

# The influence of selective vitamin D receptor activator paricalcitol on cardiovascular system and cardiorenal protection

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**Abstract:** The ubiquitous distribution of vitamin D receptors in the human body is responsible for the pleiotropic effects of vitamin D-receptor activation. We discuss the possible beneficial effects of a selective activator of vitamin D receptor, paricalcitol, on the cardiovascular system in chronic heart failure patients and chronic kidney patients, in light of new trials. Paricalcitol should provide additional clinical benefits over the standard treatment for chronic kidney and heart failure, especially in cases of cardiorenal syndrome.

**Keywords:** vitamin D deficiency, cardiovascular system, albuminuria, inflammation

## Introduction

Vitamin D has important roles in physiological processes, and is primarily involved in calcium and phosphorus homeostasis and bone metabolism.<sup>1</sup> The active form of vitamin D, or 1 alpha, 25-dihydroxyvitamin D<sub>3</sub> (calcitriol), binds to its vitamin D receptor (VDR), a kind of nuclear receptor, and activates the VDR to interact with the retinoid X receptor (RXR) to form the VDR/RXR/co-factor complex, which binds to vitamin D response elements in the promoter region of the target gene.

The ubiquitous VDR distribution in the human body (intestine, kidney, bone, parathyroid gland, immune system, smooth muscle, and myocardium) is responsible for the pleiotropic effects of VDR activation.<sup>2</sup> Namely, despite its classical action on the musculoskeletal system, vitamin D acts on the cardiovascular system, systemic inflammation, oxidative stress, and immune regulation.<sup>3</sup> Vitamin D has multiple effects on the immune system, including an anti-inflammatory effect.<sup>4</sup>

Indeed, in many epidemiological studies, vitamin D deficiency has been identified as a risk factor for many diseases not traditionally associated with vitamin D and mineral metabolism, such as cancer, cardiovascular disease, hypertension, and diabetes.<sup>5</sup> A meta-analysis of observational studies examined the association of 25(OH) vitamin D concentrations with cardiometabolic disorders, and the highest concentrations of 25(OH) vitamin D in serum were associated with a 43% reduction in cardiometabolic disorders, in comparison with the lower concentrations. The conclusions from the meta-analysis indicated that higher levels of vitamin D among middle-aged and elderly populations were associated with a substantial decrease in cardiovascular disease, type 2 diabetes, and metabolic syndrome.<sup>6</sup> There was also an association of 25(OH) vitamin D concentrations with blood pressure, where each incremental increase in 25(OH) vitamin D (10 nmol/L) correlated with a decrease in systolic blood pressure, by approximately 0.2 mmHg.<sup>7</sup> Evidence showed an inverse association between vitamin D and visceral adiposity.<sup>8</sup>

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## Mechanisms of vitamin D effects on the cardiovascular system

The mechanisms for these observed relationships remain unclear. Some suggested mechanisms are the higher atherosclerosis risk factors prevalent in vitamin D deficiency states, such as diabetes and hypertension. Some direct effects of vitamin D on the cardiovascular system could also be involved. Namely, these effects beyond the mineral and bone metabolism could be a consequence of the ubiquitous distribution of VDRs in the cardiovascular system (cardiomyocytes, vascular smooth muscle cells, and endothelial cells).<sup>9</sup> Stimulation of VDRs with vitamin D has been shown to have a direct impact on the cardiovascular system. Several mechanisms have been proposed in the model of vitamin D's protective effects on the cardiovascular system, including its influence on inflammation, endothelial dysfunction, vascular compliance, inflammation, cell proliferation, and differentiation, as well as its effects relating to parathyroid hormone (PTH) and the renin-angiotensin system. These latter two processes are involved in the initiation and development of endothelial damage and atherosclerosis.<sup>10,11</sup> There is clear evidence of VDR agonism's impact on the inhibition of cytokines involved in calcification and atheroma formation,<sup>12,13</sup> on the inhibition of proteins implicated in arterial calcification,<sup>14</sup> and on preventing thrombosis.<sup>15</sup>

Data from animal models also suggest a direct effect of vitamin D on cardiac and vascular structure. VDR knockout mice show hypertrophic hearts, cardiac fibrosis, and increased cardiac mass.<sup>16</sup> A protective effect of VDR agonists against cardiac hypertrophy and cardiac fibrosis, possibly through a reduction in cardiac oxidative stress, has also been demonstrated.<sup>17</sup> Vitamin D therapy also ameliorates oxidative stress injury in some experimental models.<sup>18</sup> In vitro, vitamin D reduces interleukin (IL)-6 synthesis and nuclear factor- $\kappa$ B activity, and prevents advanced glycation end-product-induced inhibition of endothelial nitric oxide-synthase production.<sup>18</sup>

## Interventional studies on vitamin D replacement therapy and cardiovascular system

Despite observational and epidemiological data, it is unclear from interventional studies how vitamin D would affect cardiovascular risk. A Women's Health Initiative study<sup>19</sup> showed no effect of calcium plus low-dose (10  $\mu$ g/d) vitamin D supplementation on coronary or cerebrovascular risk in 36,282 postmenopausal women followed for 7 years.<sup>19</sup> Zittermann et al<sup>20</sup> studied overweight subjects

with pronounced vitamin D deficiency ( $<30$  nmol/L), and observed a significant improvement in risk markers (triglycerides and tumor necrosis factor- $\alpha$ ) after supplementation for 1 year with a daily dose of 83  $\mu$ g vitamin D3. Recently Elamin et al<sup>21</sup> conducted a systematic review and meta-analysis to find evidence of vitamin D's effect on cardiovascular-event risk factors. They summarized randomized trials of vitamin D used in an interventional mode, and they could not demonstrate a significant effect of vitamin D on death, stroke, myocardial infarctions, lipid fractions, blood pressure, or blood glucose values. It is also important to mention that they analyzed randomized trials with enrolled participants without severe vitamin D deficiency. In contrast, a previous meta-analysis<sup>22</sup> of randomized controlled trials on vitamin D supplementation demonstrated that vitamin D supplements were associated with decreases in total mortality rates.

## Vitamin D and chronic kidney disease

Cross-sectional studies have demonstrated an inverse relationship between vitamin D levels and cardiovascular disease in both the general<sup>23</sup> and chronic kidney populations.<sup>24</sup> Additionally, there is a higher prevalence of vitamin D deficiency in populations with chronic kidney disease.<sup>25</sup> There is mineral homeostasis deterioration in renal failure, with disturbances in phosphorus, calcium, PTH, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and fibroblast growth factor-23 concentrations. Kidneys cannot excrete phosphorus, which leads to hyperphosphatemia, and consequently to elevated serum PTH and decreased serum 1,25-dihydroxyvitamin D.<sup>26</sup> Such abnormalities are recognized as disease called chronic kidney disease–mineral and bone disorder (CKD–MBD), a broad clinical syndrome encompassing mineral, bone, and calcific cardiovascular disturbances (vascular and valvular calcifications).<sup>27</sup>

Lower 1,25(OH)<sub>2</sub> vitamin D levels have been also associated with worsened coronary calcification,<sup>28</sup> suggesting a PTH-independent link between vitamin D and survival.

Teng et al<sup>29</sup> reported in a historical cohort study among 51,037 chronic hemodialysis patients; the group that received vitamin D had a significant 2-year survival advantage over patients who did not receive it.

## Selective vitamin D receptor activation

Traditionally, because of the kidney's lack of 1- $\alpha$  hydroxylation, in chronic kidney disease patients, 1,25-dihydroxyergocalciferol (calcitriol) is used for treatment

of secondary hyperparathyroidism.<sup>30</sup> Secondary hyperparathyroidism is the main clinical feature of CKD-MBD, characterized by abnormally elevated serum concentrations of PTH, and abnormalities in serum calcium, phosphorous, and vitamin D concentrations. It can lead to many clinical complications, such as bone fractures and vascular calcifications. Vascular calcifications and consequently increased arterial stiffness could produce higher pulse pressure and lead to left-ventricular hypertrophy,<sup>31</sup> arrhythmias, or finally to death. Indeed, arterial calcifications are correlated with cardiovascular mortality, left-ventricular hypertrophy, and the presence of coronary artery disease.<sup>32</sup> Atherosclerotic cardiovascular disease is the most common cause of mortality in the dialysis population.<sup>33</sup> The mortality rate from cardiovascular disease in patients with end-stage renal disease varies between 40% and 50%.<sup>34,35</sup>

Vitamin D is often administered to chronic kidney patients to mitigate the detrimental effects on bone health and mineral metabolism, although this treatment may be limited by elevations in serum calcium and phosphorus. The main action of vitamin D used for CKD-MBD is based on the suppression of high PTH production in the chief-cells of parathyroid glands and on the control of secondary hyperparathyroidism. Vitamin D can correct parathyroid hormone levels and prevent bone disease. Synthetic 1,25-dihydroxyvitamin D (calcitriol) binds more selectively to the VDR than does vitamin D or 25-hydroxyvitamin D. In chronic kidney patients, calcitriol effectively suppresses PTH production and improves bone histology.<sup>36</sup> The therapeutic use of calcitriol mainly aims to raise the intestinal absorption of calcium, to protect bone against osteomalacia, and to control parathyroid function.

As vitamin D can promote the increase of serum calcium and phosphorus levels, there are concerns about the possible side effects of vitamin D preparations. Hyperphosphatemia and hypercalcemia have been shown to promote calcification of the vasculature, myocardium, and cardiac valves. Undesirable effects of vitamin D, such as an increase in calcium and phosphate, may favor the development of vascular calcifications. Vascular calcification and calcification of arteriolar media are the main pathophysiological features of cardiovascular disease in the kidney disease population. Vascular calcification is currently accepted as an actively regulated process similar to bone formation, with changes in the phenotype of vascular smooth muscle cells resulting in osteoblast-like cells that produce calcification-regulating proteins.<sup>37</sup> Bas et al<sup>38</sup> demonstrated that high doses of calcitriol given to uremic rats produced aortic calcifications;

these changes were partially reversible several weeks after discontinuation of calcitriol administration. This process of vascular calcification was not correlated with vitamin D alone. Indeed, in animals, vitamin D excess would not induce calcification if serum phosphate was controlled, and it seems that phosphorus has a pivotal role in the promotion of vascular calcification in a vitamin D-administration environment.<sup>39</sup> Newer vitamin D analogs have been suggested to be less calcemic than is calcitriol.<sup>40</sup>

Several new vitamin D analogs have been developed for treatment of secondary hyperparathyroidism, with a reduced risk of hypercalcemia and hyperphosphatemia. The third generation of vitamin D analogs comprises a group of 1- and 25-hydroxylated vitamin D compounds with structure modifications (19-nor-1,25-dihydroxyvitamin D2 or paricalcitol), which have fewer calcemic and less phosphatemic effects when compared to calcitriol.<sup>41</sup> Vitamin D analogs have different effects on nuclear VDRs than does calcitriol, through different response elements in various target genes. Experimental work shows that for similar serum concentrations of calcium and phosphate, paricalcitol produces less vascular calcification than does calcitriol, suggesting differential effects at the cellular level.<sup>42</sup> Such new vitamin D analogs, because of the unique properties of nuclear VDRs, are named selective vitamin D receptor activation agents. The term “selective” means that the molecule acts mostly on the parathyroid gland, more so than on intestine and bone, resulting in lower serum calcium and phosphorus blood concentrations. Such selective VDR-activation agents are reported to have anti-inflammatory and antithrombotic effects, and could inhibit vascular smooth muscle cell proliferation, the renin-angiotensin system, and vascular calcification and stiffening, and could regress left-ventricular hypertrophy.<sup>43</sup>

## Paricalcitol and cardiorenal protection

Paricalcitol is the third generation of vitamin D analog, and is a selective activator of VDR used for the treatment of secondary hyperparathyroidism.<sup>44</sup> Compared with calcitriol, paricalcitol reduces PTH, with significantly fewer episodes of hypercalcemia in hemodialysis patients.<sup>45</sup> Reduced episodes of hypercalcemia among patients who received paricalcitol compared to calcitriol could be explained due to reduced stimulation of intestinal calcium transport proteins.<sup>46</sup> Calcitriol in uremic rats fed with a high-phosphorus diet enhances intestinal calcium absorption, because calcitriol promotes calbindin expression, whereas paricalcitol does not.<sup>47</sup> There are also data on lower absorption rates of

calcium and phosphorus among patients receiving paricalcitol, compared with calcitriol.<sup>48,49</sup>

The vascular calcification process in chronic kidney disease is also directly influenced by paricalcitol. Activation of VDR has been shown to decrease the process of vascular calcification, the main cardiovascular feature of chronic kidney disease, through suppression of calcification inducers such as type I collagen, bone sialoprotein, interleukin-1 $\beta$ , and tumor necrosis factor- $\alpha$ , or through activation of calcification suppressors: matrix Gla protein, osteopontin, and osteocalcin.<sup>50</sup> Li et al<sup>51</sup> demonstrated direct protection from vascular calcifications with paricalcitol, and found that paricalcitol could influence proteins involved in the smooth muscle cell calcification process, including bone morphogenetic protein-2 (BMP2), tumor necrosis factor- $\alpha$ , and osteopontin. Osteopontin could directly regulate vascular calcification and was found to contribute to the inhibitory actions of paricalcitol in the calcification of smooth muscle cell. The direct influence of paricalcitol on VDRs located on vascular smooth muscle cells could be explained by different effects of paricalcitol on target genes involved in the pathogenesis of vascular calcifications, independently of previously suggested mechanisms, such as modulation of the inflammatory response or different hyperphosphatemic and hypercalcemic effects.

Paricalcitol seems to have several mechanisms of action, because activation of the VDR intervenes in pathways associated with cardiovascular disease (suppression of renin transcription, antiproliferative effects, antifibrotic effects).<sup>52</sup> Data support a potential role of selective VDR activation in preventing the pathogenesis of atherosclerosis in chronic kidney disease. Activation of VDR also impacts the cardiovascular system by decreasing the activation of the renin-angiotensin-aldosterone system. There is evidence of an inverse relationship between vitamin D levels and plasma renin activity.<sup>53</sup> Paricalcitol was found to decrease angiotensinogen, renin, renin receptor, and vascular endothelial growth factor mRNA levels in a rat model of chronic renal failure.<sup>54</sup>

In a rat model of gentamicin-induced renal injury, paricalcitol prevented upregulated inflammatory cytokines (tumor necrosis factor- $\alpha$ , interleukin-1 $\beta$ , interferon- $\gamma$ ), nuclear factor- $\kappa$ B and phosphorylated ERK1/2 expression, and adhesion molecules (monocyte chemoattractant protein-1, ICAM-1, VCAM-1), and they reversed the transforming growth factor (TGF)- $\beta$ 1-induced epithelial-to-mesenchymal transition process and extracellular matrix accumulation.<sup>55</sup> Paricalcitol has significant immunomodulatory activity via VDR agonism, based on

its inhibition of dendritic cells, which are important in the pathogenesis of atherosclerosis.<sup>56</sup> The antioxidative properties of paricalcitol were demonstrated, in an animal model of contrast-induced nephropathy, by lower levels of serum malondialdehyde and kidney thiobarbituric acid-reacting substances in the paricalcitol group.<sup>57</sup> Antifibrotic effects of paricalcitol were reported by Meems et al<sup>58</sup> in an animal model: paricalcitol reduced myocardial fibrosis and preserved diastolic left-ventricular function due to pressure overload associated with reduced fibrosis. A similar study revealed the protective effect of enalapril and paricalcitol, alone or in combination, on cardiac oxidative stress in uremic rats.<sup>59</sup> Paricalcitol prevented cisplatin-induced kidney injury by suppressing fibrotic, apoptotic, and proliferative factors in an animal model; paricalcitol suppressed expression of TGF- $\beta$ 1, Smad signaling, mitogen-activated protein kinase signaling, p53-induced apoptosis, and p27(kip1).<sup>60</sup> Additionally, combination of enalapril and paricalcitol reduced glomerulosclerosis, proteinuria, and inflammation – when measured as monocyte chemoattractant protein-1 (MCP-1) in uremic rats – via suppression of TGF- $\beta$ 1 and Smad2.<sup>61</sup> Paricalcitol combined with enalapril had an additional protective effect on aortic inflammatory and oxidative injury biochemical markers in atherosclerotic mice.<sup>62</sup> Kong et al<sup>63</sup> tested, in an interesting study of spontaneously hypertensive rats, the effects of losartan, paricalcitol, doxercalciferol, a combination of losartan and paricalcitol, or a combination of losartan and doxercalciferol, on the development of left-ventricular hypertrophy. Echocardiography demonstrated a 65% to 80% reduction in left-ventricular wall thickness with losartan, paricalcitol, or doxercalciferol monotherapy, and almost complete prevention of left-ventricular hypertrophy with the combination therapies. Renal and cardiac renin expression was markedly increased in losartan-treated animals, but nearly normalized with combination therapy. These data demonstrate that vitamin D analogs have potent antihypertrophic activity, partly by suppressing renin in the kidney and heart. Paricalcitol also suppresses the progression of left-ventricular hypertrophy, myocardial and perivascular fibrosis, and myocardial arterial vessel thickness in uremic rats by upregulating the VDRs.<sup>64</sup> Fraga et al<sup>65</sup> demonstrated that paricalcitol prevented decrease in myocardial VDR expression. As VDRs are expressed in cardiac myocytes, the effect of paricalcitol could have a clinical impact on uremic cardiomyopathy, a common complication in patients with chronic kidney disease, characterized by cardiac fibrosis, cardiac hypertrophy, and diastolic dysfunction. Wu-Wong et al<sup>66</sup> demonstrated that VDR activation with

paricalcitol improved endothelial function, measured as endothelial-dependent vasorelaxation in a chronic kidney disease rat model, independently of the parathyroid hormone suppression effect.

As vascular calcification is associated with cardiovascular disease in chronic kidney patients, there is concern over vitamin D's possible effects on calcium, phosphorus, and consequently, on vascular calcifications. Mizobuchi et al<sup>67</sup> demonstrated that paricalcitol, in contrast to calcitriol and doxercalciferol, had no effect on the serum calcium-phosphate product or aortic calcium content in uremic rats. A higher dose of paricalcitol still had no effect, but lowering doxercalciferol levels did not increase the calcium-phosphate product; rather, it increased the aortic calcium content, suggesting independent paricalcitol-mediated mechanisms for protection from vascular calcification. Cardús et al<sup>68</sup> tested the effects of calcitriol and paricalcitol on vascular smooth muscle-cell calcification in an animal end-stage renal disease model, and concluded that calcitriol, but not paricalcitol, increased calcification of vascular smooth muscle cells, independently of the levels of calcium and phosphate.

Besides these experimental data, observational studies in hemodialysis patients reported improved cardiovascular and all-cause survival among those receiving selective VDR activation therapies. The selective VDR activation agent paricalcitol has been associated with greater survival than nonselective VDR activators such as calcitriol. Indeed, one observational study demonstrated a better 36-month survival rate of patients on dialysis treated with paricalcitol, compared with calcitriol.<sup>69</sup> A possible explanation for the differential effects of paricalcitol and calcitriol on survival is mineral metabolism. Calcitriol could have a larger gastrointestinal absorption rate of calcium and phosphorus than does paricalcitol, so vascular calcification and death from cardiovascular causes could be increased in patients receiving calcitriol. Another observational study among 7731 hemodialysis patients also demonstrated better survival in patients on doxercalciferol and paricalcitol, versus calcitriol.<sup>70</sup> A recent observational study<sup>71</sup> also revealed that paricalcitol was associated with improved 2-year survival in dialysis patients, even with low serum iPTH levels, so the differential effects of paricalcitol and calcitriol on survival are not correlated only with different effects on mineral metabolism or on PTH; they could be related to additional pleiotropic effects of paricalcitol.

## Paricalcitol in clinical trials

Despite some animal models and small studies of human participants, there are only a few human randomized trials

that might clarify the influence of selective VDR activation on the cardiovascular system in chronic kidney and/or chronic heart failure patients. Paricalcitol appears to block the renin-angiotensin-aldosterone system, and could have an effect on proteinuria via the suppression  $\beta$ -catenin-mediated gene transcription and prevention of podocyte dysfunction.<sup>72</sup> In a small study on diabetic and nondiabetic nephropathy, paricalcitol reduced proteinuria mostly in patients with diabetic nephropathy.<sup>73</sup> Another study demonstrated, in 220 chronic kidney patients, the reduction in proteinuria through paricalcitol treatment, independent of any concomitant use of agents to block the renin-angiotensin-aldosterone system.<sup>74</sup>

In the VITamin D and Omega-3 TriaL (VITAL),<sup>75</sup> a randomized clinical trial, paricalcitol demonstrated the additional effect of lowering albuminuria in patients with diabetic nephropathy. The study enrolled 281 patients being treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. The antiproteinuric effect was stronger when sodium dietary intake was higher. This renal protective effect seemed to be associated with renin transcription suppression, together with an antifibrotic and antiproliferative effect, and possibly with lower blood pressure in the paricalcitol group. These antiproteinuric effects were correlated with paricalcitol, and returned to baseline values upon paricalcitol withdrawal. As albuminuria is a surrogate end point, further clinical data are needed to establish the potential effects of selective VDR activation on hard end-point markers in chronic renal disease.

Despite plenty of observational data on the association of vitamin D with decreased cardiovascular-related morbidity and mortality, Paricalcitol Capsule Benefits in Renal Failure-Induced Cardiac Morbidity (PRIMO),<sup>76</sup> a randomized controlled trial on a group of 227 patients with chronic kidney disease with mild-to-moderate left-ventricular hypertrophy and preserved left-ventricular ejection fraction, could not demonstrate the influence of 48 weeks of paricalcitol therapy on the left-ventricular mass index or on Doppler measures of diastolic dysfunction.

## Conclusion

The anti-inflammatory and anti-oxidative properties of paricalcitol could influence clinical end points and result in improvement of cardiovascular and inflammatory parameters in chronic heart failure patients, chronic kidney patients, and uremic patients on renal replacement therapy. The effect of the selective activation of VDR on the cardiovascular system,

inflammation, and oxidative stress is not fully understood. Although one study<sup>76</sup> examined the impact of paricalcitol on heart function, participants in this study were chronic renal patients, and were not receiving renal replacement therapy, despite uremic cardiomyopathy being the most prevalent among dialysed patients.

Studies in future should emphasize the influence of oral or intravascular treatment with paricalcitol on cardiac function, endothelial function (flow-mediated dilatation), vascular morphology (plaque formation and intima media thickness), and markers of inflammation and oxidative stress in chronic kidney and heart failure patients. Paricalcitol should provide additional cardioprotective and renoprotective effects, with significant clinical benefits for chronic kidney and heart failure, especially in concomitant kidney and heart dysfunction, which is a common clinical presentation recognized today as cardiorenal syndrome. Paricalcitol could produce notable and measurable clinical benefits, superior to those of standard cardiorenal syndrome treatments.

## Disclosure

The authors report no conflicts of interest in this work.

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