

# VITAMIN D AND CARDIOVASCULAR DISEASES : WHERE DO WE STAND IN 2010?

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## Introduction.

Apart from its standard phosphocalcic effects, vitamin D (VTD) has been shown to play a major role in different non-phosphocalcic-metabolism diseases (1). VTD is an important gene mediator and up to 3% of the human genome is directly or indirectly regulated by VTD (2). From a clinical point of view different randomized, controlled trials (RCTs) and meta-analyses of interventional studies have shown that VTD supplementation had positive effects on the risk of fractures (3), risk of falls in the elderly (4), cancer risk (5), infectious diseases (6) and even all-cause mortality (7). As well as these most interesting findings, increasing evidence has suggested that VTD could also play an important role in the cardiovascular system: it seems that various diseases such as cardiovascular diseases (CVD), hypertension and Type 2 diabetes could also be significantly improved by VTD supplementation. In this paper we review the potential interest of VTD in CVD, based on research evidence.

## Evidence from animal and laboratory research.

Laboratory experiments on cells and animals have shown a particular interaction between VTD metabolism and CVD. For example:

- As in most human cells Vitamin D receptors (VDR) are distributed in vascular smooth-muscle cells (VSMCs), macrophages and lymphocytes. VSMCs and endothelial cells contain the enzyme 1- $\alpha$ -hydroxylase, which allows the hydroxylation of 25-OH vitamin D on the carbon in position 1 to produce the most active metabolite of VTD, 1,25(OH)<sub>2</sub> vitamin D (8-10).
- VTD induces prostacyclin in VSMCs, which prevents thrombus formation, cell adhesion and smooth muscle cell proliferation (11).
- VTD regulates the expression of the vascular endothelial growth factor, MMP9, myosin, elastin, type 1 collagen and  $\gamma$ -carboxyglutamic acid (12;13)
- VTD suppresses pro-inflammatory IL-6 and TNF- $\alpha$ . (14)
- VTD is an inhibitor of the renin-angiotensin system in mice (15)
- VTD receptor KO mice develop cardiac hypertrophy (16)

• A transgenic rat model which constitutively expressed 24-hydroxylase (an enzyme that transforms 1,25(OH)<sub>2</sub> vitamin D into the inactive 1,24,25 (OH)<sub>3</sub> vitamin D) developed aortic atherosclerosis and hyperlipidemia (17).

Even if these studies seem promising, it must be admitted that their application to human clinical practice remains risky

## Case-control studies.

Different case-control studies have suggested that lower vitamin D status was associated with an increased risk of myocardial infarction (18-20). However, biases in these early studies may have influenced the results (VTD determination was assessed *after* the outcome...).

## Prospective studies.

In evidence-based medicine, these studies are much more interesting than case-control studies. Artaza *et al.* have recently reviewed the results of five extensive studies (21), which included approximately 40,000 patients. Table 1 summarizes the results of these studies. The results observed by the authors tend to show that the patients in the lowest quintiles of 25-OH vitamin D presented a globally higher CV risk compared to those in the highest quintiles. The patients with 25(OH)D serum levels of approximately 20 ng/ml were at lower risk than those with lower values.

## Randomized controlled trials

To the best of our knowledge, no RCT with CVD as primary outcome has been published yet. However, two RCTs, the Women's Health Initiative (WHI) Study (22) and the British Doctors' Study (23) reported a non-significant decrease in CVD incidence and mortality, myocardial infarction and coronary heart disease. In the WHI study, the amount of vitamin D provided to the participants (400 IU/day) was largely insufficient to raise the 25(OH)D levels – which, in fact, were not assessed. The results of this study are therefore quite difficult to interpret. On the other hand, in the British Doctors' Study, where a capsule of 100.000 IU was given to the treated group every four months, the mean 25(OH)D levels observed on a

single occasion, in September (one of the months in which the general population presents the highest 25(OH)D levels), three weeks after the administration, were only 29.7±8.3 vs. 21.4±8.4 ng/mL in the placebo group. Even if statistically significant, such a small difference between the treated and placebo group is difficult to understand. It is certainly plausible that, due to lack of compliance or to galenic problems linked to the "capsule" of vitamin D, the supplementation was not sufficient to induce any clinical effect.

## Conclusion.

There is laboratory evidence that vitamin D has a significant impact on the cardiovascular system. Low levels (<15 ng/ml) appear to be an independent risk factor for CV events. However, a causal relationship has yet to be supported by large interventional trials. Unfortunately, well-designed (with the treated group > 30 ng/ml) RCTs are clearly lacking. In our opinion, patients at CV risk should be treated with vitamin D supplements in order to obtain a minimal value of 30 ng/ml.

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Table 1 : Summary of five large prospective studies as reviewed by Artaza et al.

Reference	N	Population	Follow-up (yrs)	Key findings
Dobnig 2008, Arch Int Med (24)	3,258	Single center, referred For coronary angiography	7.7	Lower 2 quartiles with higher all-cause CV mortality
Giovannuci 2008, Arch Int Med (25)	18,255	Health Professionals Follow-up Study, men 40 to 70 yrs.	Up to 10	Adjusted hazards for MI compared with 25OHD levels ≥30 ng/mL: ≤ 15: 2.09; 15 to 22.5: 1.43; 22.6 to 29.9: 1.60
Pilz 2008, JCEM (26)	3,316	Single center, referred for coronary angiography	7.7	Low 25OHD associated with increased fatal/non fatal strokes
Wang, 2008, Circulation (27)	1,739	Framingham Offspring Study	5.4	Low 25OHD serum levels (<15 vs. > 15 ng/mL) associated with increased CV events
Melamed, 2008, Arch Int Med(28)	13,311	3 <sup>rd</sup> National Health and Nutrition Examination Survey (NHANES III)	8.7	Lowest quartile (<17.8 ng/mL) with higher all-cause mortality than highest quartile.