<sub>2</sub> and D<sub>3</sub> (1,25-D) forms through enzymatic modification in the liver (25-hydroxylation) and kidney (1 $\alpha$ -hydroxylation).<sup>[12,13]</sup> Vitamin D mediates its effects via the VDR, a member of the steroid receptor superfamily. Vitamin D receptor is a ligand-activated transcription factor that forms a heterodimer with the retinoid X receptor, which results in the recruitment of other nuclear proteins to form the transcriptional pre-initiation complex.<sup>[14]</sup> Vitamin D receptors have been identified in over 30 human tissues, including the intestine, kidney, bone, parathyroid gland, immune system, smooth muscle, and myocardium.<sup>[15]</sup> Recent evidence demonstrates extrarenal expression of 25-D 1 $\alpha$ -hydroxylase (CYP27B1) in several tissues, including hair follicles, lymph nodes, the tonsils, the colon, parasympathetic ganglia, the adrenal gland, the pancreas, the brain,<sup>[16]</sup> and the vasculature.<sup>[17]</sup> The selective VDR activation in multiple tissues (Figure 2) explains the autocrine and paracrine actions of vitamin D, including those on the cardiovascular system.



**Figure 2.** Impact of vitamin D receptor activators on cardiovascular endpoints and patient outcome. ANF, atrial natriuretic factor;

ANP, atrial natriuretic peptide; BMP-2, bone morphogenetic protein-2; BNP, brain natriuretic peptide; IL-1 $\beta$ , interleukin-1 $\beta$ ; LV, left ventricular; MGP, matrix Gla protein; PAI-1, plasminogen activator inhibitor-1; TGF- $\beta$ , tumour growth factor- $\beta$ ; TNF- $\alpha$ , tumour necrosis factor- $\alpha$ ; VEGF, vascular endothelial growth factor.

The binding of 1,25-D to the ubiquitously present VDR leads to activation of downstream endocrine, paracrine, and/or autocrine loops to maintain homeostasis in the kidney, bone, immune, and cardiovascular systems.<sup>[14]</sup> Holick and colleagues concluded that the synthesis, metabolism, and feedback loops of vitamin D and VDR have widespread systemic responses.<sup>[13,18]</sup> Vitamin D receptor activation is increasingly recognized as a vital component in maintaining renal, cardiovascular, and bone tissue health.

## 25-Hydroxyvitamin D and 1 $\alpha$ ,25-dihydroxyvitamin D Deficiency

Currently, there is no defined cut-off for deficiency of 25-D or 1,25-D; however, most studies have defined vitamin D deficiency as serum 25-D levels of <20 ng/mL with normal levels >30 ng/mL as desired. Vitamin D deficiency has been associated with several pathological states, including cancer, infectious diseases; Type 2 diabetes mellitus, hypertension, and cardiovascular disease.<sup>[8,18–20]</sup> Several studies have shown survival benefit with vitamin D therapy in the general population, as well as in patients with CKD (pre-dialysis and dialysis; Table 1). A meta-analysis of randomized trials evaluating the impact of ergocalciferol and cholecalciferol among patients with a variety of health conditions showed an association between supplemental vitamin D intake and reduced all-cause mortality rates.<sup>[21]</sup> Differential effects on mortality between types of VDR agonists were seen in a large, well-controlled historical cohort receiving IV paricalcitol (a synthetic 1,25-D analog, 19-nor-1,25-dihydroxyvitamin D<sub>2</sub>) and IV calcitriol (synthetic 1,25-dihydroxyvitamin D<sub>3</sub>) in the USA.<sup>[22]</sup> Paricalcitol was shown to confer improved 3-year survival in haemodialysis patients; a similar significant trend was observed in those who were switched from calcitriol to paricalcitol.<sup>[22]</sup> In comparison with calcitriol, doxercalciferol (a synthetic 1 $\alpha$ -D, 1 $\alpha$ -hydroxyvitamin D<sub>2</sub>), and paricalcitol showed similar effects on mortality rates in haemodialysis patients.<sup>[23]</sup> To date, no studies have demonstrated increased mortality in patients receiving VDR agonist therapy. In addition, observational studies have noted a clinical advantage and cost reduction when VDR agonist therapies have been used.<sup>[24–26]</sup> Studies demonstrating decreased mortality or hospitalization costs following VDR agonist therapy in patients with CKD are listed in Table 1.<sup>[22–35]</sup>

**Table 1. Studies demonstrating decreased mortality or hospitalization costs following vitamin D receptor activator therapy in patients with chronic kidney disease<sup>a</sup>**

Study	Sample size (n)	Key inclusion criteria	Follow-up time	Primary endpoint(s)	Potential confounding variables
Decrease in mortality					
Teng <i>et al.</i> <sup>22</sup>	67 399	Patients undergoing long-term haemodialysis Initiated vitamin D treatment between 1999 and 2001	36 months	Mortality rates in paricalcitol users (n = 29 021) vs. calcitriol users (n = 38 378)	Age, sex, race, diabetes status, duration of dialysis, study entry period, SMR, dialysis access, and baseline laboratory values (e.g. calcium, phosphorus, and PTH levels) <sup>b</sup>
Shoji <i>et al.</i> <sup>27</sup>	242	Patients with ESRD undergoing long-term haemodialysis	Mean 61 $\pm$ 23 months	Mortality rates in alfalcidol users (n = 162) vs. non-users (n = 80)	Age, diabetes status, systolic BP, non-HDL-cholesterol, and pre-existence of IHD, CIMT, or carotid artery calcification <sup>b</sup>
Teng <i>et al.</i> <sup>28</sup>	51 037	Patients with ESRD who initiated chronic	24 months	2-year mortality rates in patients receiving	Baseline age, gender, race, diabetes status, arteriovenous

		haemodialysis between 1 January 1996 and 31 December 1999		activated injectable vitamin D ( $n = 37\ 173$ ) or not ( $n = 13\ 864$ )	access, systolic BP, BMI, laboratory values (e.g. blood albumin, WBC count, haemoglobin), hospitalizations, and SMR <sup>b</sup>
		Survived $\geq 90$ days after haemodialysis initiation			
Kalantar-Zadeh <i>et al.</i> <sup>29</sup> and Lee <i>et al.</i> <sup>31</sup>	58 058	Patients undergoing maintenance haemodialysis (>3 months duration) between 1 July 2001 and 30 June 2003	24 months	Mortality rates in patients receiving vitamin D (paricalcitol or calcitriol; $n = 39\ 305$ ) or not ( $n = 18\ 753$ )	Indicators of osteodystrophy (e.g. calcium, phosphorus, PTH, alkaline phosphatase), age, gender, race, diabetes status, time on dialysis, SMR, vitamin D dose <sup>b</sup>
Naves-Diaz <i>et al.</i> <sup>30</sup>	16 004	Patients using only oral vitamin D who initiated or were undergoing chronic haemodialysis between January 2000 and June 2004	Median 16 months (range 3–54)	Mortality rates in patients receiving vitamin D ( $n = 7203$ ) or not ( $n = 8801$ )	Age, gender, country, centre, diabetes status, time on dialysis, vascular access, weight, laboratory values (e.g. blood albumin, haemoglobin, creatinine), and delivered dose of dialysis <sup>b</sup>
Tentori <i>et al.</i> <sup>23</sup>	14 586	Patients who initiated chronic haemodialysis between January 1999 and September 2004	Median 37 weeks	Mortality rates in patients receiving calcitriol ( $n = 3212$ ), paricalcitol ( $n = 2087$ ), doxercalciferol ( $n = 2432$ ), or no vitamin D ( $n = 6855$ )	Age, gender, race, cause of ESRD, year of dialysis initiation, time on dialysis prior to first vitamin D administration, laboratory values (e.g. serum calcium, phosphorus, PTH), and SMR <sup>b</sup>
		Survived for $\geq 30$ days after first administration of vitamin D			
Wolf <i>et al.</i> <sup>32</sup>	1000	Patients who initiated long-term haemodialysis between 1 July 2004 and 30 June 2005 (ArMORR)	3 months	All-cause mortality rates stratified by 25D and 1,25D levels at baseline, and by subsequent active vitamin D therapy	Age, gender, race, season, US state, cause of ESRD, BP, BMI, dialysis access, dialysis dose, SMR, and co-morbidities <sup>b</sup>
		Not receiving oral or injectable vitamin D at baseline			
Wolf <i>et al.</i> <sup>33</sup>	9303	Patients who initiated long-term haemodialysis between 1 July 2004 and 30 June 2005 (ArMORR)	12 months	All-cause mortality rates between non-Hispanic white ( $n = 5110$ ), Hispanic white ( $n = 979$ ), and black ( $n = 3214$ ) patients stratified by use of active vitamin D therapy	Age, gender, cause renal failure, BP, BMI, vascular access at initiation, SMR, and co-morbidities <sup>b</sup>

Shoben <i>et al.</i> <sup>34</sup>	1418	Pre-dialysis patients with Stage 3 or 4 CKD and hyperparathyroidism	Median 1.9 years	Mortality rates in oral calcitriol users ( <i>n</i> = 429) vs. non-users ( <i>n</i> = 989)	Age, race, gender, site, number of clinic visits, BMI, systolic BP, diabetes status, co-morbidities, medication use (i.e. ACEI, ARB, statin, erythropoietin, or oral calcium), baseline laboratory values (e.g. PTH, albumin, calcium, phosphorous levels), and eGFR <sup>b</sup>
		First oral calcitriol treatment between 1999–2007 (users)			
		Outpatient nephrology clinic visit within the previous year			
Kovesdy <i>et al.</i> <sup>35</sup>	520	Male pre-dialysis patients with Stage 3–5 CKD and HPT	Median 2.1 years	All-cause mortality rates in calcitriol users ( <i>n</i> = 258) vs. non-users ( <i>n</i> = 262)	Age, race, co-morbidities, smoking, diastolic BP, BMI, use of phosphate binders, eGFR, laboratory assessments (e.g. WBC count, % lymphocytes, levels of PTH, calcium, phosphorus, albumin) <sup>c</sup>
		Undergoing evaluation and treatment from 1 January 1990 to 30 June 2005			
Decrease in hospitalizations and/or cost of treatment					
Schumock <i>et al.</i> <sup>24</sup>	66 019	Pre-dialysis patients with CKD with SHPT	72 months	Annualized estimates of healthcare costs and utilization, stratified by evidence of SHPT ( <i>n</i> = 667) or no SHPT ( <i>n</i> = 65 352)	Age, gender, insurance plan type, payer type, geographic region, physician specialty, pre-index co-morbidities, and pre-index total healthcare costs <sup>d</sup>
		Diagnosis based on ≥1 medical or facility claim between 1 January 2000 and 31 December 2004			
		Continuously enrolled in a health plan for ≥12 months prior and ≥6 months after initial claim			
		Not receiving VDR activator therapy			
Melnick <sup>25</sup>	NA	Patients initiating chronic haemodialysis and receiving vitamin D treatment between January 1999 and December 2001	12 months	Hospitalization risk in patients receiving paricalcitol vs. calcitriol	Age, gender, race, diabetes status, treatment, average dose/day, and laboratory values (e.g. serum albumin, alkaline phosphatase, calcium, phosphorus, iPTH) <sup>c</sup>
Dobrez <i>et al.</i> <sup>26</sup>	11 443	Patients initiating chronic haemodialysis (>60 days) and who received parenteral vitamin D therapy (>10 IV injections) between 1 January 1999 and 30 November 2001	~36 months	Total number of all-cause hospitalizations and total number of days for all-cause hospitalizations and during the observational period, and	Age, gender, race, CMS region, diabetes status, co-morbidities, time on dialysis prior to initial vitamin D therapy, time in study, and laboratory values (e.g. serum PTH, calcium,

	risk of first hospitalization after initiation of vitamin D therapy	alkaline phosphatase, albumin) <sup>e</sup>
	Comparison between paricalcitol users ( <i>n</i> = 4611) and calcitriol users ( <i>n</i> = 6832)	

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ArMORR, Accelerated Mortality on Renal Replacement prospective cohort study; BMI, body mass index; BP, blood pressure; CIMT, carotid intima-media thickness; CMS, Center for Medicare/Medicaid Services; D, dihydroxyvitamin D; eGFR, estimated glomerular filtration rate; GLM, general linear models; IHD, ischaemic heart disease; IV, intravenous; HDL, high-density lipoprotein cholesterol; HPT, hyperparathyroidism; iPTH, intact parathyroid hormone; OLS, ordinary least squares; PTH, parathyroid hormone; NA, not available; SHPT, secondary hyperparathyroidism; SMR, standardized mortality rate; VDR, vitamin D receptor; WBC, white blood cell.

<sup>a</sup>May not include all variables; see original reference for further details of study design and statistical methodology.

<sup>b</sup>Fixed variables used in multivariate Cox proportional-hazards regression models.

<sup>c</sup>Fixed variables used in Poisson regression models.

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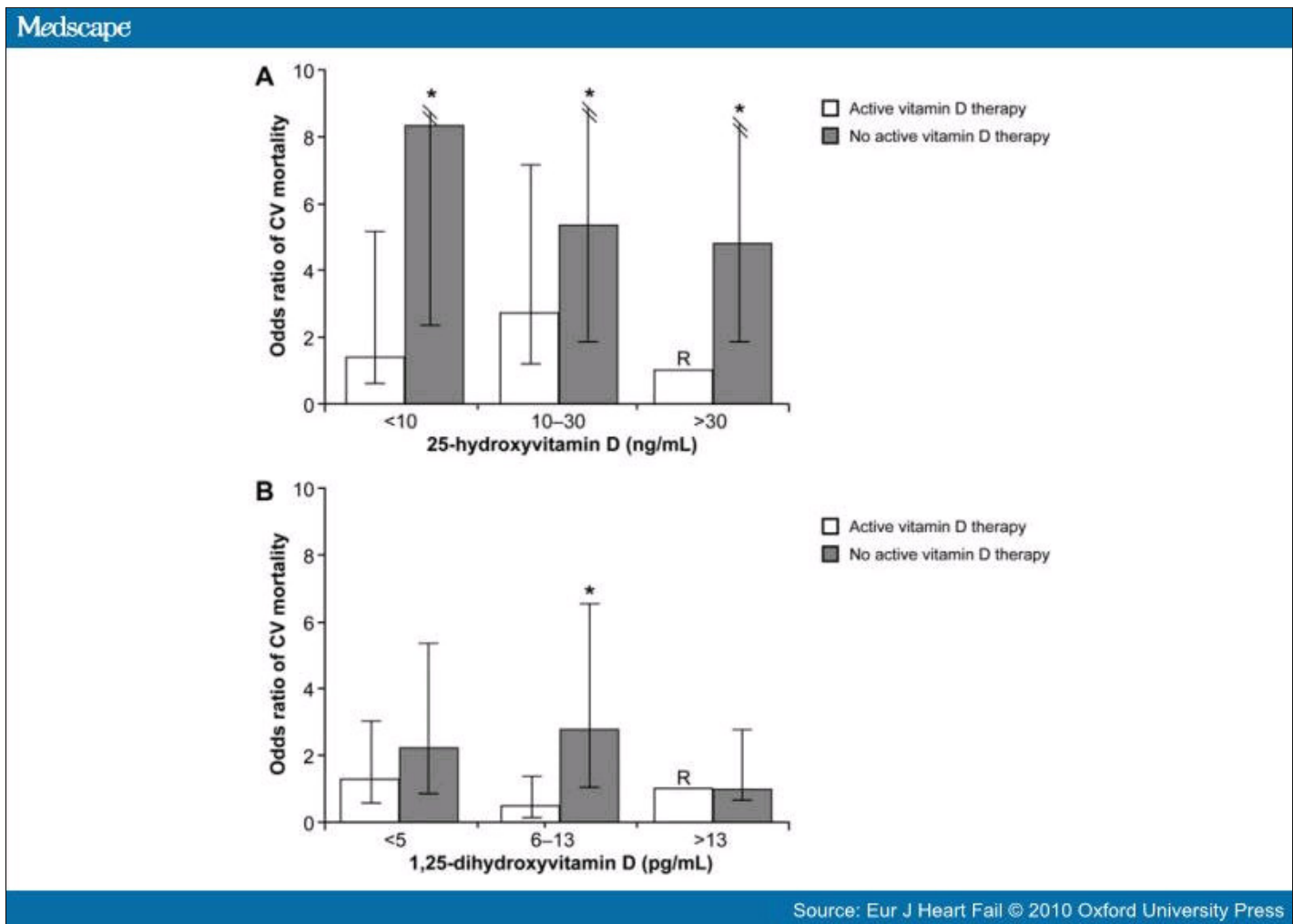
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The Accelerated Mortality on Renal Replacement (ArMORR) prospective, cross-sectional studies of 1,25-D and 25-D deficiencies in incident haemodialysis patients support the association between reduced mortality risk following the introduction of VDR agonist therapy when given in conjunction with dialysis.<sup>[32,33]</sup> When compared with patients with the highest 25-D or 1,25-D levels who received VDR agonist therapy, untreated 25-D or 1,25-D deficient patients showed significantly elevated risk for early cardiovascular-related (Figure 3) and all-cause mortality by multivariate-adjusted analysis (odds ratio = 0.60; 95% CI, 0.37–0.91; *P* < 0.01). This association has been observed in patients with moderate renal impairment (Stage 3–5 CKD, pre-dialysis) and supports the use of VDR agonists in the early stages of CKD to lower mortality risk.<sup>[34,35]</sup> The survival benefit with VDR agonist therapy needs to be further explored because a recent meta-analysis examining the effects of vitamin D therapy on mortality cited a lack of beneficial effect on patients.<sup>[36]</sup> However, there were a number of limitations to this study, notably the absence of inclusion of prospective studies and inability to directly compare older established therapies with newer, more selective treatments. The KDIGO initiative has the mission to create evidence-based guidelines for the diagnosis, evaluation, prevention, and management of CKD; this effort currently includes the classification of Stages 1–5 CKD with an updated perspective on the pathophysiology of CKD as it relates to renal and extrarenal pathways for vitamin D actions and effects.<sup>[11]</sup>



**Figure 3.** Odds ratio by multivariate-adjusted (covariates used in multivariate models included age, gender, race, aetiology of renal failure, blood pressure, body mass index, dialysis access at initiation, dialysis dose, facility-specific standardized mortality rates, and co-morbidities at the initiation of dialysis) analysis for 90-day cardiovascular mortality in haemodialysis patients according to baseline (A) 25-D and (B) 1,25-D levels (reprinted by permission from Macmillan Publishers Ltd: Wolf *et al.* <sup>32</sup> ©2007). R, reference groups (patients who were treated with active vitamin D and had 25-D levels  $\geq 30$  ng/mL or 1,25-D levels  $\geq 13$  pg/mL).

Studies in animals and humans have found that vitamin D hormonal regulation in CKD is not driven solely by parathyroid hormone (PTH) levels and renal phosphate metabolism. Shimada *et al.* performed an *in vivo* experimental study to evaluate the effects of fibroblast growth factor-23 (FGF-23) on phosphate and 1,25-D metabolism, which included a control group of animals subjected to parathyroidectomy (PTX), and found that FGF-23 reduced serum phosphate and 1,25-D levels even in the PTX animals. These effects were independent of renal phosphate reabsorption and thought to be associated with possible extrarenal mechanisms.<sup>[37]</sup>

## Vitamin D Deficiency and the Cardiovascular System

### Cardiovascular Morbidity and Mortality

Numerous epidemiological and clinical studies have suggested a strong association between vitamin D deficiency and cardiovascular disease in the general population.<sup>[38]</sup> The various cardiovascular effects of vitamin D deficiency and reduced VDR activation include hypertension, vascular calcification, smooth muscle cell proliferation, and fibrosis, which lead to myocardial and arterial thickening, atherogenesis, and left ventricular hypertrophy (LVH).<sup>[39]</sup> Serum 25-D levels are significantly depleted in most patients with end-stage heart failure (i.e. CHF) and may be independently associated with poor clinical outcomes,<sup>[40]</sup> elevated risk for myocardial infarction,<sup>[20]</sup>

and increased duration of decompensated heart failure.<sup>[41]</sup> A recent report<sup>[42]</sup> highlighted the importance of VDR signalling as a potential mechanism to control foam cell formation and atherosclerotic cardiovascular disease.

Recent longitudinal data from 1739 individuals in the Framingham Offspring Study who had no previous cardiovascular disease showed an association between low 25-D levels and incident cardiovascular disease.<sup>[43]</sup> Patients with 25-D levels below a threshold of 15 ng/mL showed an approximately doubled age- and sex-adjusted 5-year rate of cardiovascular disease and a significantly elevated risk for cardiovascular events by multivariable-adjusted analysis [hazard ratio (HR) = 1.62; 95% CI, 1.11–2.36;  $P = 0.01$ ] compared with those with 25-D levels  $\geq 15$  ng/mL. Cardiovascular events included myocardial infarction, coronary insufficiency, angina, stroke, transient ischaemic attack, peripheral claudication, or heart failure.<sup>[43]</sup> Low 25-D and 1,25-D levels significantly correlated with all-cause and cardiovascular mortality in a prospective, cross-sectional study among 3258 patients undergoing scheduled coronary angiography.<sup>[8]</sup> Patients with vitamin D deficiency (defined as those with 25-D levels  $\leq 20$  ng/mL) demonstrated an increased risk for all-cause mortality (HR = 2.34, 95% CI, 1.48–3.39) compared with those without vitamin D deficiency. In addition, three observational studies in patients with CKD (dialysis dependent and non-dialysis dependent) reported an association of low serum 25-D levels with an increased risk for death or a composite of death and ESRD.<sup>[44,45]</sup>

### Blood Pressure

High blood pressure is a well-characterized independent risk factor for cardiovascular disease. The renin–angiotensin system (RAS) is a key regulator of blood pressure and is implicated as a mechanism for hypertension in vitamin D deficiency. Preclinical studies of the RAS confirm its involvement in regulating blood pressure and volume homeostasis to modulate cardiovascular and renal outcomes. Renin synthesis, the first and rate-limiting component of the RAS cascade, increased several-fold in the juxtaglomerular cells of VDR knockout mice with concomitant plasma RAS activation; VDR activation of RAS was independent of calcium and PTH.<sup>[46,47]</sup> Treatment of experimental models of CKD<sup>[48]</sup> and diabetic nephropathy<sup>[49]</sup> with angiotensin-converting enzyme inhibitor or angiotensin receptor II blocker and VDR agonist paricalcitol effectively prevented progression of kidney disease, mirroring the effect of aliskiren, a new oral direct renin inhibitor.<sup>[50]</sup>

In VDR-null mice, renin mRNA was more than three times higher and plasma levels of angiotensin II were more than 2.5 times higher than in wild-type mice. Interestingly, despite higher renin mRNA expression, the VDR-null mice response to salt loading and dehydration was the same for wild-type mice, suggesting that the mechanism of VDR activity on blood pressure was separate from the physiological effects of changes in renal tubular salt load and volume depletion.<sup>[51]</sup> A recent study showed that plasma 25-D levels inversely correlate with the risk of incident hypertension.<sup>[52]</sup> The analyses of data from 12 644 subjects in the third National Health and Nutrition Examination Survey (NHANES) demonstrated a modest but significant inverse correlation between serum 25-D levels and blood pressure after adjustment for age, gender, ethnicity, and physical activity.<sup>[53]</sup>

Possible relationships between vitamin D and arterial dysfunction were evaluated in stable patients with ESRD who were on haemodialysis. Aortic pulse wave velocity (PWV), brachial artery distensibility (BAD), flow-mediated distensibility (FMD), and arterial calcification were measured, and 1,25-D levels were determined using radioimmunoassay. Univariate analyses found a negative correlation between 1,25-D and PWV ( $-0.616$ ,  $P < 0.0001$ ) and positive correlations between 1,25-D and BAD ( $0.632$ ,  $P < 0.01$ ) and FMD ( $0.741$ ,  $P < 0.0001$ ), but no correlation between 1,25-D and arterial calcification.<sup>[54]</sup>

### Vascular Calcification

Vascular calcification is a common manifestation of cardiovascular disease in patients with CKD, and serum 1,25-D levels have been shown to inversely correlate with vascular calcification.<sup>[55]</sup> A sub-analysis among patients without baseline coronary artery calcification from the Multi-Ethnic Study of Atherosclerosis demonstrated that low 25-D levels were associated with an increased risk for coronary artery calcification, independent of other cardiovascular disease risk factors over a 3-year follow-up period.<sup>[56]</sup> The impact of VDR agonists on vascular calcification is variable depending on the dose administered.<sup>[57,58]</sup> Low or clinically relevant doses of VDR agonists correlate with

decreased deposition of calcium and improved therapeutic outcomes, whereas high doses may actually induce vascular calcification, [59,60] an effect that is reversible with the cessation of treatment and probably indirectly mediated by hypercalcaemia and hyperphosphataemia.<sup>[61]</sup> In contrast to the potentially harmful effects of vascular calcification observed following high doses of VDR agonists,<sup>[60]</sup> VDR activation has a number of potential ameliorative effects on both inhibitors and inducers of calcification (Figure 2).

### Myocardial Effects

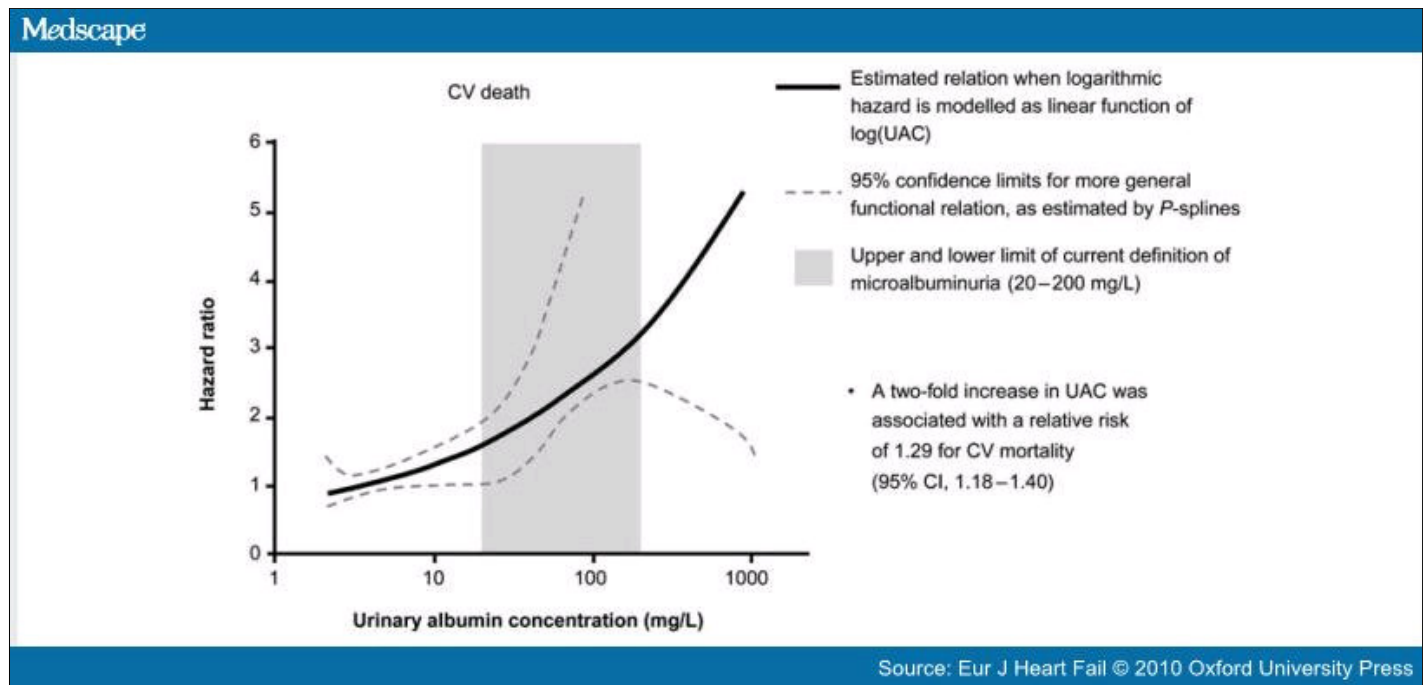
There is growing evidence to suggest an inversely proportional association of low vitamin D levels and myocardial infarction. In a prospective nested case-controlled study among 18 225 men in the Health Professionals Follow-Up Study, men with vitamin D deficiency (25-D levels <15 ng/mL) were at increased risk for myocardial infarction after adjustment for matched variables compared with those with vitamin D levels >30 ng/mL (relative risk, 2.42; 95% CI, 1.53–3.84;  $P < 0.001$ ).<sup>[20]</sup> Vitamin D receptor and 1- $\alpha$ -hydroxylase are expressed by the myocytes, and it is proposed that signalling downstream of VDR may have an antihypertrophic effect on the cardiac muscle.

In preclinical studies, VDRs were up-regulated in response to cardiac hypertrophic conditions.<sup>[62,63]</sup> In the absence of expression, VDR knockout mice develop cardiomyocyte hypertrophy and display notable effects on the systemic and myocardial RAS (e.g. increased atrial natriuretic peptide, renin) and matrix proteins involved in cardiac remodelling (i.e. increased matrix metalloproteinases and reduced expression of tissue inhibitors of metalloproteinases).<sup>[64,65]</sup> Exogenous administration of calcitriol (i.e. synthetic 1,25-D<sub>3</sub>) or paricalcitol (i.e. synthetic 1,25-D<sub>2</sub>) has shown improvements in left ventricular structure and function, myocardial collagen, and cardiac output compared with control in two different *in vivo* models of cardiac hypertrophy.<sup>[66,67]</sup>

Patients with CKD are deficient in both 25-D and 1,25-D, which are associated with arterial parameters of increased PWV and arterial stiffness along with elevated LVH and cardiovascular mortality in dialysis patients.<sup>[32,54]</sup> Treatment with a VDR agonist has been associated with reduced LVH in haemodialysis patients, without causing effects on heart rate, blood pressure, or total peripheral resistance.<sup>[68]</sup>

### Proteinuria and Albuminuria

Microalbuminuria and macroalbuminuria have been identified as risk factors for cardiovascular death. Therapies that reduce proteinuria demonstrate notable cardioprotective and renoprotective responses.<sup>[69–72]</sup> In the Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus (NIDDM) With the Angiotensin II Antagonist Losartan (RENAAL) study, baseline albuminuria was shown to be a determinant risk for cardiac events in patients with renal events, regardless of the initiating complication (cardiovascular or renal).<sup>[73]</sup> Data from the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study, a large postal questionnaire study, demonstrated that urinary albumin excretion is a predictor of all-cause and cardiovascular mortality in the general population (Figure 4).<sup>[74]</sup> Reduced proteinuria has been observed with exogenous 1,25-D<sub>3</sub> treatment in animal models independent of its PTH-lowering effects,<sup>[75]</sup> as well as in patients with Stage 3/4 CKD with sHPT treated with paricalcitol despite the use of renin–angiotensin–aldosterone system inhibitors,<sup>[76]</sup> and in patients with immunoglobulin A nephropathy following calcitriol treatment.<sup>[77]</sup> Agarwal *et al.*<sup>[76]</sup> reported a reduction in proteinuria in 51% of patients with CKD treated with oral paricalcitol compared with 25% of those who received placebo ( $P = 0.004$ ).



**Figure 4.** Hazard ratio (The effects of urinary albumin concentration on cause-specific hazards of cardiovascular risk were calculated using a Cox proportional-hazards model adjusted for explanatory variables, which included sex, age, presence of diabetes mellitus, use of antihypertensive drugs, use of lipid-lowering drugs, smoking, family history of cardiovascular disease, previous myocardial infarction, previous stroke, and urinary albumin concentration doubling.) for cardiovascular death by urinary albumin concentration: PREVEND study (reproduced with permission from Hillege *et al.*<sup>74</sup>). UAC, urinary albumin concentration.

### Implications and Limitations for Clinical Practice

The detrimental effects of vitamin D deficiency on cardiovascular morbidity and mortality are clear; however, it has yet to be established whether vitamin D substitution and pharmacological VDR activation can ameliorate cardiovascular risks. There are a growing number of preclinical and clinical research studies investigating the mechanisms of non-classical effects of vitamin D therapy, particularly on cardiovascular tissue.

Activation of the VDR pathway appears to be important for cardioprotection; VDR can be activated by endogenous 1,25-D or exogenous VDR agonists (e.g. calcitriol and paricalcitol).<sup>[78]</sup> A limitation of exogenously added 25-D is the impairment of CYP27B1 in patients with CKD, even in extrarenal tissues,<sup>[79]</sup> which hinders its conversion to active 1,25-D. Newer vitamin D agonists that do not depend on functional CYP27B1 activity have an advantage over traditional vitamin D therapies, especially in the later stages of CKD. It is important to note that VDR activation with an exogenous agent for the treatment of CKD requires screening for abnormal changes in calcium and phosphorus in the urine and serum.<sup>[80]</sup> Hypercalcaemia affects a number of pathological processes and is associated with vascular calcification and the development of cardiovascular disease.<sup>[81–84]</sup> These findings reiterate the need to monitor patients and ensure proper maintenance of calcium and phosphorus, thus providing optimal therapy in what appears to be a relatively narrow therapeutic window of endocrine effects for exogenous, non-selective VDR agonists, such as calcitriol, and prodrugs that require activation in the liver (e.g. alfacalcidol [1 $\alpha$ -hydroxyvitamin D<sub>3</sub>] and doxercalciferol).<sup>[60]</sup> This is in contrast to the active, more selective VDR agonists paricalcitol and maxacalcitol (a 1,25-D, 1,25-dihydroxy-22-oxavitamin D<sub>3</sub>), which may further improve cardiovascular and renal benefits, as well as survival, with fewer adverse calcaemic and phosphataemic effects.<sup>[39]</sup>

### Perspectives

The existing evidence is compelling but not substantial, and there is a need for large, randomized clinical trials to specifically evaluate the cardiovascular effects of vitamin D. The key outcomes in these studies should include well-established cardiovascular risk factors such as

blood pressure, vascular calcification, proteinuria, and LVH. The VITamin D and Omega-3 Trial (VITAL; clinical trial number NCT00421733; <http://www.clinicaltrials.gov>) evaluated the efficacy and safety of paricalcitol capsules for reduction of albuminuria among patients with Type 2 diabetes and Stage 3 or 4 CKD who were receiving optimal treatment with angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers. The study is now complete, and results are forthcoming. The Paricalcitol in Renal Failure-Induced cardiac MOrbidity study (PRIMO; clinical trial number NCT00497146; <http://www.clinicaltrials.gov>) is currently ongoing and is a long-term (18 month), randomized, double-blind, placebo-controlled study to investigate the effects of paricalcitol capsules on the progression of LVH in patients with Stage 3B/4 CKD. Other outcomes to be assessed in this trial include changes in other measures of left ventricular function (e.g. ejection fraction), diastolic function (e.g. mitral annular relaxation velocity), and biological and inflammatory biomarkers.

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