# **Editorial**

## Vitamin D Supplementation and Cardiovascular Disease Risk

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any studies, <sup>1,2</sup> but not all, have shown that low bone density is associated with increased cardio-vascular disease (CVD) risk. Vitamin D deficiency is common in the elderly and is associated with osteoporosis; however, the association of endogenous 25-OH vitamin D (25-OH D) levels with CVD events is controversial. <sup>3,4</sup> CVD rates are higher during winter seasons and at increased geographic latitudes where average serum vitamin D levels are lowest. <sup>5</sup> Low 25-OH D levels have been found in stroke<sup>6</sup> and heart failure patients. <sup>7</sup> Moreover, 25-OH D deficiency is associated with hypertension, obesity, <sup>8</sup> glucose intolerance, <sup>8</sup> and the metabolic syndrome, <sup>9</sup> which may be responsible, at least in part, for its association with increased CVD risk.

### Article p 846

Although vitamin D supplementation improves bone strength, elevated serum vitamin D levels may be associated with lower levels of vascular calcification. In subjects at moderately high risk for coronary heart disease, endogenous serum vitamin D levels were inversely correlated with the extent of coronary artery calcification as determined by cardiac computed tomography. 10 Vitamin D also has intriguing antiinflammatory properties11 that have potential therapeutic benefit in several autoimmune diseases and allograft rejection. In 2 small clinical trials,12,13 vitamin D supplementation lowered C-reactive protein levels. Additionally, 1,25(OH)<sub>2</sub>D induces relaxation of vascular smooth muscle cells and downregulation of renin production by the kidneys. Finally, the observation of reduced mortality risk with 1,25(OH)<sub>2</sub> D supplements among patients with renal failure<sup>14</sup> supports a possible CVD protective role of vitamin D. Accordingly, it is reasonable to hypothesize that vitamin D supplementation may lower CVD risk.

In this issue of *Circulation*, Hsia et al<sup>15</sup> present the results from the Women's Health Initiative (WHI), the first large randomized clinical trial evaluating vitamin D supplementation and CVD risk. This study of 36 282 postmenopausal women randomized to placebo or calcium carbonate 500 mg with 25-OH D<sub>3</sub> 200 IU twice daily reported no treatment

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Circulation is available at http://www.circulationaha.org DOI: 10.1161/CIRCULATIONAHA.106.686238 effect on coronary or cerebrovascular risk over a 7-year period. Although the findings alleviated concerns that calcium and vitamin D supplementation taken to improve bone health may cause adverse CVD consequences, they have dampened enthusiasm about decreasing CVD risk with supplementation.

Several possibilities may explain the discrepancies between the earlier observational studies and the WHI study. First, as discussed in the present study, the investigators may have used an inadequate dose of vitamin D. The current recommended daily allowance is 200 IU for adults 20 to 50 years of age, 400 IU for adults 51 to 69 years of age, and 600 IU for adults ≥70 years. However, the average older adult needs at least 800 IU vitamin D daily to achieve a serum 25-OH D concentration sufficient to maximally suppress parathyroid hormone levels, 16 and older adults with dark skin and limited sun exposure may require ≥2000 IU daily. Although full-body sun exposure provides 10 000 IU vitamin D per day, 16 nowadays most people spend little time in the sun. Thus, some experts argue that the current recommended daily allowance recommendations for 25-OH D are woefully inadequate.16 Schleithoff et al17 reported that patients with heart failure treated with 2000 IU/d vitamin D experienced a reduced serum concentration of tumor necrosis factor (an inflammatory cytokine) and an increased concentration of interleukin-10 (antiinflammatory cytokine). Witte et al,18 using smaller doses of vitamin D (400 IU/d), were unable to demonstrate a beneficial effect on the levels of cytokines in patients with heart failure. Thus, treatment with vitamin D doses higher than the recommended daily allowance may be required to reduce CVD risk.

Second, placebo-treated patients in the WHI trial were allowed to take calcium and/or vitamin D supplements, which may have led to attenuation of the effect of the active treatment. In fact, mean vitamin D consumption at baseline was  $368\pm266$  IU/d in the placebo group.

Third, only patients at high risk for suffering a CVD event or those with vitamin D deficiency may benefit from vitamin D supplementation. Hsia et al reported that women with higher body mass index and multiple coronary heart disease risk factors had a lower risk for CVD events with calcium/vitamin D supplementation than with placebo. Individuals with obesity have reduced endogenous vitamin D levels; thus, increasing vitamin D levels in these patients may be beneficial, as opposed to individuals whose serum vitamin D level is normal. Unfortunately, the prevalence of vitamin D deficiency in the WHI patients is unknown because serum levels were not assessed before treatment. Additional studies are needed to determine whether patients with vitamin D defi-

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ciency experience a reduction in CVD events with supple-

Finally, although there may be an association between low 25-OH D levels, subclinical atherosclerosis, and CVD risk factors, vitamin supplementation may not alter this process. The absence of an improvement in clinical outcomes with supplementation may be similar to that observed with homocysteine, in which altering the serum concentration with folate and B vitamins does not lower CVD risk. Likewise, the results from this vitamin D clinical trial echo similar studies regarding supplementation with the antioxidant vitamins A, C, and E and beta-carotene; the association with reduced CVD risk seen in observational studies failed to be demonstrated in randomized clinical trials.

Nevertheless, several interesting observations emerge from the study by Hsia et al. First, vitamin D supplementation was associated with a smaller increase in low-density lipoprotein cholesterol, waist circumference, and weight over time compared with placebo but a slightly greater increase in blood pressure. Second, women with self-reported statin use were at lower risk for stroke if assigned to calcium/vitamin D supplementation. This finding deserves further study because it has been hypothesized that statins may activate vitamin D receptors.<sup>19</sup> Third, most of the women enrolled in the study were white (83%), and whether vitamin D supplementation may beneficially affect CVD risk in black and Hispanic women, who generally have significantly lower levels of endogenous 25-OH D levels than white women, is unknown.20

The WHI study findings make it less likely that we will eventually improve CVD outcomes with vitamin D supplements. Nevertheless, the potential association of low vitamin D levels with inflammation and CVD risk is provocative, and questions remain as to whether supplementation at higher doses may be required to lower future cardiovascular risk.

#### Disclosures

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