Review

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# Vitamin D's Role in Cardiovascular Diseases

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**This article explores the correlation between vitamin D levels and cardiovascular health, focusing on hypertension, atherosclerosis, and cardiac dysfunction. Cardiovascular diseases (CVDs) rank as the leading global cause of death, underscoring the significance of exploring vitamin D's potential role in maintaining a healthy cardiovascular system. It discusses vitamin D's mechanisms of action, including genomic and non-genomic pathways, and explores risk factors like smoking, obesity, and hypertension, linked to vitamin D deficiency. Additionally, it delves into its role in regulating the renin-angiotensin system, cardiac hypertrophy, and inflammation. The link between vitamin D supplementation and a lower risk of cardiovascular events, including hypertension, atherosclerosis, and heart failure, is considered. However, inconsistent results from supplementation trials call for further research to establish efficacy for cardiovascular health. In conclusion, the article emphasizes the importance of vitamin D for cardiovascular well-being and calls for comprehensive studies to explore its therapeutic potential in treating cardiovascular disease (CVD).**

**Keywords:** cardiovascular diseases; heart failure; vitamin D; renin-angiotensin-aldosterone system; hypertension

## Introduction

The greatest cause of illness and mortality worldwide has been the attribution of cardiovascular diseases (CVDs). CVD contributes to prevalent and life-threatening conditions [1]. While arterial lesions are clinically significant [2], venous pathologies related to CVD can also lead to severe consequences. It was once thought to be a condition exclusive to the Western world, but recent research has shown that populations in developing and even low-income countries are also affected. More than 17.7 million deaths worldwide in 2015 were attributed to CVD, or 31% of all deaths, based on World Health Organization's (WHO's) data [3]. Hence CVD is the leading cause of death worldwide. 17.9 million people are estimated to face mortality from CVD in 2016. In the United States (US), 48% of adults greater than the age of 20 years suffered from CVD, between 2013 and 2016, with an estimated cost of $351.3 billion going towards their treatment alone between 2014 and 2015 [4].

The pathophysiology of CVD manifests through two main mechanisms. Narrowing and obstruction of vessel lumen, occurring either chronically or acutely. The former causes atherosclerosis or coronary artery disease (CAD) while the latter causes thrombosis as in myocardial infarction (MI) and embolism. Another mechanism revolves around the weakening of the vessel wall causing dilation or rupture of a vessel as in the case of a berry's aneurysm. Timely diagnoses of cardiovascular (CV) pathologies are often difficult for two reasons. First, coronary artery disease often remains asymptomatic until an advanced stage. Second, heart disease symptoms can overlap across various pathologies. Symptoms include palpitations, chest pain, hemoptysis, edema, and general malaise. While chest pain remains the most common symptom of acute MI in both men and women, women are more likely to experience atypical symptoms such as upper back pain, neck pain, fatigue, nausea, and vomiting [5]. Endothelial cells (EC), forming a continuous lining along blood vessels, play a crucial role in regulating vascular and cardiac functions. Maintaining a non-thrombogenic EC layer involves factors like laminar flow, vascular endothelial growth factor (VEGF), and strong adhesion to the basement membrane. Trauma or EC loss disrupts this balance, contributing to cardiovascular disease through thrombosis and vasoconstric-

tion. Therapies for endothelial dysfunction involve statins, angiotensin-converting enzyme inhibitors, and low-dose aspirin. For non-endothelial dysfunction-related cardiovascular disease, treatments include beta-blockers, alpha-beta blockers, and nitrates [6].

Vitamin D, acting through vitamin D receptor (VDR), has multifaceted effects on various biological systems, including the cardiovascular system. Emerging evidence highlights its crucial role in regulating cellular components within the cardiovascular system and endothelial function. While vitamin D deficiency has been linked to several cardiovascular diseases, its precise relevance remains to be fully understood [7].

Human skin synthesis, which is reliant on sunshine exposure, is the principal vitamin D source in our body. It's challenging to predict how much sunlight we need subjectively to get enough vitamin D as it is dependent upon so many different factors including our age, skin color, latitude, season, or time of the day [8]. Moreover, the majority of individuals have diets deficient in vitamin D as vitamin D is scarce in popular food sources [9]. Thus, in many cases where there is insufficient exposure to sunshine, vitamin D supplementation may therefore be required to meet the daily Recommended Dietary Allowance (RDA) [10].

The pathophysiology of multiple CVD such as hypertension (HTN) atherosclerosis and peripheral arterial disease is significantly correlated with endothelial dysfunction. Nitric oxide (NO), a crucial vasoactive compound, has a potent vasodilator effect that gives protection against both vascular lesions and arterial inflammation. According to several studies, vitamin D and VDR may be crucial in controlling the synthesis of NO and endothelial function [11].

This review aims to explain how vitamin D may potentially play a role in lowering the likelihood of major cardiovascular diseases and intends to clarify the relationship between vitamin D levels and cardiovascular health.

## Mechanism of Action of Vitamin D

### *Vitamin D can Cause its Actions in 2 Ways*

#### Genomic and Non-Genomic

For vitamin D to carry out its action through the genomic pathway it has to be converted into its hormonal form 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] which acts as a ligand for the transcription factor VDR. Three domains make up the VDR: the C-terminal portion of the ligand binding domain, the region that acts as a hinge, and the N-terminal DNA-binding domain with two zinc containing regions that attach to the grooves of the DNA in specific locations referred to as the vitamin D response elements (VDREs) [12]. To produce the biologically active form of vitamin D, 1,25$(OH)_2$D, the renal enzyme 1$\alpha$-hydroxylase initially converts the inactive precursor, 25-hydroxyvitamin D [25(OH)D] [13].

The VDR belongs to the steroid receptor family, which also includes receptors for retinoic acid, thyroid hormone, sex hormones, and adrenal steroids. The VDR and Retinoid X Receptor (RXR) heterodimerize, forming an activated VDR/RXR complex. This complex binds to specific sites on DNA known as VDREs, influencing gene expression and mediating vitamin D's effects on various tissues [14]. The binding of 1,25$(OH)_2$D induces a conformational change that facilitates interaction with RXR and co-regulatory complexes, essential for gene transcription [15].

#### Non-Genomic

Some effects of 1,25$(OH)_2$D are too rapid to be explained by influencing gene expression and hence, these effects are said to have a non-genomic pathway. Because various vitamin D substitutes managed to elicit the rapid responses of 1,25$(OH)_2$D despite being unable to bind to the vitamin D receptor situated in the nucleus (VDRn), Norman [16] first proposed the existence of a second membrane receptor known as vitamin D receptor present on the membrane (VDRm). The basal-lateral membranes of the intestinal epithelium contain a binding protein for 1,25$(OH)_2$D that controls $Ca^{+2}$ transport across those membranes [17]. The name Membrane-associated rapid response steroid (MARRS) binding protein was given to this receptor [18]. The receptor is concentrated in the caveolae near the plasma membrane, where it binds to phospholipase A2 and caveolin-1 (Fig. 1) [19].

## Risk Factors of Heart Diseases

The heart is one of the most vulnerable organs of the body. Framingham's study identified typical risk factors that can be avoided or changed to lower the chance of heart disease (Table 1) [20]. The Framingham's study is one of the most significant studies in the context of cardiovascular diseases [21]. Both active and passive tobacco use, and secondhand smoke, can raise one's chance of atherosclerosis and other CVDs [22]. Beyond the natural increase in mortality in diabetic people, the death rate nearly doubles when diabetes is coupled with CVD symptoms such as myocardial infarction or stroke, leading to a decrease in life expectancy of about 12 years [23]. Through well-known and established pathways like dyslipidemia, hypertension, and type 2 diabetes mellitus, obesity can lead to coronary atherosclerosis [24]. Hyperlipidemia presents more risk for cardiovascular complications than diabetes, smoking or hypertension [25]. Obesity and high blood triglycerides were univariate risk factors for new coronary events in older men. A study observed that CVD was present amongst 292 of 664 males (44%) with an average age of 80 years [26].

The aspects of heart diseases which are not under human control are genetic predisposition to heart diseases and old age.

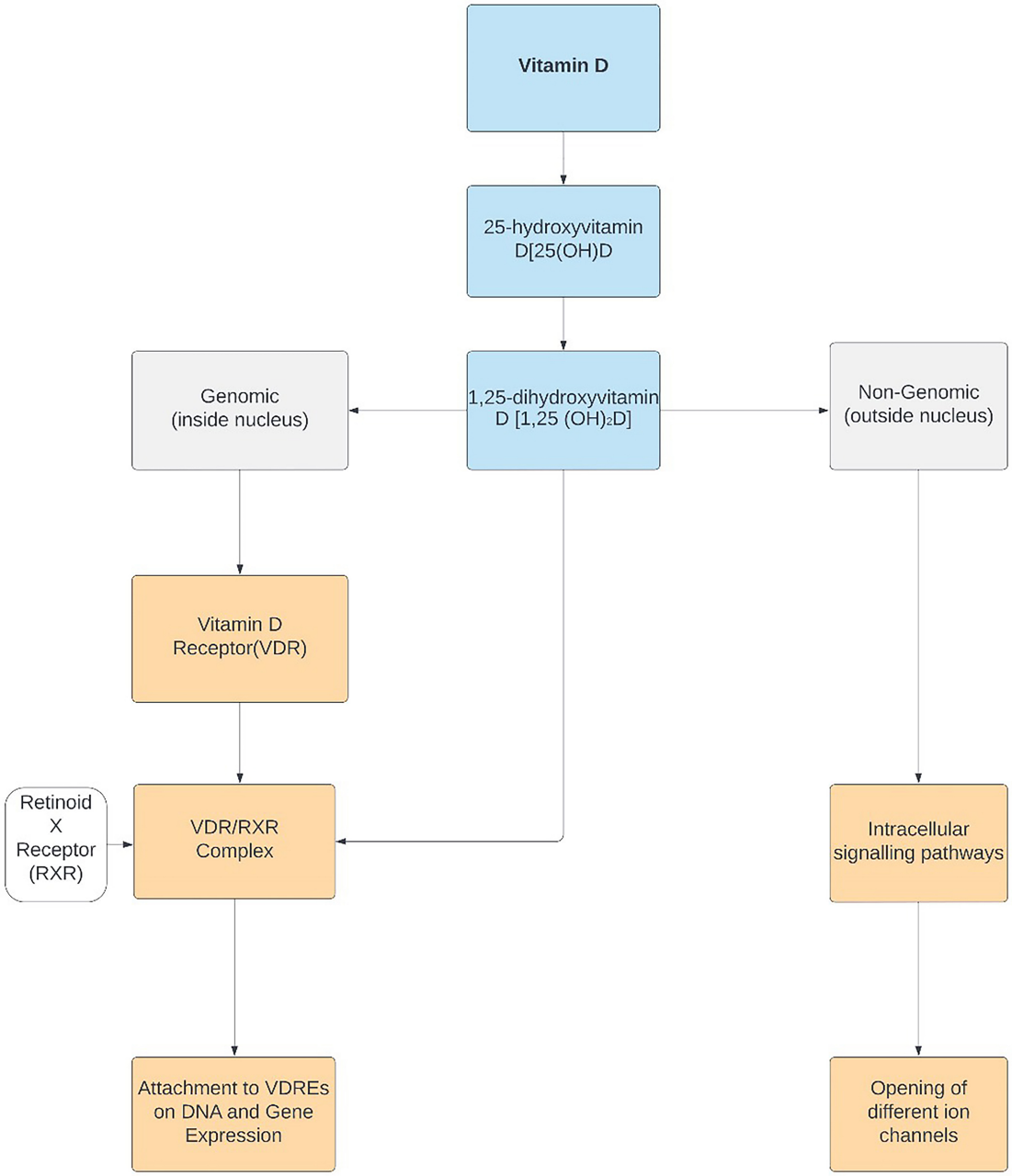


**Fig. 1. Summary of the mechanism of action of $1,25(OH)_2D$.**

## Pathophysiology

There is growing information that vitamin D benefits CV health. The presence of the vitamin D signaling cascade in the human heart, suggests a direct role for this hormone in cardiac physiology, helping explain the link between vitamin D status and CV outcomes [27].

Most human cells and tissues contain vitamin D receptors, which suggests that vitamin D has various benefits outside of the skeletal system, especially for the immune and cardiovascular systems. Vitamin D insufficiency is associated with increased death rates and the prevalence of cardiovascular conditions, and it has been implicated in various cardiovascular risk factors. Several proposed mechanisms suggest that inadequate vitamin D levels may contribute to cardiovascular risks through the dysregulation of nitric oxide, increased oxidative stress, or changes in inflammation-related pathways [28].

When vitamin D binds to the VDR and shifts to the nucleus, it has a biological effect. By first interacting with the RXR and secondly, with the vitamin D response element (VDRE), vitamin D increases the expression of certain genes [29]. Vitamin D binding protein polymorphisms could alter its interaction with vitamin D, potentially raising the risk of cardiovascular diseases or a deficiency in vitamin [30].

**Table 1. Risk factors of heart diseases according to Framingham studies.**

| Factors that increase the risk of heart diseases | Factors that decrease the risk of heart diseases |
|---|---|
| Smoking | Physical activity |
| High LDL | High HDL |
| High normal blood pressure | Gender (female) |
| ECG abnormalities | Positive social interaction |
| Atrial fibrillation | |
| Enlarged left ventricle | |
| Obesity and increased BMI | |
| Physiological factors | |
| Diabetes mellitus | |
| Gender (male) | |
| Sleep apnea | |
| Genetics | |
| Menopause | |

Table Notes: HDL, high density lipoprotein; LDL, low density lipoprotein; ECG, electrocardiogram; BMI, body mass index.

Limiting 1,25$(OH)_2$D/VDR signaling can result in increased renin/angiotensin activity with high blood pressure and cardiac hypertrophy, decreased availability of the vasodilator nitric oxide with resulting compromised blood vessel relaxation, endothelial cell dysfunction, increased levels of pro-inflammatory cytokines, and more vascular smooth muscle cells proliferating and migrating. These outcomes have been shown in experimental investigations in laboratory animals [31].

### *Vitamin D and Renin-Angiotensin-Aldosterone System*

Hypertension has been linked to inappropriate Renin-Angiotensin-Aldosterone system (RAAS) stimulation. The rate limiting enzyme of the renin angiotensin system is renin. The primary effector of the renin angiotensin system is Angiotensin II (Ang II), using Ang II receptors [32]. Ang II promotes the production of aldosterone by the adrenal cortex which in turn brings about a rise in blood volume and hence, blood pressure. Moreover, in those who have essential hypertension, an inverse connection between blood levels of 1,25$(OH)_2$D3 and plasma renin has been noted [33].

It is hypothesized that, under normal physiological circumstances, vitamin D3 opposes other renin-stimulating substances to maintain suitable renin levels in the body in addition to maintaining the blood calcium content. As a result, a vitamin D supplement may prove to be helpful for the cardiovascular system, by counter balancing RAAS pathway and lowering plasma renin and therefore, Ang II levels, by increasing plasma 1,25-dihydroxycholecalciferol levels. Decreased Ang II would serve to lower aldosterone levels, blood volume and blood pressure. Hence, a vitamin D supplement may potentially be used to treat hypertension conversely, a vitamin D deficiency may raise the risk of hypertension [32].

### *Vitamin D and Cardiac Hypertrophy*

Vitamin D receptor activation is advantageous for reducing the underlying causes of cardiovascular diseases, such as hypertension, endothelial dysfunction, atherosclerosis, vascular calcification, and cardiac hypertrophy, according to results from interventional trials employing either dietary vitamin D with vitamin D receptor agonists. Vitamin D receptor analogues are currently not approved to be utilized in the management of cardiovascular illnesses despite the fact that they have been shown to be useful and play a substantial role in the control of cardiovascular activity [34].

Low concentrations of vitamin D2 and vitamin D3 are linked to an increased risk of myocardial infarction, congestive heart failure, and cardiovascular disease-related death [35].

A lack of vitamin D causes the left ventricular cardiomyocytes to enlarge, as well as an increase in the infiltration of inflammatory cells and the expression of pro-inflammatory adipokines in the intraperitoneal epicardial adipose tissue (EAT) fat. The aforementioned outcomes are associated with insufficient expression of suppressor of cytokine signaling-3 (SOCS3) in cardiomyocytes and EAT. When considered collectively, the findings of this study suggest that vitamin D modulates cardiovascular processes through a variety of pathways that include direct effects on the hypertrophy of cardiomyocytes and an altered inflammatory profile. In the population that is vitamin deficient, this may be a factor that leads to increased atherogenesis and impaired heart function [35].

The alleviation of capillary deficiency brought on by vitamin D receptor stimulation by vitamin D3 and 19-nor-1,25-$(OH)_2$-vitamin D2 may limit the expanse of cardiac fibrosis, which would be essential in forestalling the enlargement of the left ventricle [36]. Secondary hyperparathyroidism and elevated levels of parathyroid hormone (PTH)

are brought on by vitamin D insufficiency. It has been discovered that PTH makes cardiac myocytes' protein kinase C (PKC) active. The left ventricular hypertrophy that results from the stimulation of this PKC is caused by the stimulation of fetal protein in cardiac myocytes in addition to other hypertrophic growth factors [36].

### *Vitamin D and its Anti-Inflammatory Effect on Cardiomyocytes*

Through anti-inflammatory, antifibrotic, and anti-apoptotic pathways, vitamin D signaling enhances cardioprotection after myocardial infarction [37].

Tumor necrosis factor (TNF)-$\alpha$ and IL-6, two inflammatory mediators, are down-regulated. Vitamin D influences the expression of cyclooxygenase (COX), nuclear factor kappa B (NF-$\kappa$B), and signal cascades like Mitogen-activated protein kinase (MAPK) which are crucial in the inflammatory pathway [36].

## Vitamin D's Association with Hypertension and Atherosclerosis, and its Effect(s) on Cardiac Function

### *Vitamin D and Hypertension*

One widely known risk factor for heart disease is hypertension. One study by Bae S *et al.* [37] sought to uncover that a low vitamin D level may increase one's risk of developing diabetes and high blood pressure. A randomized, double-blind, placebo-controlled study conducted by Nasri *et al.* [38] showed that patients with diabetes mellitus whose diets were supplemented with vitamin D saw decreased blood pressure [38]. Notably, vitamin D receptors are found in various tissues, including blood vessels and the RAAS, which regulates blood pressure [39] as shown in (Fig. 2).

Vitamin D may contribute to blood pressure regulation through multiple mechanisms. Firstly, it can inhibit the RAAS, thereby reducing the production of renin, angiotensin II, and aldosterone, which collectively contribute to increased blood pressure. The pivotal role of the RAAS in the regulation of blood pressure is well established [40].

Secondly, vitamin D promotes the production of nitric oxide, a powerful vasodilator that relaxes blood vessels and helps lower blood pressure [41]. Furthermore, vitamin D can influence the expression of genes involved in blood pressure regulation.

Examining the relationship between vitamin D levels and hypertension has yielded a mix of results. One study found an inverse association between vitamin D levels and blood pressure, suggesting that lower vitamin D levels may increase the risk of hypertension [42] whereas, another study was not able to uncover a significant association [43]. Further research is necessary to clarify the relationship between vitamin D and hypertension and determine the potential benefits of vitamin D supplementation in managing hypertension.

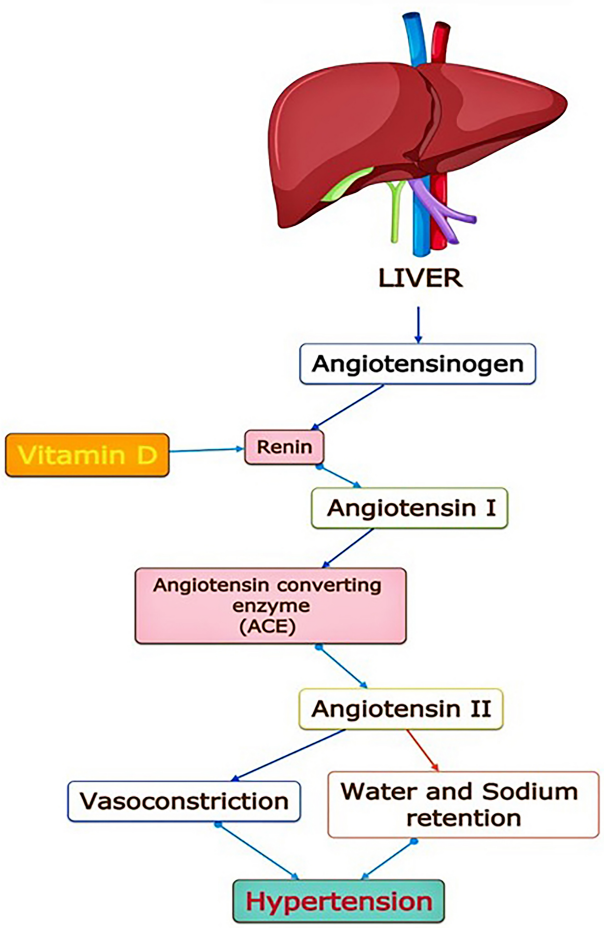


**Fig. 2. Effect of vitamin D on renin-angiotensin-aldosterone system (RAAS).**

### *Vitamin D and Atherosclerosis*

Atherosclerosis, characterized by the accumulation of plaque in arterial walls, is a major underlying cause of cardiovascular diseases such as heart attacks and strokes. Emerging evidence suggests that vitamin D can influence how atherosclerosis develops and advances [30].

Vitamin D possesses anti-inflammatory properties that can help mitigate the inflammatory processes involved in atherosclerosis. Chronic inflammation significantly contributes to the development of atherosclerotic plaques. Vitamin D plays a role in inhibiting pro-inflammatory cytokines and promoting anti-inflammatory ones, thereby modulating the inflammatory response within arterial walls [44].

Vitamin D is implicated in maintaining the health of blood vessels and the proper function of the endothelium. Endothelial dysfunction, characterized by impaired nitric oxide availability and increased oxidative stress, is an early event in atherosclerosis. Vitamin D can enhance endothelial function by promoting the production of nitric oxide, reducing oxidative stress, and improving vascular relaxation [45].

While observational studies have indicated a correlation between reduced levels of vitamin D and an en-

hanced likelihood of atherosclerosis, evidence from interventional studies is limited and inconclusive [46] (mentioned in the section "Vitamin D3 supplementation and CVS outcomes"). Further randomized controlled trials are required to determine whether vitamin D treatment is effective in halting or delaying the development of atherosclerosis.

### *Vitamin D and Cardiac Functions*

Vitamin D may directly influence cardiac functions and cardiovascular outcomes. The existence of vitamin D receptors in cardiac muscle cells, points towards vitamin D's potential role in regulating cardiac functions. Experimental studies have shown that vitamin D can impact cardiac muscle contractility and improve myocardial function [47]. Vitamin D receptors present in cardiac myocytes play a role in maintaining calcium homeostasis, which is vital for proper myocardial contraction. Further reinforcing this idea was a study in which VDR deletion was found to impair myocardial contractility and lead to cardiac hypertrophy [48].

### *Vitamin D and Coronary Heart Disease*

Coronary artery diseases are diseases characterized by a reduced supply of oxygen and nutrients to the myocardium. They are classified into two types: stable ischemic heart disease and acute coronary syndrome (ACS). ACS is subdivided into unstable angina, ST-elevated myocardial infarction (STEMI), and non-ST-elevated myocardial infarction (NSTEMI). EAT cells play an integral role in the progression of atherogenesis through the production of proinflammatory cytokines in coronary arteries, leading to coronary artery disease. Expression of the transcription factor NF-$\kappa$B occurs in these cells. This transcription factor causes the transcription of genes that encode pro-inflammatory cytokines such as IL-1, 1L-6, and TNF-$\alpha$, which contribute to atherogenesis in coronary arteries [48]. Vitamin D is thought to suppress NF-$\kappa$B production and hence reduce CAD risk. A study showed that vitamin D3 inhibits the expression of karyopherin-$\alpha$4 (KPNA4). KPNA4 is a protein that shuttles NF-$\kappa$B into the nucleus; thus, by inhibiting the transport of NF-$\kappa$B, it prevents the expression of genes encoding pro-inflammatory cytokines and hence lowers the risk of developing coronary artery disease [49].

### *Vitamin D and Stroke*

In a stroke, there is a complete loss or reduction in blood supply to an area of the brain, leading to ischemia and eventually infarction of that area. By lowering the risk of atherosclerosis, as mentioned, and hence lowering the chances of plaque forming in a cerebral vessel, vitamin D may play a role in reducing the risk of clot formation and stroke. This is supported by multiple studies that suggest that low levels of vitamin D are correlated with a poor prognosis after a stroke [50–52]. Vitamin D supplementation may increase nitric oxide synthase activity in endothelial cells lining cerebral blood vessels; this would lead to increased nitric oxide production and vasodilation of cerebral blood vessels, helping raise some blood flow to the areas affected by stroke [53].

### *Vitamin D and Arrhythmia*

In a normal heart, the sinus node acts as the pacemaker and dictates the heart rate and pattern of electrical depolarization that propagates through the heart. Depolarization spreads from the right atrium, throughout the atrial walls, to the atrioventricular node (AVN), and from there via the His-Purkinje system throughout the ventricles. A normal sinus rhythm has a heart rate of 60–100 beats per minute (bpm) and a normal wave progression in an electrocardiogram (ECG). An arrhythmia refers to an abnormal heart rate or rhythm. Multiple articles published have found a significant association between arrhythmias and vitamin D deficiency [54–56]. Vitamin D deficiency may contribute to this effect by enhancing the P-wave dispersion and, electromechanical delays in the left intra-atrial and inter-atrial regions [57]. Also, low vitamin D levels may prompt a decrease in calcium ion concentration in the blood by reducing its intestinal sequestration and increasing renal excretion. Calcium ion deficiency increases PTH secretion; increased PTH concentrations are correlated with atrial fibrillation [58]. Vitamin D also prevents overactivation of the RAAS pathway; RAAS elevates oxidative stress and brings about inflammation, two key effects that influence atrial remodeling and increase the risk of the development of atrial fibrillations [59].

### *Vitamin D and Heart Failure*

Heart failure (HF) is a condition characterized by the inability of the heart to pump blood properly due to a structural and functional defect in the heart. Research has shown that in the cardiomyocytes of a hypertrophic heart, the intracellular vitamin D receptor numbers are elevated, pointing towards the potential need for vitamin D to counteract such a process [60]. As discussed previously, it also plays a role in regulating calcium ion concentration and, hence, parathyroid hormone concentration. Indeed, a vitamin D deficiency brings about an indirect increase in PTH. Elevated PTH levels are associated with left ventricular hypertrophy, which progresses to heart failure [61]. Vitamin D is also thought to be involved in promoting anti-inflammatory effects by activating T helper 2 (Th2) cells, which suppress the production of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-$\alpha$, which serve to aggravate heart failure [62]. In line with this information, multiple clinical trials showed the therapeutic benefits of vitamin D supplementation in preventing or treating HF [63,64]. However, contradicting results from many other trials emphasize the need for more research to establish a more conclusive result [65,66]. The therapeutic effects of Vitamin D on CVDs are summarized in Fig. 3 [39].

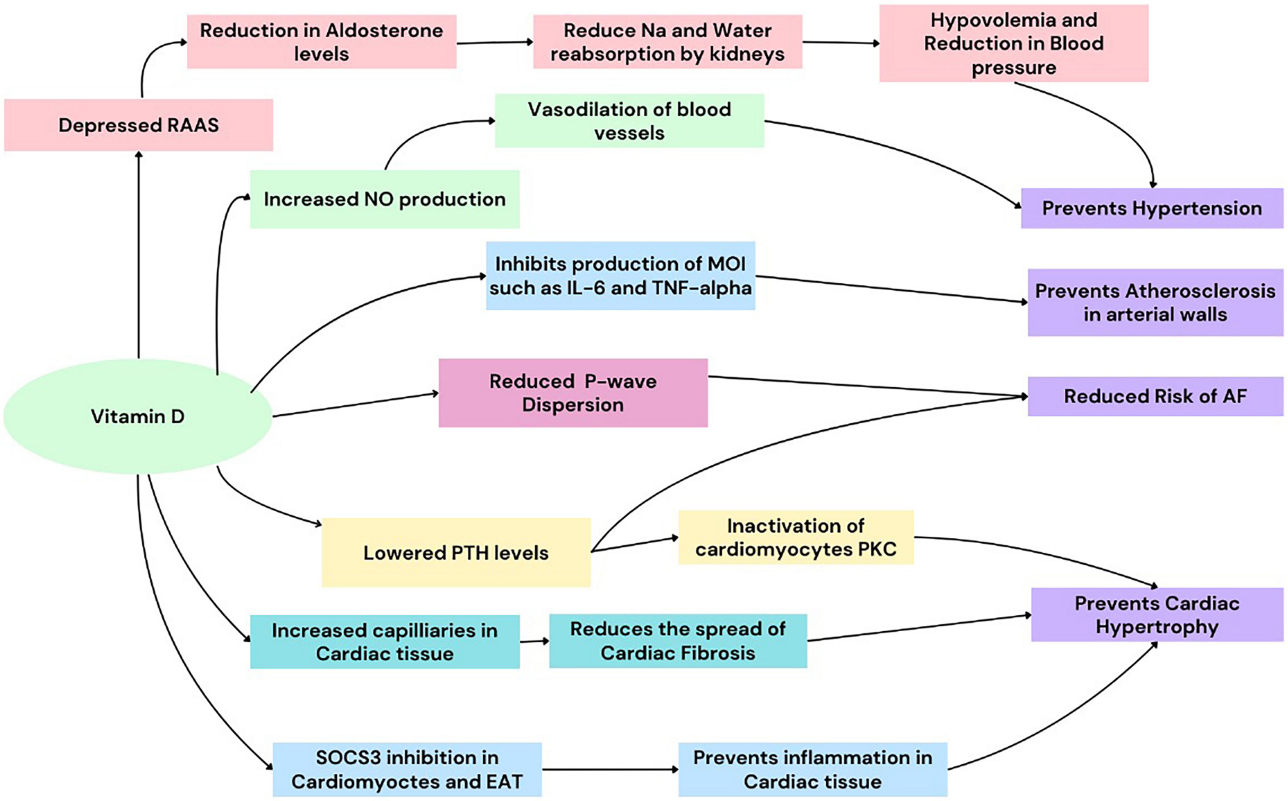


**Fig. 3. Vitamin D's role in prevention of cardiovascular diseases (CVDs).** NO, nitric oxide; MOI, mediators of inflammation; IL-6, interleukin-6; TNF-$\alpha$, tumor necrosis factor-$\alpha$; AF, Atrial Fibrillation; PTH, parathyroid hormone; PKC, protein kinase C; SOCS3, suppressor of cytokine signaling-3; EAT, epicardial adipose tissue.

## Vitamin D Deficiency, a Risk Factor for Cardiovascular Disease

The majority of experts define vitamin D deficiency as a 25(OH)D level of less than 20 ng/mL (50 nmol/L), and vitamin D insufficiency as a level of between 21 and 29 ng/mL. Although an agreement regarding the ideal level of serum 25(OH)D has not yet been established. The ideal 25(OH)D concentration is at least 30 ng/mL for all currently researched end goals [67].

25-OH vitamin D levels in serum or status of vitamin D:

- 10 (ng/mL): severely lacking
- 10–20 (ng/mL): deficiency
- 21–29 (ng/mL): insufficiency
- $\geq$30 (ng/mL): sufficiency
- $>$150 (ng/mL): toxicity

Vitamin D insufficiency was found to be associated with significant adverse CV outcomes in the 1739 Framingham Offspring Study individuals who did not have CV illness at baseline [67]. Participants in this prospective observational trial were followed up with baseline 25(OH)D levels every 5.4 years on average. The incidence of a composite CV end goal (fatal or nonfatal MI, ischemia, stroke, or heart failure) was 53% to 80% higher in people with low vitamin D levels. The increased CV risk associated with vitamin D deficiency was more pronounced in the group of Framingham children with hypertension.

Lack of vitamin D increases the likelihood of activating the renin-angiotensin-aldosterone pathway, which in turn causes the left ventricle and smooth muscle cells of the vascular system to expand [68]. Atherosclerosis, left ventricular hypertrophy and hypertension are more common in animals with vitamin D deficiency [69]. 1,25-dihydroxy vitamin D is known to decrease the synthesis of renin in humans, which may lower blood pressure [69].

In a study including over 27,000 individuals from the Intermountain healthcare system, the incidence of vitamin D deficiency (30 ng/mL) was shown to be $>$60%. Furthermore, there was a substantial correlation found between vitamin D deficiency and heart failure, stroke, myocardial infarction, Coronary Heart Disease (CHD), and overall mortality [70]. In health workers, low levels of 25(OH)D have been associated with an increased risk of myocardial infarction. 10-year follow-up of 18,225 males in the Follow-up Study, even after controlling for other CHD risk variables [71]. 96% of patients admitted with acute coronary syndromes had aberrant 25(OH)D levels below 30 ng/mL, according to a recently published multicenter research [72].

## Vitamin D3 Supplementation and CVS Outcomes

A growing body of research indicates that vitamin D may protect the cardiovascular system. Ng LL *et al*. [73] presented one such piece of evidence in a cohort study involving 1259 individuals who had suffered an acute myocardial infarction (AMI) [74]. It was found that the majority of patients in the lowest vitamin D quartile (7.3 ng/mL) were readmitted to the hospital either because their acute HF or AMI had returned. This study, along with numerous others, such as the ones listed above, supports the idea that there is an inverse link between CVD and optimal vitamin D levels by demonstrating the significant incidence of vitamin D deficiency among patients with CVD [74]. To test this hypothesis, many vitamin D supplementation trials have been carried out, and a large number of studies have been published. Bahrami LS *et al*. [75] carried out a randomized control trial (RCT) that took place in Tehran, Iran, and in this trial, males and females with Coronary Heart Disease (CHD) aged 30–60 were recruited. Results showed that the decrease in average systolic pressure and average diastolic pressure in participants given vitamin D supplements was significantly greater than in those given a placebo [75]. The findings of the above study are consistent with those of a randomized control trial conducted by Wu Z *et al*. [76] at PLA General Hospital in Beijing, China. This study recruited patients with CAD. Participants in the trial were split into two groups at random (1:1), with one receiving an oral placebo and the other receiving vitamin D supplementation. At the trial's conclusion, the vitamin D-supplemented group (VDSG) exhibited significantly lower Synergy Between Percutaneous Coronary Intervention (PCI) With Taxus and Coronary Artery Bypass Surgery (SYNTAX) scores, a measure of CAD severity, as well as lower Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) than the placebo group (PG). Further evidence of vitamin D's anti-inflammatory action, which may have assisted in lessening the severity of CAD, came from the significant decrease in high-sensitivity C-reactive protein (hs-CRP) levels in VDSG relative to the PG; renin, angiotensin-II, and aldosterone levels also decreased [76]. Vitamin D's role in preventing RAAS overactivation is known to improve prognosis among CVD patients [77] and has been discussed above. The findings of the above study are consistent with another conducted by Dalbeni A *et al*. [78] a randomized control trial that initially recruited HF patients from Verona University Hospital in Italy, the participants were divided into a 1:1 ratio and into two groups: one group was given an oral placebo and the other was given vitamin D supplements, at the end of the trial and evaluation of the participants, showed a significant increase in ejection fraction (EF), marker of cardiac health, in patients in the intervention group compared with those belonging to the placebo group, a greater decrease in SBP and DBP in the intervention group was also seen compared with the placebo group however the difference in decreases were insignificant in both cases ($p > 0.05$) [78]. Growing research indicates that while certain studies back up the use of vitamin D in the treatment of CVD, there is also evidence to the contrary. Research by Virtanen JK *et al*. [79], a randomized control experiment done in Eastern Finland, offered one such piece of evidence. Three groups of participants, each with a mean age of 68.2 years, were formed and given different amounts of vitamin D daily: 1600 International Units (IU) for the second group, 3200 IU for the third. An oral placebo was given to the first group. The major endpoint evaluation revealed that there is statistical insignificance in the differences between the Hazard Risk (HR) of the combined Interventional groups (CIG) and PG. The disparities between the HR of CIG and PG for MI, stroke, CVD mortality, and increased major cardiovascular events were likewise [79]. The outcomes of this research were aligned with the VITAL (vitamin D and omegA-3 triaL) study conducted by Manson JE *et al*. [80], a randomized control trial in which participants were recruited from the United States. Participants were divided into two groups: PG and VDSG. After the end of the intervention period, the results were analyzed, and the differences in major CV events that occurred in the two groups were deemed statistically insignificant; furthermore, the supplementation was also ineffective in reducing the risks for secondary cardiovascular endpoints [80]. Zittermann A *et al*. [81] conducted effect of vitamin D on all-cause mortality in heart failure (EVITA), a randomized control trial that recruited participants with HF between the ages of 18 and 79. The study's findings align with the growing body of evidence against the use of vitamin D in CVD treatment. Participants were randomly assigned to either a PG or 4000 IU/day of vitamin D3 supplementation. The study found no significant differences in all-cause mortality or secondary endpoints between the two groups. However, IG participants required more mechanical circulatory support (MCS) implantation than PG participants. Supplementing patients with HF with vitamin D did not significantly reduce mortality rates [81]. The conflicting results of the studies and many others on the effectiveness of vitamin D in the treatment of CVD emphasize the dire need for more research to establish a more valid conclusion with regards to the therapeutic effects of vitamin D supplementation in improving the prognosis of CVD patients. The results of the supplementation trials have been summarized in Table 2 (Ref. [75,76,78–81]) for convenience.

## Treatment/Management and Prevention of CVD with Vitamin D

Hypertension and vitamin D insufficiency are common health concerns in the United States. A study in 2007 with Hispanic black and Mexican American participants

**Table 2. Criteria and results of RCT conducted.**

| Study by | POS | PR | Parameters indicative of CV health | Major outcome | Conclusion | Limitations |
|---|---|---|---|---|---|---|
| Bahrami LS *et al.* (2018) [75] | 8 wks | n = 80<br>IG = 40 (32 analyzed)<br>PG = 40 (35 analyzed) | -Serum inflammatory markers (e.g., TNF)<br>-PAB<br>-Lipid Profile<br>-PTH<br>-Mean SBP and DBP | -PTH = Decrease in IG is significant ($p$ = 0.003)<br>-SBP and DBP = Decrease in IG is significant ($p$ = 0.09 and $p$ = 0.010 respectively) | Vitamin D is moderately effective | -Small POS<br>-Small sample size |
| Wu Z *et al.* (2015) [76] | 6 mts | n = 90<br>IG = 45<br>PG = 45 | -SYNTAX scores<br>-SBP and DBP<br>-hs-CRP<br>-Renin, Angiotensin-II, and aldosterone<br>-Serum lipid profile<br>-PTH | -SYNTAX scores: IG > PG ($p < 0.001$)<br>SBP and DBP (mm of Hg): decrease in IG > decrease in PG and significant ($p$ = 0.01 for SBP and $p < 0.01$ for DBP)<br>-hs-CRP: decrease in IG > PG ($p < 0.001$)<br>-Renin, Angiotensin-II and aldosterone: significant decrease in IG vs PG<br>-PTH: decrease in IG vs PG is significant ($p < 0.001$) | Vitamin D is effective in the treatment | -Small sample size<br>-Participants recruited from a single area<br>- Low diversity<br>-Sunlight exposure not standardized |
| Dalbeni A *et al.* (2014) [78] | 6 mts | n = 36<br>IG = 18 (13)<br>PG = 18 (10) | -EF<br>-PIP and natriuretic -peptides<br>-Lipid profile<br>-SBP and DBP<br>-Renin<br>-PTH | -EF: significant increase in IG vs PG (6.71 vs –4.30%, $p < 0.001$)<br>-PIP = Only increased in the placebo group<br>-SBP (mm of Hg) = Significantly decreased in IG (129.6 to 122.7, $p < 0.05$) | Vitamin D is effective in the treatment | -Small sample size |
| Virtanen JK *et al.* (2022) [79] | 5 yrs | n = 2495<br>IG, 1600 IU/day (IG-1) = 832, 3200 IU/day (IG-2) = 833<br>PG = 830 | -Primary endpoint: major CV events<br>-Secondary outcomes: MI, stroke and CVD death | -Insignificant differences in HR of major CV events ($p$ = 0.9)<br>-Insignificant differences in HR of secondary outcomes, MI, $p$ = 0.98 and stroke, $p$ = 0.97<br>-CVD death = 0.85 | Vitamin D is ineffective in the treatment | -Low diversity |
| Manson JE *et al.* (2018) [80] | 3.8–6.1 yrs | n = 25,871<br>IG = 12,927<br>PG = 12,944 | -Primary end-point = Major CV events<br>-Secondary end-point = coronary revascularization and components of major CV events | Insignificant differences in major CV events, i.e., IG = 396 and PG = 409, ($p$ = 0.69 and HR = 0.97) | Vitamin D is ineffective in the treatment | -Single dosage |

**Table 2. Continued.**

| Study by | POS | PR | Parameters indicative of CV health | Major outcome | Conclusion | Limitations |
|---|---|---|---|---|---|---|
| Zitterman A *et al.* (2017) [81] | 3 yrs | n = 400<br>IG = 199<br>PG = 201 | -Primary end-point: all-cause mortality<br>-Secondary end-point = Hospitalization, resuscitation, high urgent listing for HT and MCS implantation | -Insignificant difference in all-cause mortality:<br>IG = 19.6% PG = 17.9% ($p$ = 0.726, HR = 1.09)<br>-Insignificant difference in hospitalization rate:<br>IG = 67.4% PG = 60.0% ($p$ = 0.075)<br>-MCS implantation is significantly greater in IG | Vitamin D is ineffective in the treatment | -Gender bias (participants mostly male)<br>-Low statistical accuracy |

Table Notes: Full forms of the abbreviations used in Table 2. MI, myocardial infarction; CVD, cardiovascular disease; CV, cardiovascular; IG, Interventional Group; PG, placebo group; PAB, Pro-oxidant-antioxidant Balance; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; MCS, mechanical circulatory support; HT, Heart Transplant; EF, ejection fraction; HR, Hazard Risk; PIP, carboxy-terminal propeptide of procollagen type I; POS, Period Of Study; PR, Participants Randomized; wks, Weeks; mts, Months; yrs, Years; IU, International Units; SYNTAX, Synergy Between Percutaneous Coronary Intervention (PCI) With Taxus and Coronary Artery Bypass Surgery; $p$-value, probability value; hs-CRP, high-sensitivity C-reactive protein; n, Number; RCT, randomized control trial.

**Table 3. An elaboration of the studies conducted to determine an association between vitamin D and cardiovascular diseases.**

| Reference | Type of study | Population | Time frame | Conclusion | Exclusion criteria |
|---|---|---|---|---|---|
| Gotsman I *et al.* [82] | Cross-sectional | Jerusalem, Israel (40 years of age or older) (data retrieved electronically) | 4 years | Vitamin D deficiency is highly prevalent in HF patients and is a significant predictor of reduced survival. | – |
| Judd S *et al.* [83] | Cross-sectional study | US population greater than 2 months of age and a total of 7699 | 1 day | SBP is inversely associated with serum vitamin D concentrations. | who had been previously told they had hypertension |
| Oh J *et al.* [84] | Cross-sectional | Obtained macrophages from 76 obese, diabetic, hypertensive patients with vitamin D deficiency (25-hydroxyvitamin D <80 nmol/L | – | Reduced vitamin D receptor signaling as a potential mechanism underlying increased foam cell formation and accelerated cardiovascular disease in diabetic subjects. | Excluded people recently diagnosed with diabetes mellitus, pregnancy, known coronary artery disease, and normal vitamin D levels [serum 25(OH)D ≥80 nmol/L]. |
| Scragg R *et al.* [85] | Cross-sectional study | US civilian population is restricted to 12,644 people aged > or = 20 years | 4 years | Vitamin D status was inversely associated with BP. | People who were on anti-hypertensive medication |

**Table Notes:** US, United States; BP, Blood Pressure; HF, heart failure.

demonstrated an inverse correlation between serum vitamin D concentrations and systolic blood pressure [85]. In another study, a cross-sectional survey on a sample of people representative of the US population had similar findings [83]. However, a 2009 meta-analysis showed limited evidence that vitamin D supplementation might reduce blood pressure in hypertensive patients [86]. The relationship between vitamin D and cardiovascular health is complex. Some research implies conflicting correlations between cardiovascular disorders, such as vitamin D deficiency speeding the production of foam cells in obese hypertension patients [84]. Additionally, vitamin D deficiency is prevalent in heart failure patients and may predict reduced survival [86]. The results of the three meta-analyses and a cohort study mentioned have been summarized in Table 3 (Ref. [82–85]).

## Limitations

The assessment of vitamin D levels in this study was restricted to patients currently under medical treatment, potentially limiting the generalizability of the data to the wider population. Another noteworthy limitation pertains to the single-point measurements of vitamin D levels, which may not accurately reflect the individuals' long-term vitamin D status, given the fluctuating nature of these levels over time.

Furthermore, it is crucial to acknowledge the potential presence of gender bias in the study's design, as one study included a higher proportion of females while other studies comprised a larger number of males. Such imbalances could influence the overall findings and warrant careful consideration during data interpretation.

Additionally, the inclusion of patients with pre-existing conditions, such as diabetes and ischemic heart disease, in the group receiving vitamin D supplements may introduce confounding factors that could influence the observed outcomes.

As a result, the findings must be interpreted with these limitations in mind, and future research should address these problems in order to gain a more complete understanding of the link between vitamin D levels and health outcomes.

## Conclusion

In summary, this review sheds light on the complex relationship between vitamin D and CVD. Beyond evidence and explanation of this correlation, it also provides a unique perspective as to how CVD should be prevented, treated, and potentially cured, which would not only help lower mortality and increase life expectancy but would also serve to improve the quality of life overall in CVD patients. The unclear results of vitamin D supplementation trials emphasize the need for more research, especially randomized controlled trials before using vitamin D supplementation as a treatment for cardiovascular disease. To strengthen the evidence base and enhance the reliability of findings, future studies should focus on including a diverse population, encompassing various age groups, ethnicities, and patients with comorbidities such as diabetes or hypertension. Furthermore, long-term longitudinal and cohort studies are needed to analyze the chronic effects of vitamin D on health. Investigating the impact of varying vitamin D doses on cardiovascular health could elucidate its implications and help determine an optimal dose for maximal efficacy.

## Availability of Data and Materials

Not applicable.

## Author Contributions

HI was involved in conceptualizing the article and its formatting. HI and MA were involved in devising the methodology. HI, AKN and IA were involved in editing the preliminary drafts of the manuscript and in the interpretation of data. HI, SMH, HUR, and MMUH were involved in data collection. SMH was involved in table drawing. FZ, TI and AKN were involved in developing figures. FZ and ZT were involved in visualization. FZ, HI, TI, ZT, and RI were involved in topic selection and acquisition of data. MA was involved in data curation. AKN and TI were involved in the supervision of the whole process. All authors contributed significantly to editorial changes of important content. All authors read and approved the final manuscript. All authors participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.

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## Conflict of Interest

The authors declare no conflict of interest.

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