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Vitamin D, Calcium, and Cardiovascular Disease: a“D”vantageous or “D”etrimental? An era of uncertainty

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Abstract

While the function of vitamin D in regulating calcium homeostasis is well established, there has been growing interest in its role in the prevention of numerous chronic diseases, including cardiovascular disease (CVD). There is mounting epidemiological evidence suggesting that vitamin D deficiency is linked to increased CVD risk. However, the results of previous vitamin D supplementation trials have yielded mixed results in regards to cardiovascular health, and the results of on-going large-scale randomized controlled trials are not yet available. Further complicating the issue, calcium supplementation, which is often prescribed concurrently with vitamin D, has been associated with increased CVD risk in some (but not all) studies. Thus, it is currently unclear whether vitamin D supplements, particularly for those that are deficient, can help prevent the development of CVD. In addition, there has not been uniform consensus regarding the threshold of 25-hydroxyvitamin D levels that constitutes “sufficiency” across organizational guidelines. This review will provide an update on the most recent evidence regarding the effects of vitamin D and calcium supplements on CVD clinical outcomes, summarize ongoing vitamin D trials, and discuss the current but remarkably disparate recommendations regarding vitamin D deficiency screening and supplementation.

Keywords

Vitamin D; Calcium; Supplementation; Cardiovascular Disease; Prevention

Introduction

Cardiovascular disease (CVD) is a leading cause of mortality worldwide, estimated to account for 30% of all deaths [1]. Thus, identifying modifiable risk factors and treatments

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remains a high priority for CVD prevention. Vitamin D deficiency, primarily known for its role in bone and mineral regulation, has garnered interest for its potential role in many other disease processes, including CVD. There is strong evidence from observational studies that have linked low serum levels of 25-hydroxyvitamin D [25(OH)D] with poor cardiovascular outcomes [2]. Vitamin D is an attractive interventional target, as serum 25(OH)D levels are modifiable and treatment is relatively inexpensive. Furthermore, as it is estimated that approximately one billion people in the world have either deficient or insufficient levels of 25(OH)D, vitamin D intervention can potentially impact a large population [3].

Despite encouraging results from observational epidemiological studies, randomized controlled trials (RCTs) of vitamin D supplements have yielded mixed results regarding cardiovascular outcomes [4-8]. However, to date, no large-scale trial of vitamin D supplements with CVD as a primary outcome has been completed [9]. While several large-scale RCTs are currently underway, the lack of persuasive evidence has resulted in differing guidelines and practices regarding the definition of vitamin D deficiency, populations to be screened, and the ideal level of supplementation.

Because vitamin D promotes the intestinal absorption of calcium, vitamin D is often prescribed in conjunction with calcium supplementation, particularly in populations at risk for bone loss, such as post-menopausal women and older adults [10]. However, there is now some evidence that calcium supplementation may increase risk for CVD [11]. This underscores the necessity in evaluating calcium and vitamin D supplementation effects on not only bone, but on cardiovascular outcomes as well.

Vitamin D Metabolism and Measurement

Vitamin D is a fat-soluble pro-hormone that is a precursor to the active steroid hormone 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. There are 3 possible sources of vitamin D – food, pill supplements, and sunlight. Specifically, vitamin D is obtained either exogenously as vitamin D3 (cholecalciferol) or D2 (ergocalciferol) from diet or supplements, or endogenously through D3 production in the skin. Traditionally, endogenous cutaneous synthesis was the main process by which individuals obtain vitamin D, accounting for 90% of an individual's vitamin D requirement [12]. However recently, there has been an increased use of vitamin D supplements in the U.S. population [13]. There are few natural food sources of vitamin D, primarily oily fish, liver, and egg yolks; thus many individuals rely on fortified food or dietary supplements for vitamin D intake [14, 15].

In the skin, ultraviolet B (UVB) radiation from sunlight converts 7-dehydrocholesterol into previtamin D_3, which then isomerizes to vitamin D3. However, several factors affect the skin's ability to produce vitamin D3, including age, race, use of sunscreen, season, and geographic location. Older people have less 7-dehydrocholesterol in their epidermis, decreasing their capacity to produce vitamin D3 [16]. Certain races, including African Americans, tend to have lower 25(OH)D levels because the increased pigmentation in darker skin inhibits vitamin D production [17]. Likewise, sunscreen use, seasons with less sunlight, and latitudes further from the equator reduce the amount of UVB radiation that enters the skin, thereby reducing vitamin D production [12].

Following either consumption or endogenous synthesis, vitamin D is then hydroxylated by 25-hydroxylase in the liver, to become 25-hydroxyvitamin D [25(OH)D]. This is the main circulating form of vitamin D, and is used to define an individual's vitamin D status. 25(OH)D will then undergo a second hydroxylation by 1α-hydroxylase to form the active metabolite, $1,25(OH)_2D$ (calcitriol). This 1-hydroxylation primarily occurs in the kidneys and is responsible for the majority of calcitriol production; however, there are extra-renal forms of 1α-hydroxylase, which is also found in cells implicated in the pathogenesis of CVD, such as vascular smooth muscle cells (VSMCs), endothelial cells, and macrophages [18-20]. This allows for local production of calcitriol, which is thought to play an autocrine/paracrine function. Although there are $1,25(OH)_2D$ assays, it is not considered an accurate indicator of overall vitamin D status, due to $1,25(OH)_2D$'s shorter half-life and lower circulating concentration compared to 25(OH)D, as well as parathyroid hormone (PTH)'s tight regulation of its level in the blood [21]. In fact, $1,25(OH)_2D$ levels are often normal in individuals with vitamin D deficiency, and therefore do not accurately represent vitamin D stores.

While 25(OH)D is currently the best measure of vitamin D status, it is not necessarily representative of an individual's bioavailable vitamin D. Importantly, 85-90% of all circulating 25(OH)D is bound to vitamin D binding protein (VDBP), 10-15% is bound to albumin, and less than 1% is free [22, 23]. Because clinical assays do not distinguish between bound versus unbound 25(OH)D, an individual with low total 25(OH)D may have adequate bioavailable 25(OH)D.

Racial differences of Vitamin D and CVD

Blacks have lower total 25(OH)D than whites, but paradoxically low 25(OH)D appears to be a stronger risk factor for CVD in whites compared to blacks [24-27]. One prior study had concluded that blacks may have similar levels of bioavailable vitamin D as whites due to less overall VDBP [28], a finding that might potentially explain this racial paradox. However, studies evaluating 25(OH)D with VDBP genotypes have yielded mixed results [24, 25, 29], and more recent evidence has disputed the existence of racial differences in VDBP concentration [30, 31]. Thus, differences in VDBP do not appear to be the explanation for why 25(OH)D is a stronger CVD risk factor in whites than blacks. Further research is needed in this area.

Vitamin D Mechanisms on CVD

While the mechanisms by which vitamin D deficiency relates to CVD are uncertain, low vitamin D levels are thought to increase CVD risk by contributing to established cardiovascular risk factors, including hypertension, diabetes, and inflammation (Figure 1).

Hypertension

Most clinical studies, although not all, have found an inverse association between 25(OH)D serum levels and blood pressure [32-34]. A recent meta-analysis of eight studies with 283,537 participants found that individuals in the top third of serum 25(OH)D levels had a 30% lower risk of developing hypertension compared to those in the bottom third [33].

Furthermore, Vimaleswaran *et al.* provided evidence for a potential causal relationship between low vitamin D levels and increased blood pressure in a Mendelian randomization study [35]. Activated vitamin D is thought to affect blood pressure through inhibition of the renin-angiotensin-aldosterone system (RAAS) [36-38].

Nonetheless, results of clinical trials that tested the effects of vitamin D supplements on blood pressure have predominantly had null results. While some small clinical trials have shown positive results [39], the highest quality trials and most meta-analyses of vitamin D supplementation trials have documented a null relationship [40, 41]. In the recent DAYLIGHT trial with 534 pre-hypertensive/hypertensive participants, there was no difference in blood pressure between those treated with 4000 IU/day of vitamin D compared to those only treated with 400 IU/day [42]. However, a recently published meta-analysis reported that while vitamin D did not reduce blood pressure in the overall population, daily vitamin D dosing of >800 IU/day for <6 months in participants older than 50 years old significantly reduced both systolic and diastolic blood pressure [5]. Further evidence is needed.

Diabetes

Low vitamin D levels are thought to promote diabetes through increased insulin resistance and pancreatic beta-cell dysfunction resulting in decreased insulin secretion [43, 44]. Most epidemiologic studies show an association between low 25(OH)D serum levels and increased incidence of type 2 diabetes mellitus [45, 46]. Grubler *et al.* recently published a RCT (n=185) which found that vitamin D supplementation of 2,800 IU/day for 8 weeks in obese hypertensive patients with vitamin D deficiency reduced HbA1c levels by 3.52 mmol per mol of vitamin D [47]. However, Jorde *et al.* performed a RCT with a larger sample size (n=511) and longer intervention time (5 years) and found no evidence that vitamin D supplementation of 20,000 IU/week over a 5-year period prevented the progression from pre-diabetes to diabetes [4]. Their study population on average was not vitamin D deficient (mean 25(OH)D = 24 ng/ml); however the authors reported that subgroup analysis in subjects with low baseline 25(OH)D yielded results similar to the main trial results. Furthermore, several systematic reviews and meta-analyses also concluded that vitamin D supplementation did not reduce HbA1c levels or improve beta cell function and insulin resistance [48-51].

Inflammation

Suboptimal levels of vitamin D are also thought to contribute to an increased inflammatory profile. Pro-inflammatory cytokines, such as IL-1, Il-2, Il-6, and tumor necrosis factor-α (TNF-α) are down-regulated by calcitriol [52]. Furthermore, vitamin D may protect against endothelial dysfunction, promote an anti-atherogenic macrophage phenotype, and protect against VSMC changes that would result in increased inflammatory molecules and overall increased risk of atherosclerosis [53]. Yet, results of vitamin D supplementation on inflammation are mixed. One study of 332 participants found that one year of vitamin D supplementation decreased serum IL-6 levels, although other inflammatory markers including C-reactive protein (CRP) levels were increased [54]. However, a meta-analysis of vitamin D supplementation in obese and overweight participants suggested that

supplemental vitamin D did not have a statistically significant impact on inflammatory markers such as CRP, TNF-α, and IL-6 [55]. Additional research needs to be done.

Cardiac Structure/Function

Vitamin D may also influence CVD risk by directly affecting the heart. Animal studies have shown evidence that low vitamin D levels contribute to left ventricular hypertrophy, cardiac fibrosis, reduced ejection fraction, and cardiomyocyte apoptosis [56-58]. However, few studies examine the association between 25(OH)D and myocardial structure and function in humans. Further research needs to be done to clarify this relationship [59].

Calcium Mechanisms on CVD

As the physiology of vitamin D and calcium are intertwined, it is perhaps unsurprising that there is growing evidence that calcium itself plays a role in CVD. In general, calcium is thought to protect against CVD development through several potential mechanisms, including lowering blood pressure, decreasing lipid levels and improving glycemic control [60].

Despite these potential benefits, there has been recent concern that calcium supplements might increase CVD risk. Although this topic remains highly controversial, there are several proposed mechanisms by which transiently elevated calcium levels (conferred by calcium supplement intake) could contribute to cardiovascular risk (Figure 1). High serum calcium levels may increase blood coagulability, as platelets have calcium-sensing receptors and may be activated with elevated serum calcium. A randomized trial of 100 post-menopausal women found that calcium supplementation reduced the time to clot initiation compared to placebo [61]. It is also thought that the rapid bolus of calcium from supplementation, unlike dietary calcium, may acutely elevate serum calcium and promote vascular calcification [62]. However, observational studies have yielded inconsistent evidence for the association between supplemental calcium intake and arterial calcification [63].

Calcium, often taken alongside vitamin D, has long been prescribed to reduce the risk of osteoporosis and other bone diseases. While calcium can be obtained in dietary forms, such as dairy products, certain vegetables, and fortified foods, many people do not achieve the recommended intake levels through diet alone. It is estimated that approximately 50% of the U.S. adult population takes calcium supplements [64]. The Institute of Medicine (IOM) recommends a daily intake level of 1,000 mg/day for men 19–70 years old and women 19–50 years old and 1,200 mg/day for individuals who are older [65]. Gallagher *et al.* found that hypercalcemia occurred in 8.8% of participants and hypercalciuria occurred in 30.6% of participants at a calcium intake of 1,200 mg/day [66]. Thus, it is possible that even at recommended levels of calcium supplementation, individuals may be at risk of the purported adverse cardiovascular effects of high calcium levels.

Observational Studies and Mendelian Randomization Studies on Vitamin D and CVD

Vitamin D deficiency has been associated with increased all-cause mortality [67-69] and increased risk of CVD outcomes, including cardiovascular mortality [2, 68], myocardial infarction (MI) [70, 71], coronary heart disease (CHD) [25, 26], stroke [27, 29, 72], and heart failure (HF) [24].

In a 2015 analysis of the Copenhagen vitamin D (CopD) study (n=247,574), both high and low levels of serum 25(OH)D were associated with increased incidence of cardiovascular outcomes, including CVD, stroke, and acute myocardial mortality [73]. Serum 25(OH)D was non-linearly associated with CVD mortality in a “reverse J-shaped” pattern, consistent with another study which found increased mortality risk at high vitamin D levels >50 ng/ml [69]. Interestingly, in the CopD study, the lowest CVD mortality risk occurred at 70 nmol/L (28 ng/ml), a level lower than the Endocrine Society's guidelines for vitamin D sufficiency of 30 ng/ml [74], but higher than the level deemed adequate for health (20 ng/ml) by the IOM [65].

While these observational studies yield promising results, there are substantial limitations. With any observational study, there is concern about confounding, that is, some key variables are either not measured or are crudely assessed. Individuals with adequate vitamin D levels might also be engaging in other health-promoting behaviors such as physical activity and healthy diet. Furthermore, these observational studies cannot prove causation in the relationship between vitamin D and cardiovascular outcomes. It is possible that the results are due to reverse causation, in which low 25(OH)D status may be reflective of poor health in general. For example, if individuals are less healthy, they may be less mobile and are less likely to spend time outdoors, and therefore have less exposure to sunlight and synthesize less vitamin D. Additionally, individuals in poor health may be obese, allowing for vitamin D sequestering in adipose tissue and consequently a lower 25(OH)D status [75].

Although RCTs are the gold standard for proving causation, Mendelian randomization studies can provide insight into causation, as genetic studies are largely free of the confounding factors that plague observational studies. Manousaki *et al.* recently performed such an analysis using data from the SUNLIGHT consortium (n=33,996) and found that genetically low 25(OH)D levels were not associated with increased risk of coronary artery disease [76]. This is consistent with another Mendelian randomization study, which found an association between genetically low 25(OH)D concentrations and all-cause mortality, but no association with cardiovascular mortality [77]. Although not conclusive, these two studies suggest that the positive results from observational studies may be due to confounding factors rather than a true causal relationship between vitamin D and cardiovascular outcomes.

Observational Studies of Calcium and CVD Outcomes

Observational studies have yielded mixed results regarding whether calcium intake is associated with increased risk of CVD. An analysis of 72,245 women in the prospective

cohort Nurses' Health Study with 24 years follow-up found that women taking >1,000 mg/day calcium supplements had a 29% lower risk of incident CHD compared to those not taking supplements, but did not have a statistically significant different risk of incident stroke [78]. Similarly, an analysis of 6,236 participants in the Multi-Ethnic Study of Atherosclerosis (MESA) did not find a strong association between dietary or supplementary calcium with incident CVD events over 10 years of follow-up [79].

In contrast, another recent analysis of 5,448 adults, also from MESA, found that while higher overall dietary calcium intake was associated with a decreased risk of incident coronary atherosclerosis as measured by the coronary artery calcium (CAC) score, the use of calcium supplements was associated with 22% increased risk for incident CAC [80]

Finally, a meta-analysis of prospective cohort studies, involving 757,304 participants, found a U-shaped association between dietary calcium intake and cardiovascular mortality. Total daily dietary calcium intake (i.e. from food sources) that were either higher or lower than 800 mg were associated with increasing risk of cardiovascular mortality [81]. However, meta-analysis of 6 studies did not find calcium supplements to be associated with cardiovascular mortality [81].

. These mixed results suggest that further clinical trials must be done to evaluate the impact of calcium supplementation on cardiovascular outcomes.

Randomized Controlled Trials (RCT) of Vitamin D and CVD Outcomes

Unfortunately, RCT results thus far have not been promising. However, most published trials have either had a relatively small sample size, did not include CVD outcomes as a specified outcome prior to study start, or did not collect CVD outcomes in a rigorous fashion. There are multiple large-scale vitamin D supplementation trials currently underway. The largest of which are the VITamin D and OmegA-3 TriaL (VITAL), a placebo-controlled, double-blind 2×2 factorial trial of over 25,875 multi-ethnic participants randomized to 2,000 IU/day of vitamin D_3 and omega-3 fatty acid supplements for 5 years [82], and the D-Health Trial, a placebo-controlled trial with 21,315 participants randomized to 60,000 IU/month of vitamin D_3 for 5 years [83].

Table 1 provides a list of additional ongoing clinical trials of vitamin D supplementation for outcomes related to CVD or its risk factors [82-89]. These studies have their limitations. Most ongoing trials are studying older populations, and the results may not be generalizable to younger individuals. Furthermore, only one trial required a low vitamin D status [25(OH)D < 30 ng/ml] as an enrollment criterion. If vitamin D intervention is effective, the effect would likely be most pronounced in vitamin D deficient individuals; thus benefits may not be seen in a population that started with adequate vitamin D levels.

As we await the results of these ongoing trials, meta-analyses of completed RCTs may shed light on the effect of vitamin D supplementation on CVD outcomes. In a 2015 meta-analysis of 13 RCTs of oral vitamin D supplementation in adults with chronic kidney disease, there was no significant effect on all-cause mortality, cardiovascular mortality, or serious cardiovascular adverse events compared [90]. Of note, the trials in this meta-analysis were

not initially designed to collect data on mortality or cardiovascular events, and therefore may not accurately reflect true outcomes. Another meta-analysis of 21 vitamin D trials found no statistically significant difference in those supplemented with vitamin D compared to placebo for the outcomes of cardiac failure, MI, and stroke [7].

The Vitamin D Treating Patients with Chronic Heart Failure (VINDICATE) study was a randomized, placebo-controlled, double blind trial of vitamin D supplementation in patients with HF and vitamin D deficiency [91]. The study found that while one year of 4,000 IU/day of vitamin D_3 did not improve 6-minute walk distance, their primary outcome, those receiving vitamin D supplementation showed a 6.1% improvement in ejection fraction and a decrease in left ventricular end diastolic diameter. While this sample was relatively small (n=229) and not particularly generalizable (participants were all male HF patients), it does provide some new encouraging evidence on the potential effects of vitamin D supplementation. Conversely, a recent meta-analysis of 7 RCTs investigating whether vitamin D supplementation has protective effects in patients with chronic HF, found that while vitamin D may decrease PTH levels and some inflammatory markers, there was no statistically significant improvement in left ventricular function [92]. However, the meta-analysis was limited by the small sample sizes and relatively short follow-up duration of the included trials; the VINDICATE trial was both larger in size and had a longer follow-up compared to all trials included in the meta-analysis.

RCTs of Calcium Supplementation and CVD

Since the Auckland Calcium Study, which first introduced the notion that calcium supplements may increase cardiovascular risk, there has been increased interest in investigating the effects on calcium supplementation on CVD outcomes [93].

The results of calcium supplementation trials have been mixed. A meta-analysis of 15 RCTs (8,151 participants) of calcium supplementation >500 mg/day found that calcium supplements were associated with a 27% increased risk of MI compared to placebo [94]. However, more recently, in 2014 Lewis *et al.* published results of a 3-year intervention of 1200 mg calcium supplementation vs. placebo in older women (n=1103) on common carotid artery intimal medial thickness (CCA-IMT) and carotid atherosclerosis [95]. They found no difference in CCA-IMT or carotid atherosclerosis between the two groups. Furthermore, they found that participants with the highest tertile of total calcium had decreased carotid atherosclerosis compared to those in the lowest tertile (OR=0.67, 95% CI 0.5-0.9). Thus, this trial did not yield evidence that supports the claim that calcium supplementation increases carotid atherosclerosis, although this was a surrogate end-point.

While these trials evaluated the effect of calcium supplementation alone, in clinical practice, calcium is often co-administered with vitamin D. Therefore, it is paramount to study the effect of the co-administered supplement on cardiovascular health, as the effects could differ from the monotherapies alone. If vitamin D does have a protective effect against CVD, it could attenuate the possible negative effects of calcium on cardiovascular health.

With the exception of the landmark Women's Health Initiative (WHI) study, in which 36,282 postmenopausal women were randomized to either 1000 mg calcium with 400 IU vitamin D daily or placebo, few trials have examined the effect of co-administered calcium and vitamin D (CaD) supplementation [96]. However, the results of the WHI study have presented uncertainty. Initially, Hsia *et al.* found that CaD supplementation was not associated with increased or decreased coronary or cerebrovascular risk [8]. Yet, in a meta-analysis that incorporated a secondary analysis of WHI data that removed participants with personal use of calcium supplements (for concern regarding potential interaction) and combined those results with the results from 7 other studies, Bolland *et al.* found that calcium supplements with or without vitamin D had a 24% increased risk of MI compared to placebo [11]. There are several limitations to this study, including controversy about removing users of personal calcium supplements from the Bolland analysis, lack of cardiovascular endpoints as primary outcomes, and the lack of adherence in taking study pills during the WHI study itself [96]. Further RCTs with CaD supplementation and cardiovascular outcomes need to be done to clarify whether CaD has a beneficial or harmful effect on cardiovascular health.

Current Vitamin D Guidelines

Given the absence of strong evidence, there is a lack of consensus regarding vitamin D deficiency screening and management. Several organizations have issued recommendations concerning either populations who should be screened for vitamin D deficiency, laboratory cutoff values to be considered deficient, or recommended intake of vitamin D (Table 2) [65, 74, 97-102]. However, these recommendations are all based on evidence for optimal bone health. To our knowledge, no organization has issued guidelines for vitamin D intake specifically to prevent CVD, as the current evidence is insufficient to support such a recommendation.

Two of the most widely cited recommendations are the IOM's 2010 guidelines [65] and the Endocrine Society's 2011 guidelines [74]. Notably, despite their widespread acceptance, there are several major discrepancies between the two documents [103]. While the IOM does not consider a serum 25(OH)D level above 20 ng/ml to confer additional benefit for bone health, the Endocrine Society considers a serum 25(OH)D level of 30 ng/ml to be optimal. Both organizations differ in their recommended daily intake to achieve these vitamin D levels. Additionally, while both advise against routine vitamin D screening in the general population, the Endocrine Society considers additional groups to be at risk for deficiency compared to the IOM, including African-American and Hispanic populations, older adults with history of fracture, and obese individuals.

In the face of varying guidelines, physicians understandably may express confusion about whom to screen and treat in their clinical practice. A study of the National Ambulatory Medical Care Survey found that the rate of diagnoses for vitamin D deficiency increased from 2007 to 2010 [104]. Most diagnoses were for non-specified disease, thus vitamin D screening was likely used for preventative care, rather than for diagnostic purposes in symptomatic patients. However, these surveys were administered prior to the update in the IOM and Endocrine Society guidelines, so it is possible that vitamin D screening has declined following the release of the guidelines. Additionally, a small study by Tarn *et al.*

suggested that the uncertainty inherent in the varying vitamin D guidelines does not get conveyed to patients, resulting in patients getting unnecessarily screened and treated for vitamin D deficiency [105]. While not representative of all clinical practices, it underlines the importance of providing consistent vitamin D guidelines to minimize variations in patient care.

Conclusion

In summary, despite intriguing evidence from animal studies and observational studies that low vitamin D is associated with increased risk for CVD, there is insufficient evidence at this time to prove a causal relationship and to prove that vitamin D supplementation is effective in reducing cardiovascular risk. Although calcium supplementation is widely used for maintaining bone health, there is some evidence that it may increase CVD risk. Due to the seemingly conflicting effects of low vitamin D and high calcium levels on CVD, further research is needed to examine the effect of combined CaD supplementation on specific cardiovascular outcomes. Until the results of ongoing large-scale RCTs are available, it is important for clinicians to be aware of the differing vitamin D guidelines to best care for their patients and weigh the potential risks and benefits before prescribing supplementation.

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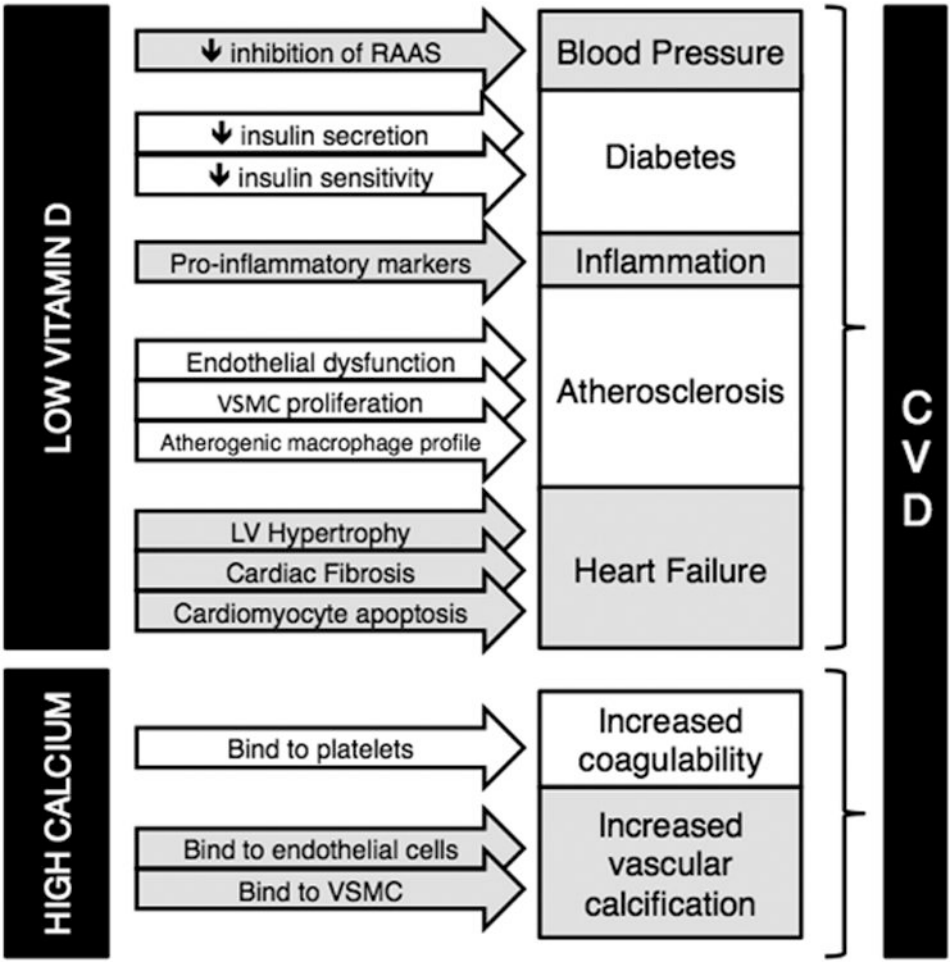

Fig. 1.

Proposed mechanisms by which vitamin D deficiency and high calcium levels (typically from calcium supplementation and not dietary calcium sources) may increase cardiovascular disease risk. RAAS: renin-angiotensin-aldosterone system; VSMC: vascular smooth muscle cell; LV: left ventricular

Table 1

Summary of ongoing large, randomized controlled trials with vitamin D supplementation as an intervention. Note that outcomes listed are only those related to cardiovascular disease risk factors or outcomes. Participant demographics of sex and race were included for trials with published baseline demographics. Only trials with a sample size of 400 participants or more were included

Study	Sample Size	Participants	Participant Demographics	Intervention (vs. placebo)	Intervention Period	Primary Endpoint	Other endpoints	Location	Primary End Date
VIDA[84]	5,110	50-84 years	58% M, 42% F 83.2% White 16.8% Other	100,000 IU/month	3.3 years (median)	CVD	Blood pressure, HR variability, Arterial waveform	New Zealand	2016
EVITA[85]	400	CHF patients, 18-79 years, 25(OH)D <30ng/ml		4,000 IU/day	3 years	All-cause mortality	Event-free survival	Germany	2016
VITAL[82]	25,875	≥50 years M ≥55 years F	49.4% M, 50.6% F 75.3% White 20.2% Black 4.5% Other	2,000 IU/day	5 years	Cancer, CVD		United States	2017
VIDAL (Feasibility Study)[86]	1,600	65-84 years		100,000 IU/month	2 years	Cause - specific mortality		United Kingdom	2017
D2D[87]	2,362	Prediabetes ≥30 years		4,000 IU/day	3 years	Diabetes		United States	2017
DO-Heafth[88]	2,152	≥70 years		2,000 IU/day	3 years	Blood Pressure		Europe	2017
FIND[89]	2,495	≥60 years		1600 IU/day, 3200 IU/day	5 years	CVD, Cancer		Finland	2018
D-Health[83]	21,315	60-84 years	54.1% M, 45.9% F 94.5% White 5.5% Other	60,000 lU/month	5 years	All-cause mortality	Total CV events, Diabetes, High blood pressure	Australia	2019

Table 2

Summary of guidelines regarding vitamin D deficiency screening and supplementation. Note that all threshold and treatment values are to promote optimal serum 25-hydroxyvitamin D levels for bone health, and not the prevention of cardiovascular disease.

Agency (Year of Guideline)	Country	Screening	Deficiency Threshold	Recommended Dietary Intake	Upper Level Intake
Institute of Medicine (2010)	United States, Canada[a]		Deficient: <20 ng/ml	600 IU/day (19-70years) 800 IU/day (≥70 years)	4,000 IU/day
Endocrine Society (2011)	International	Individuals at risk for deficiency[c]	Deficient: <20 ng/ml Insufficient: 21 -29 ng/ml Sufficient: ≥30 ng/ml	Minimum 600 IU/day (may need 1,500-2,000 IU/day to ensure 30 ng/ml or higher)	4,000 IU/day[b]
United States Preventative Services Task Force (2014)	United States	Symptomatic adults			
American Geriatric Society (2013)	United States	Not necessary if supplementation within recommended limits	Deficient: <30 ng/ml	1,000 IU/day (>65 years)	10,000 IU/day
National Osteoporosis Foundation (2014)	United States			800-1,000 IU/day (>50 years)	
Scientific Advisory Committee on Nutrition (2016)	United Kingdom		Deficient: <25 ng/mL	400 IU/day	4,000 IU/day
National Institute for Health and Care Excellence (2014)	United Kingdom	Individuals symptomatic or at high risk for deficiency[c]		400 IU/day for at-risk groups	

[a] IOM is a U.S. organization, but the IOM Vitamin D report was funded by the U.S. and Canadian governments.

[b] The Endocrine Society recognizes that supplementation up to 10,000 IU/day in people aged 19 years and older may be needed to correct for deficiency.

[c] Risk factors for deficiency include: African-American and Hispanic ethnicity, pregnant or lactating women, older adults with history of falls or fractures, obesity (BMI >30 kg/m^2), granuloma-forming disorders, malabsorption syndromes, chronic kidney disease, liver failure, conditions that cause weakening of bone, certain medications including anticonvulsants