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Recent Advances in Association Between Vitamin D Levels and Cardiovascular Disorders

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Abstract

Purpose of Review In this review, we discuss the evidence that vitamin D affects cardiovascular disease through interventional and observational studies and their corresponding association mechanisms. We also highlight the need for further research to definitively conclude clinical recommendations based on preliminary data and determine the extent to which vitamin D levels may impact the incidence and prognosis of major cardiovascular diseases in the future.

Recent Findings Cardiovascular disease has long been recognized as the leading cause of morbidity and mortality worldwide, with many risk factors implicated in its pathogenesis. Vitamin D is a risk factor that, despite being known to be crucial for its role in maintaining bone health, also has several extra-skeletal effects due to vitamin D receptors in vascular smooth muscle and cardiomyocytes. Recent studies have documented a significant association between higher vitamin D levels and lower risk of each cardiovascular disease entity; 11 studies between serum vitamin D and heart failure, 7 studies between serum vitamin D and hypertension, 8 studies between serum vitamin D and coronary artery disease, and 5 studies between serum vitamin D and atrial fibrillation.

Summary More studies documenting a significant association between increased serum vitamin D and cardiovascular disease are in the context of heart failure compared to hypertension, coronary artery disease, and atrial fibrillation. Conversely, a significant association between increased serum vitamin D and a lower risk of atrial fibrillation is reported in fewer studies compared to the association of vitamin D with other cardiovascular disease entities. Although there is evidence documenting a clear significant association of vitamin D under each category, further research is still needed to definitively conclude the role of vitamin D in cardiovascular disease management.

Keywords Vitamin D · Heart failure · Hypertension · Coronary artery disease · Atrial fibrillation

Introduction

Cardiovascular disorders (CVD) are the leading cause of morbidity and mortality globally, despite advancements in preventive and therapeutic measures, thus burdening the global healthcare system [1]. Along with known risk factors such as smoking, diabetes, and dyslipidemia [2], new risk factors with possible implications for the prognosis and treatment of CVD are being studied, leading to a new focus on serum vitamin D levels and their impact on CVD. Low vitamin D levels are prevalent across all age groups and countries, especially in the Middle East [3]. Vitamin D has a pleiotropic role in the human body. While it is crucial for maintaining bone health, recent studies have discovered that it has extra-skeletal effects, especially a significant role in cardiovascular (CV) health [4]. Vitamin D deficiency (VDD) is an independent risk factor and predictor of major CV pathologies [5]. A meta-analysis of

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observational studies including 849,412 subjects suggested a significant association between low serum 25-hydroxyvitamin D (25(OH)D) levels and the CVD risk [6].

The vitamin D receptor (VDR) is in vascular smooth muscles and cardiomyocytes. Vitamin D binding to the VDR allows retinoid X receptor binding and further, resulting in a complex that binds to vitamin D response elements. This process aids in regulating vitamin D response genes [7]. Studies have indicated that the combination of the active form of vitamin D [1,25-dihydroxyvitamin D; 1,25(OH)2D] with the VDR has a wide range of possible CV advantages, including decreased synthesis of renin, promotion of relaxation of vascular smooth muscle cells, and decreasing the production of atherosclerotic plaque-forming foam cells [8]. Wong et al. demonstrated a reduction in endothelium-dependent aortic contraction, thereby causing a reduction in blood pressure (BP) after the vitamin D3 prescription [9].

Observational studies have suggested an inverse association between low serum vitamin D levels and an increased risk of Myocardial infarction (MI) and CVD mortality [10]. To date, CVDs in which the role of vitamin D has been mostly investigated include coronary artery disease (CAD), heart failure (HF), hypertension (HTN), and atrial fibrillation (AF) [11, 12]. VDD is a highly prevalent comorbidity in these conditions and is associated with worse short-term and long-term prognoses [13, 14]. An analysis of previous data demonstrated that the relationship between 25(OH)D and the risk of CVD might not be linear and may plateau between 50 and 75 mol/L. Others have proposed a U-shaped relationship, with a modest increase in CVD risk at both low (< 50 nmol/L) and high (> 125 mol/L) 25(OH)D levels. The shape of the association between vitamin D and CVD over a wide spectrum of 25(OH)D levels is yet to be determined [15]. The hypothesis that vitamin supplements "improve" or "maintain" overall health and lower the risk of diseases, including CVD, has previously been formulated but never been fully established [16, 17].

This review highlights scientific evidence from recent studies focusing solely on patients with CVDs, specifically HF, HTN, CAD, and AF. Our review included interventional studies with vitamin D supplementation and observational studies measuring vitamin D status. This review of recent research attempts to ascertain the association between vitamin D levels and the incidence and prognosis of major CVDs.

Association of Vitamin D with HF

Definition and Prevalence of HF

HF is a challenging health condition frequently resulting from dysfunctional cardiac activity, leading to reduced ventricular filling or blood ejection [18]. Despite ongoing advances in therapy, diagnosis, and prevention, this illness is growing at an alarming rate globally and is linked to higher patient morbidity and mortality [19, 20]. Globally, HF affects over 64.3 million people, and its incidence is increasing daily [18, 21]. It affects approximately 1–2% of adults in developed nations and can affect up to 10% of adults over 70. At age 55, men have a 33% lifetime risk of HF, and women have a lifetime risk of 28%. The mortality risk from HF within the first five years was very high, at over 50%. According to a significant meta-analysis, the 1, 2, 5, and 10-year survival rates of HF patients were 87, 73, 57, and 35%, respectively, leading to a huge burden [22].

Role of Vitamin D in HF

Hypovitaminosis D is observed to be quite widespread in patients with HF, with rates ranging from 80 to 95%, even in sunny climates. According to some studies, it is attributed to the progression of HF and may be a standalone predictor of mortality in patients with HF. Although prospective vitamin D supplementation trials have produced conflicting results, vitamin D treatment may benefit patients with HF positively. The small number of high-risk patients and insufficient sample sizes in these trials are significant drawbacks [23, 24].

Mechanisms of Association Between Vitamin D and HF

Vitamin D has pleiotropic effects on chronic HF [25••]. It negatively influences natriuretic peptides, augmented collagen synthesis, oxidative stress, endothelial dysfunction, and fibrosis, which are likely mechanisms underlying CVDs, such as cardiac hypertrophy and HF [26]. It is a significant regulator of the renin–angiotensin–aldosterone system (RAAS). Therefore, VDD can lead to uninhibited RAAS activation and contribute to the worsening of HF by retaining salt and water [20]. Additionally, it controls the metabolism of Parathyroid hormone (PTH) and calcium, which are crucial for cardiac remodeling and contractility. Low amounts of vitamin D cause calcium levels to decrease, which affects contractility and causes systolic dysfunction. Inadequate PTH production can also impair LV systolic function by causing myocardial fibrosis and hypertrophy [23, 27].

Vitamin D has immunomodulatory properties, as immune cells express 1-α-hydroxylase to control the concentration of calcitriol. By activating anti-inflammatory T-helper cells such as Th2 cells and suppressing Th1 and Th17 cells, it reduces the symptoms of inflammation. Increased levels of the anti-inflammatory cytokines IL-4 and 10, tumor necrosis factor-alpha, and decreased levels of the proinflammatory cytokines IL-1 and IL-6 have all been linked to adequate serum 25(OH)D levels. Conversely, a lack of vitamin D has been linked to proinflammatory cytokine profiles and chronic inflammatory conditions. In a 2019 study,

Roffe-Vazquez et al. discovered that the cluster with the lowest levels of 25(OH)D had the lowest levels of vitamin D intake, IL-10, and IL-12p70, but the highest levels of TNF-a, IL-8, and IL-17A [20].

There is evidence from numerous studies that HF is related to low vitamin D levels. A recent study found that higher serum 25(OH)D levels were associated with a lower risk of HF when using the inverse-variance weighted technique. Additionally, they performed a reverse Mendelian randomization analysis, in which the amount of serum 25(OH)D was adversely associated with genetic susceptibility to HF [25••].

Vitamin D Effects on Physical Activity, BP, and Quality of Life in HF Patients

An 8-week study on the effects of short-term vitamin D supplementation in patients with HF was conducted by Hosseinzadeh et al. in 2019 [28]. They investigated how it was related to both physical activity and BP. Only a minor positive correlation between the 25(OH)D level and the 6-Minute Walk Test was observed in their results. After vitamin D-3 treatment, no appreciable changes in BP or 6-Minute Walk Test were seen. Another study by Woo et al. [29] in 2022 assessed the 6-Minute Walk Test and quality of life six months after receiving therapy for vitamin D insufficiency. Patients in the vitamin D group showed statistically significant improvements with the 6-Minute Walk Test distance and quality of life at six months. Moretti et al. [30] concluded in a study that the quality of life scores, including composite overall and clinical summary, significantly improved in vitamin D treatment compared to placebo. Further evidence is needed to prove that vitamin D insufficiency impacts physical activity, BP, and quality of life in individuals with HF.

Role of Vitamin D as a Predictor for Risk of Hospitalization Due to HF

A prospective study of approximately 19000 individuals in 2017 demonstrated that patients with VDD had an increased risk of hospitalization for HF compared with patients with normal levels, reporting a hazard ratio (HR) of 1.61 [24]. Another significant 2019 study examined the relationship between vitamin D status and the pattern of fatality rates and hospitalization risk in HF patients. The results of this investigation showed that the CV hospitalization rates, as well as the 5-year mortality rates, were significantly increased ($p = 0.023$, HR = 1.74) and that the 5-year mortality rate had increased ($p = 0.05$, HR = 1.55) in patients with VDD [31].

The prevalence of VDD in elderly patients is high; hence, Porto et al. conducted a novel randomized clinical trial to assess the risk of HF in the elderly owing to the high frequency of vitamin D insufficiency in geriatric individuals. Low levels of 25(OH)D were found to be significantly correlated with the occurrence of HF, particularly in males and obese individuals [27]. In another key study on the geriatric population in the United States, patients with 25(OH)D deficiency had a significantly greater likelihood of being admitted to the hospital (HR = 1.8). Hospitalization risk was also statistically higher in frail elderly than in non-frail elderly people (HR = 1.7) [32]. As most studies suggest a positive correlation between low vitamin D levels and higher rates of HF hospitalization, a definitive causal association must be established in future clinical trials.

Role of Vitamin D as a Predictor of Mortality Rates Due to HF

A randomized control trial conducted on 10,974 individuals reported that vitamin D supplementation decreased overall in-hospital mortality in patients (6.5 vs. 9.4%, Odds ratio (OR): 0.67, $p < 0.001$) as well as in-hospital mortality within seven days and 30 days (0.9 vs. 2.5%, OR: 0.34, and 3.8 vs. 6.5%, OR: 0.56, both $p < 0.001$) [29]. Another observational study followed up for five years suggested that vitamin D levels less than 24.13 ng/mL predicted higher 5-year mortality ($p = 0.045$) and suboptimal clinical outcomes ($p = 0.03$) [19]. Cubbon et al. [33] conducted a study on patients receiving CHF therapy. They reported that each 2.72-fold increase in 25(OH)D concentration was related to a 14% decrease in all-cause mortality (95% Cl = 1, 26%; $p = 0.04$) over a mean follow-up period of 4 years.

In contrast, a randomized control trial conducted on 5110 patients concluded that a daily vitamin D dose of 4000 IU did not reduce mortality in patients with advanced HF but was associated with a greater need for MCS implants. These data indicate caution regarding long-term supplementation with moderately high vitamin D doses [34]. Most of these have suggested that VDD is associated with higher mortality rates in patients with HF. However, a few studies also suggest caution regarding high doses of vitamin D; this needs to be explored in future studies for conclusive results. The studies documenting the association between vitamin D and HF have been shown in Table 1.

Association of Vitamin D with HTN

Prevalence of HTN

One of the most prevalent diseases family physicians observe in primary care is HTN [35]. Essential HTN is a major risk factor for CVD and stroke. It is one of the leading causes of mortality and disability [36, 41••]. It affects approximately a billion people worldwide (approximately 25%); by 2025,

Table 1 Recent studies on Association of Vitamin D and Heart Failure (HF)

Author, Year	Country, WHO Region	Aim	Design, Population	n	Age (y)	Gender (Male%, female %)	Intervention/ Investigation	Observation	Significant Association
Gao et al. (2022) [25••]	China, Western Pacific	To determine whether there is a causal relationship between serum vitamin D levels and HF.	MR, Data for 25(OH) D derived UKB and for HF traits from the HERMES consortium.	vitamin D = 443,734 HF = 47,309/930,014 NA NA			For primary analysis: IVW, MR used.	MR analysis showed that increased serum 25(OH) D was associated with a lower risk of HF in the IVW method (OR = 0. 81; 95%CI, 0.70–0.94, p = 0.006). In the reverse MR analyses, the genetic predisposition to HF was negatively correlated with serum 25(OH) D level (OR = 0. 89; 95%CI, (0.82–0.97), p = 0.009).	Yes
Woo et al. (2022) [29]	South Korea, Western Pacific Region	To determine the safety and efficacy of vitamin D3 (cholecalciferol) supplementation and its corresponding effect on both endothelial and ventricular function in patients with stable HF.	RCT, HF patients with 25(OH) D levels < 75 nmol/L	73	66.0 ± 9.6	42% 58%	Randomized to receive 4000 IU vitamin D daily or a placebo for 6 months.	Endothelial dysfunction did not improve with Vitamin D supplementation (EndoPAT: baseline, 1.19 ± 0.4 vs. 6 months later, 1.22 ± 0.3, p = .65). However, patients' BP, 6-MWT, and EQ-5D questionnaire scores improved after vitamin D treatment. Left atrial diameter also underwent significant reduction.	Yes
Kusunose et al. (2021) [23]	Japan, Western Pacific	To compare the outcomes of vitamin D supplemented patients to those of a matched cohort by using big data from actual HF hospitalizations.	RCT, NA	10974	79	52.2% 47.8%	Oral 25(OH) D 3 vitamin therapy was given at a daily dose of 0.5–1.0 g/day.	Supplementation with vitamin D decreased overall in-hospital mortality in patients (6.5 vs. 9.4%, OD: 0.67, p < 0.001) as well as in-hospital mortality within 7 days and 30 days (0.9 vs. 2.5%, OR: 0.34, and 3.8 vs. 6.5%, OR: 0.56, both p < 0.001).	Yes
Aparicio-Ugarriza et al. (2020) [32]	United States, Region of Americas	To determine whether 25(OH) D deficiency is related to an increased risk of all-cause hospitalizations and deaths in elderly with HF, as well as the differential effect of frailty.	Retrospective cohort, Veterans with HF.	284	67.3	97% 3%	The status of 25(OH) D was divided into two categories: deficiency (30 ng/mL) and non-deficiency (> 30 ng/mL). Patients were divided into non-frail (FI.21) and frail (FI.21) categories using a 44-item Frailty Index (FI) and analyzed.	There were 131 deaths and 617 hospitalizations over the median follow-up of 1136 days (IQR = 691), with 68% of these occurring in patients with 25(OH) D deficiency. Patients with 25(OH) D deficiency had a significantly greater likelihood of being admitted to the hospital: HR = 1.8 (95% CI: 1.3–2.5), p < 0.001. Hospitalization risk was higher for frail elders than for non-frail elders: HR = 1.7 (95% CI: 1.2–2.7), p < 0.05. Death rates did not significantly correlate with 25(OH) D deficiency.	Yes

Table 1 (continued)

Author, Year	Country, WHO Region	Aim	Design, Population	n	Age (y)	Gender (Male%, female %)	Intervention/ Investigation	Observation	Significant Association
Hosseinzadeh et al. (2019) [28]	Iran, Eastern Mediterranean	To investigate the effects of vitamin D supplementation on HF patients' BP and physical activity.	RCT, HF patients with low EF < 50% and class III of NYHA.	39	63	69.2% 30.8%	The parameters evaluated were 6MWT, 25 (OH) D levels, BP. In the intervention group, the mean 25(OH) D level was increased to 28.9 ± 11.7 ng/mL (p 0.001).	By the end of the trial there was a poor but non-significant reduction in SBP (−0.033 ± 4.71 mmHg, p = 0.531) in the intervention group, while there were no changes in the control group. A negligible but statistically insignificant (p = 0.325) decrease of 6MWT was observed in the intervention group (−6.6 ± 29.2 m) compared to the placebo (−14.1 ± 40.5 m).	No
Roffe-Vazquez et al. (2019) [20]	Mexico, Region of Americas	To investigate the correlation between vitamin D and inflammatory cytokines, atherosclerotic parameters, and lifestyle factors in the perspective of HF during a 12-month period.	Longitudinal, Proved diagnosis of HFrEF (LVEF < 40%) NYHA III or IV.	17	49 to 82	82.4% 17.6%	The 25(OH) D levels, inflammatory cytokines, lifestyle determinants, biochemical markers, and anthropometric data were included.	Cluster analysis results showed that, in comparison to patients from cluster one, patients from cluster three, who had the lowest levels of 25(OH) D, presented with the least vitamin D intake, IL-10 (1.0 ± 0.9 pg/mL), and IL-12p70 (0.5 ± 0.4 pg/mL), but had the higher levels of TNF-α (9.1 ± 3.5 pg/mL), IL-8 (55.6 ± 117.1 pg/mL), IL-17A (3.5 ± 2.0 pg/mL), total cholesterol (193.9 ± 61.4 mg/dL), LDL cholesterol (127.7 ± 58 mg/dL), and Apo-B (101.4 ± 33.4 mg/dL) levels.	Yes
Perge et al. (2019) [19]	Hungary, European Region	To evaluate the role of vitamin D levels on clinical outcomes of HF patients undergoing CRT.	Prospective, observational, Symptomatic HF (NYHA II-IVa), LVEF < 35%, and wide QRS complex in the baseline ECG.	136	67	81% 19%	5-year follow-up, medical therapy and related adverse medical events were reported in addition to an assessment of the NYHA classification. At the 6-month follow-up echocardiogram, blood assays were repeated.	The primary endpoint was 5-year all-cause mortality, and 58 people reached it during follow-up. The secondary endpoint, which was attained by 45 patients, was the lack of a satisfactory clinical response, which was determined as an increase in LVEF of less than 15% after 6 months. Vitamin D levels less than 24.13 ng/mL predicted 5-year mortality (p = 0.045) and a suboptimal clinical outcome (p = 0.03) after adjusting for all relevant baseline variables.	Yes

Table 1 (continued)

Author, Year	Country, WHO Region	Aim	Design, Population	n	Age (y)	Gender (Male%, female %)	Intervention/ Investigation	Observation	Significant Association
Nolte et al. (2019) [31]	Germany, European Region	To study the relationship between 25(OH) D levels and mortality, hospitalizations, cardiovascular risk factors, and echocardiographic parameters in patients with asymptomatic DD or newly diagnosed HFpEF.	Prospective, observational, DIAST-CHF. Outpatients.	787	67.2	53% 47%	Participants were evaluated by a physical examination, echocardiogram, and a 6MWT and monitored for up to 5 years. The Short Form 36 questionnaire was used to assess the quality of life.	A greater 5-year mortality rate was largely related to lower 25(OH) D levels (per 10 g/mL reduction), p = 0.05, HR = 1.55 [1.00; 2.42]. Additionally, lower levels of 25(OH) D (per 10 ng/mL reduction) were linked to a higher likelihood of cardiovascular hospitalizations, p = 0.023, HR = 1.74 [1.08; 2.80], and remained significant after adjusting for age, p = 0.046, HR = 1.63 [1.01; 2.64], baseline NT-pro BNP, p = 0.048, HR = 1.62 [1.01; 2.61], and other chosen baseline characteristics and co morbidities.	Yes
Cubbon et al. (2019) [33]	United Kingdom, European Region	To examine whether 25(OH) D deficiency is linked to mortality and hospitalization in patients getting contemporary medicinal and device treatment for CHF.	Prospective cohort, Adults that had stable symptoms and signs of CHF for 3 months, in addition to LVEF ≤ 45%.	1802	69.6	73.2% 26.8%	The patients were evaluated at the outset, and the serum 25(OH) D concentrations were determined, as well as the hospitalization and fatality rates, using hospital databases.	73% of patients had a 25(OH) D deficiency (50 nmol/L) which is related to the male sex, diabetes, lower blood sodium, faster heart rate, and more diuretic requirement. After accounting for possible confounding variables, each 2.72-fold increase in 25(OH) D concentration (for example, from 32 to 87 nmol/L) is related with 14% decreased all-cause mortality (95% CI = 1, 26%; p = 0.04) over a mean follow-up period of 4 years.	Yes

Table 1 (continued)

Author, Year	Country, WHO Region	Aim	Design, Population	n	Age (y)	Gender (Male%, female %)	Intervention/ Investigation	Observation	Significant Association
Costanzo et al. (2018) [24]	Italy, European region	To research the association between serum vitamin D and the incidence of hospitalization for HF.	Prospective cohort, A multistage sampling method was used to enroll adults from city hall registrations in the Molise area.	19092	55.1	49% 51%	Follow-up done for 6.2 years with the baseline serum vitamin D levels being classified as deficient (less than 10 ng/mL), insufficient (10–29 ng/mL), and normal (more than 30 ng/mL). The regional hospital discharge registry was used to identify incident instances of HF hospitalization.	Vitamin D levels were found to be normal, inadequate, or deficient in 12.2%, 79.6%, and 8.2% of the population, respectively. During the follow-up period, 562 hospitalizations for HF were found. In participants with normal, inadequate, and deficient levels of vitamin D, the incidence of HF was 1.6%, 2.9%, and 5.3%, respectively. Individuals with vitamin D insufficiency had a greater risk of hospitalization for HF (HR: 1.61, 95% CI: 1.06–2.43) than those with normal levels after multivariable adjustment. Adjusting for subclinical inflammation did not affect the link between vitamin D insufficiency and HF significantly.	Yes
Porto et al. (2018) [27]	Brazil, Region of Americas	To evaluate the relationship between VDD and the risk of HF in geriatric cardiology outpatient clinic patients.	Analytical cross-sectional, old patients with medical records who came for routine cardiological examinations.	137	> 60	24.1% 75.9%	Bivariate logistic analysis, followed by multivariate logistic regression analysis was done.	VDD was associated with an increased risk of HF [OR: 12.19; 95% CI = 4.23–35.16; p = 0.000], male gender (OR: 15.32; 95% CI = 3.39–69.20, p = 0.000), obesity (OR: 4.17; 95% CI = 1.36–12.81; p = 0.012), and cardiac arrhythmia (OR: 3.69; 95% CI = 1.23–11.11; p = 0.020).	Yes

Table 1 (continued)

Author, Year	Country, WHO Region	Aim	Design, Population	n	Age (y)	Gender (Male%, female %)	Intervention/ Investigation	Observation	Significant Association
Moretti et al. (2017) [30]	United States, Region of Americas	To determine if vitamin D 3 at a comparatively high dose would replete 25(OH) D stores, improve BNP, PTH, and cardiopulmonary function, reduce inflammatory markers, and improve QOL in HF patients.	RCT, Adult patients with NYHA Class II or III HF, had been on stable and GDMT for greater than 3 months, and 25(OH) D level of ≤ 32 ng/ml.	40	67 ± 14	67% 33%	Participants were given either vitamin D3 using a dose of 10,000 IU daily for 6 months or a placebo.	The change in BNP from baseline was Δ + 30 ± 950 pg/ml for treatment vs. placebo Δ + 400 ± 1900 pg/ml, p = 0.003. PTH and exercise chronotropic response index improved in the treatment group vs. the placebo group, respectively, but both were attenuated by adjustment ((Δ-20 ± 20 pg/ml vs. Δ + 7 ± 53 pg/ml respectively (p = 0.01, adjusted p = 0.07)) and (Δ + 0.13 ± 0.26 vs. Δ-0.03 ± 02.9 respectively, p < 0.01, adjusted p = 0.17)). QOL scores, including composite overall and clinical summary scores significantly improved in treatment compared to placebo (Δ + 10 ± 15 versus − 6 ± 15, p < 0.01 and Δ + 8 ± 14 versus − 8 ± 18, p = 0.01, respectively.	Yes
Zitterman et al. (2017) [34]	Germany, European Region	To assess the individuals with advanced HF, if oral vitamin D administration lowers mortality in them.	RCT, HF with NYHA ≥ II +	5110	65.9	58.1% 41.9%	Vitamin D < 75 nmol/L patients were randomized to receive 4000 IU vitamin D daily or a matching placebo for 3 years.	The 3-year mortality rate for patients taking vitamin D (4000 IU/day) or placebo was the same, with an HR of 1.09 (95% CI: 0.69–1.71). Other secondary clinical outcomes were similar across groups (HF hospitalization, resuscitation, highly urgent listing for heart transplantation, heart transplantation, and hypercalcemia).	No

HF Heart Failure, *MR* Mendelian Randomization, *UKB* UK Biobank, *HERMES* Heart Failure Molecular Epidemiology for Therapeutic Targets, *NA* Not applicable, *IVW* inverse variance-weighted, *IU* International unit, *OR* Odds ratio, *CI* confidence interval, *RCT* Randomized control trial, *BP* Blood pressure, *6-MWT* 6-min walk test, *25(OH) D* 25-hydroxyvitamin D, *EF* Ejection Fraction, *NYHA* New York Heart Association, *SBP* systolic blood pressure, *HFrEF* Heart failure with reduced ejection fraction, *LVEF* left ventricular ejection fraction, *IL* Interleukin, *TNF-α* tumor necrosis factor-alpha, *LDL* Low-density lipoprotein, *HDL* High density lipoprotein, *Apo-B* apolipoprotein-B, *CRT* Resynchronization therapy, *ECG* Electrocardiogram, *DD* Diastolic dysfunction, *HFpEF* Heart failure with normal ejection fraction, *NT-pro BNP* N-terminal pro b-type natriuretic peptide, *CHF* congestive heart failure, *HR* heart rate, *BNP* Brain natriuretic peptide, *PTH* Parathyroid hormone, *QOL* quality of life, *GDMT* guideline directed medical therapy, *VDD* Vitamin D Deficiency

this number could rise by 29% [35]. In studies conducted on children across the globe, the prevalence was 3–12.6% [36].

Vitamin D and HTN

Numerous studies have demonstrated an inverse relationship between 25(OH)D levels and BP in healthy and hypertensive subjects [4]. Studies have also reported that Vitamin D supplementation exerts a clinically significant antihypertensive effect in VDD patients in the general population and patients with comorbidities [36]. The extensive expression of VDRs and 1, α-hydroxylase enzymes throughout the body may be responsible for the paracrine actions of vitamin D on tissues that regulate BP, glucose, and lipids. This concept supports the correlation between hypovitaminosis D and cardio-metabolic changes, causing CV morbidity and mortality [37]. The United States and Canada have established Complementary and alternative medicine, antihypertensive therapies, an area of study for treatments not frequently offered in hospitals. This therapy provides evidence that vitamin D supplementation lowers BP [35].

Mechanisms of Association

Several pathophysiological mechanisms exist between VDD and arterial HTN. First, studies on mice have revealed that mice without VDRs produce more renin and angiotensin II, which causes HTN. According to another study, renin and angiotensin II plasma concentrations are inversely related to 25(OH)D and 1,25(OH)2D levels. Second, research has demonstrated that PTH is an independent risk factor for HTN and CV events since PTH receptors are found in the cardiovascular system, and PTH infusions increase BP. Additionally, studies have shown that VDD can cause hyperparathyroidism, leading to HTN [35].

Third, changes in the inflammatory activity in the vasculature are key mechanisms in the development and progression of arterial HTN. Most studies have indicated that VDR activation is important for regulating the innate immune response. It has been demonstrated that 1,25(OH)2D3 influences the differentiation of dendritic cells, macrophages, and CD4 + and CD25 + regulatory cells. Vitamin D reduces inflammation by suppressing nuclear factor-κB and pro-inflammatory cytokine production [38]. Fourth, studies have shown that VDRs are expressed in endothelial cells, vascular smooth muscle cells, and cardiac myocytes, and 1,25(OH)2D reduces the harmful effects of advanced glycation end products on the endothelium, due to which vitamin D has antihypertensive, vasculoprotective, and nephroprotective effects [4]. Finally, vitamin D decreases inflammatory and atherosclerotic factors and enhances the function of the nitric oxide system, thereby decreasing the risk of HTN [35].

Studies Based on the Association Between Vitamin D and HTN

Panahi et al. [39] observed that eight weeks of vitamin D supplementation (50,000 IU/week, and 1000 IU/day) for patients with HTN resulted in significant decreases in mean systolic blood pressure and mean arterial pressure of 5.5 ± 16.16 ($p = 0.01$) and 3.7 ± 9.24 ($p = 0.004$) mmHg, respectively. Similar conclusions have also been made in a longer study of 1 year in which an improved systolic blood pressure ($-13.4\% \pm 8.5$ vs. $-2.4\% \pm 12.6$) in patients supplemented with and without vitamin D, respectively, was found. Systolic blood pressure and diastolic blood pressure levels were lower in the patients supplemented with vitamin D($p < 0.05$) [37]. Likewise, an investigation conducted by Sheikh et al. [4] showed that in the first and second months following the intervention, the impact of vitamin D supplementation (50,000 units weekly for two months for patients whose serum vitamin D level was less than 20 ng/ml, and 1,000 units weekly for two months for patients whose serum vitamin D level was between 20 and 30 ng/ml) on systolic blood pressure was statistically significant ($p = 0.004$ and $p = 0.024$, respectively). In the first month following the intervention, the effect of vitamin D supplementation on diastolic blood pressure was statistically significant ($p = 0.046$), but not in the second month ($p = 0.885$). Studies conducted in India, a country with a high prevalence of HTN, found that the prevalence of severe and mild-moderate VDD in hypertensive patients was 77% and 8.7%, respectively. In non-hypertensive patients, the frequencies were 22.2% and 13.9%, respectively [35].

Serum 25(OH)D and its receptor VDR were shown to be lower in children with HTN than in the control group in a specific investigation conducted on children. The findings revealed that abdominal obesity was linked to an increased risk of HTN in multivariable logistic regression models and that longer breastfeeding and higher high-density lipoprotein cholesterol were protective factors against HTN [36]. In patients with elevated BP, C-reactive protein level and neutrophil-to-lymphocyte ratio are known risk factors for morbidity and mortality. A study on the general population found that serum 25(OH)D deficiency in HTN subjects was associated with significantly low levels of C-reactive protein CRP, mean serum calcium and phosphorus, and high levels of total alkaline phosphatase. Vitamin D deficiency is associated with a 1.5-times higher risk for HTN; whereas elevated-reactive protein and alanine transaminase associate with 1.4 and 1.2-times higher risk, respectively, for HTN [40].

Another study found that ten weeks of vitamin D supplementation (50,000 IU weekly) resulted in higher 25(OH) D levels and lower PTH, total cholesterol, and low-density lipoprotein cholesterol levels, thereby causing an overall reduction in CV risk [41••]. In contrast, Theiler-Schwetz

et al. [42] examined the effects of vitamin D supplementation on 24-h BP in individuals with VDD and found no significant treatment effects on 24-h BP (all p-values > 0.30). However, there was a significant tendency for the 25(OH)D level to be adversely linked with 24-h systolic blood pressure (-0.196 per ng/mL 25(OH)D, 95% Confidence Interval = –0.325 to –0.067; p = 0.003).

The use of vitamin D supplements to prevent or treat HTN has recently been in contention due to differences in the findings of randomized trials addressing the relationship between vitamin D supplementation and HTN. Although preliminary evidence is available (Table 2), additional clinical trials are required to reach a definitive conclusion.

Association of Vitamin D with CAD

Definition and Prevalence of CAD

CAD causes the myocardium to receive insufficient oxygen and blood supply. This results in an imbalance between the supply and demand of oxygen and is caused by coronary artery blockage. Typically, it involves the development of blood flow-impairing plaques in the coronary artery lumen [43]. Globally, it is the primary cause of death. Deaths from CAD peaked in the 1960s and then began to decline, although they are still the biggest cause of mortality globally [44].

According to one study, CAD was estimated to account for 32.7% of CVDs and 2.2% of the world's overall disease burden [45]. The following categories are generally used to categorize coronary artery disease: stable ischemic heart disease, acute coronary syndrome (ACS), ST-elevation MI, non-ST elevation MI and unstable angina [43].

Overview of the Association Between Vitamin D and CAD

A significant amount of research is being conducted on CVD risk factors and treatments due to the increased death rates associated with CVD. Due to this improvement, the death rate from CVD has decreased by 20% over the past several decades. Nevertheless, 18 billion fatalities occur annually, with MI being the major cause. A recent risk factor for CVD in the human population is VDD [46••].

The direct effect of VDD on CV mortality has been established in various investigations and meta-analyses by demonstrating an increase in CV mortality for every 10 ng/ml reduction in 25(OH)D [47•].

Mechanism of Association Between Vitamin D and CAD

According to research, vitamin D influences endothelial function, cardiomyocyte proliferation, endothelial cell growth, and inflammatory processes that lead to atherosclerosis and associated thrombotic consequences [47•]. Several theories have been proposed, but the precise mechanism underlying the elevated CV risk in patients with vitamin D insufficiency remains unknown [48]. Cardiovascular cells having VDR can produce autocrine calcitriol because they contain the enzyme 1-α-hydroxylase. Calcitriol negatively regulates RAAS, whose excessive activity leads to arterial HTN and cardiac hypertrophy. Evidence links VDD to specific plaque development phases and coronary artery disease destabilization [46••].

Vitamin D protects thrombosis and inflammation by reducing cardiac ischemia–reperfusion injury and reactive oxygen species [48]. Atherosclerosis is greatly influenced by inflammation, also caused by a VDD. Chen et al. [49] used pigs as a model and revealed an intriguing relationship between vitamin D and the nuclear factor-κB pathway, which inhibits the development of CAD. KPNA4 is a membrane transporter that moves NF-κB from the cytosol to the nucleus of epicardial adipose tissue cells. Nuclear factor-κB promotes the transcription of proinflammatory cytokines like IL-6, IL-8, and tumor necrosis factor-alpha, which play a role in atherogenesis in the coronary arteries. Vitamin D-3 inhibits the transcription and translation of KPNA4 in epicardial adipose tissue cells. The shuttling of nuclear factor-κB into the nucleus is impaired due to decreased KPNA4 expression. Therefore, this paper outlines the inflammatory response, which may be reduced by sufficient intracellular 1,25(OH)2-vitamin D3 levels. Additionally, this provides a mechanistic insight into the relationship between vitamin D insufficiency and CAD.

Studies Based on the Association Between Vitamin D and CAD

Dziedzic et al. [46••] conducted a study and found that patients with single, double, or triple vessel disease had significantly lower 25(OH)D levels than patients without such lesions (median, 17 vs. 15 ng/ml; p < 0.01). Another study conducted by Verdoia et al. [47•] demonstrated that lower levels of vitamin D were statistically associated with more severe coronary disease (p = 0.001), Major adverse cardiovascular events (p = 0.01), and MI (p = 0.03). Lower vitamin D levels are associated with a threefold increased mortality risk among patients undergoing percutaneous coronary procedures. One study demonstrated that Acute Coronary Syndrome was predicted by low vitamin 25(OH)D and 1,25(OH)2D and not by vitamin D2 or D3(p > 0.05) [48].

Xu et al. [50] analyzed that vitamin D shortage increased the risk of CAD (OR = 2.891; p = 0.001, confidence range = 1.459–7.139). Another study by Norouzi et al. [51] demonstrated that lower vitamin D levels are linked to a high risk of coronary artery involvement severity. Furthermore,

Table 2 Recent studies on Association of Vitamin D and Hypertension (HTN)

Author, Year	Country, WHO Region	Aim	Design, Population	n	Age (y)	Gender (Male%, female %)	Intervention/ Investigation	Observation	Significant Association
Rendina et al. (2022) [41••]	Italy, European region	To evaluate the effects of cholecalciferol supplementation in patients with well-controlled HTN and hypovitaminosis D (<50 nmol/L), also the effects of cholecalciferol and calcitriol treatment on miR-21 expression in vivo and in vitro, respectively.	RCT, Patients enrolled at three centers (Naples, Turin, and Padua).	C-cohort = 15 P-cohort = 20	C-cohort = 59.3 P-cohort = 60.8	C-cohort = 73.3%,26.7% P-cohort = 65%,35%	The C-cohort patients were instructed to orally take 50,000 IU (1.25 mg) of cholecalciferol every week for 8 weeks and subsequently 50,000 IU of the same substance every month for 10 months. The P-cohort patients were instructed to orally take the placebo preparation.	Treatment with cholecalciferol led to higher levels of 25(OH) D and lower levels of PTH, total cholesterol, and low-density lipoprotein cholesterol in C-cohort patients, but no appreciable changes were seen in these parameters in P-cohort patients. Following intervention, the C-cohort patients experienced a statistically significant decrease in blood pressure. However, neither the C- nor the P-cohort patients' miR-21 circulating levels changed. In HEK-293 cells, treatment with calcitriol had no effect on the levels of miR-21.	Yes
Theiler-Schwetz et al. (2022) [42]	Austria, European region	To study the effects of vitamin D Supplementation on Patients with Low 25(OH) D Levels on the 24-Hour BP.	RCT, Adults with HTN and 25(OH) D serum < 30 ng/ml.	200	Subjects = 60.5 ± 10.9 Placebo = 59.7 ± 11	Subject group = 54%, 46% Placebo group = 52%, 48%	For 8 weeks, subjects were given either 2800 IU of vitamin D3, or coconut oil as a placebo, orally seven oily drops per day.	Taking into consideration multiple testing corrections, p values < 0.0026 were significant. When various baseline 25(OH) D thresholds were utilized, no significant treatment effects on 24-h BP were seen (all p-values > 0.30). The obtained 25(OH) D level did, however, have a slightly significant tendency to be negatively correlated with 24-h SBP (-0.196 per ng/mL 25(OH) D, 95% CI (-0.325 to -0.067); p = 0.003).	No
Grübler et al. (2021) [38]	Austria, European region	To investigate the effect of vitamin D supplementation on systemic markers of inflammation in a cohort of HTN patients.	RCT, Participants with arterial HTN and 25(OH)D level < 30 ng/mL.	187	60.1	53% 47%	Randomized to receive either 2800 IU of vitamin D per day or placebo for 8 weeks.	ANCOVA revealed a mean treatment effect for none of the respective outcomes and no significant results were detected in various subgroup analyses.	No
Panahi et al. (2021) [39]	Iran, Eastern Mediterranean region	To determine whether vitamin D administration in patients with essential HTN lowers SBP, DBP, and MAP.	Open-label clinical trial, Iranian patients with essential HTN.	173	NA	NA	SBP, DBP, and vitamin D levels were measured at baseline and at the end of the study. Vitamin D was administered at a dose of 50,000 IU/week, and 1000 IU/day in patients with serum vitamin D levels < 20 ng/mL and 20–30 ng/mL, respectively, for 8 weeks.	Vitamin D treatment resulted in substantial decreases in mean SBP and MAP of 5.5 ± 16.16 (p = 0.01) and 3.7 ± 9.24 (p = 0.004) mmHg, respectively. Age or gender could not reliably predict how the BP will respond to vitamin D therapy.	Yes

Table 2 (continued)

Author, Year	Country, WHO Region	Aim	Design, Population	n	Age (y)	Gender (Male%, female %)	Intervention/ Investigation	Observation	Significant Association
Barale et al. (2020) [37]	Italy, Europe	To investigate whether 1-year of vitamin D supplementation could improve SBP and DBP in poor controlled type 2 DM patients.	RCT, Poor-controlled type 2 DM patients with hypovitaminosis D.	30	71.5	70% 30%	Cholecalciferol supplementation (500 UI/kg p.o. weekly, +D) or one year of observation (−D) was performed. In comparison to the baseline, changes in BP control were evaluated at 3, 6, and 12 months.	One year of vitamin D supplementation improved SBP (−13.4% ± 8.5 vs. −2.4% ± 12.6) in +D vs. −D patients, respectively, and restored D status. SBP and DBP levels were lower in +D ($p<0.05$ for all comparisons vs. baseline). There was a correlation between the 1-year mean percentage changes in serum 25(OH) D and SBP levels ($R=-0.36$, $p<0.05$).	Yes
Kuchulakanti et al. (2020) [40]	India, South-East Asia	To investigate the association between vitamin D levels and HTN in the general population.	Prospective/ case–control, Hypertensive subjects and age and sex-matched normotensive subjects.	800	52.4 ± 4.43 53.1 ± 5.12	63.7% 36.3%	The risk factors of both groups were assessed; the serum 25(OH)D levels were estimated, and liver function tests and CRP measurements were performed.	In comparison to 111 (27.7%) normotensive participants, 164 (40.2%) of the 400 HTN subjects showed serum 25(OH) D deficiency ($p=0.0001$). When compared to the same parameters in normotensive subjects, deficiencies of serum 25(OH)D in HTN subjects were significantly associated with CRP positivity, low levels of mean serum calcium and phosphorus, high levels of mean ALP ($p<0.0001$), and abnormal ALT ($p=0.0015$). Following adjustment in the multiple logistic regression analysis, serum 25(OH)D deficiency, CRP positivity, and abnormal ALT were all significantly associated with HTN (OR: 1.78; 1.48; and 1.2 respectively) (95% CI: 1.31–2.41, 1.48–2.32, and 0.98–1.94, respectively).	Yes
Sheikh et al. (2020) [4]	Iran, Eastern Mediterranean region	To assess the impact of vitamin D supplementation essential HTN in patients with VDD.	RCT, Patients with a SBP > 140 mmHg and DBP > 90 mmHg and vitamin D deficient or insufficient.	208	55.88	NA	Calciferol pearls supplement was given to the intervention group based on serum vitamin D levels. For < 20 ng/mL, 1 vitamin D pearl (50,000 U) weekly for 2 months was given. For those between 20 and 30 ng/mL, 1 vitamin D pearl (1000 U) weekly for 2 months. The control group received a placebo pearl.	In the 1st and 2nd months following the intervention, the effect of vitamin D supplementation on SBP was statistically significant ($p=0.004$ and $p=0.024$, respectively). In the 1st month following the intervention, the effect of vitamin D supplementation on DBP was statistically significant ($p=0.046$), but not in the 2nd month ($p=0.885$).	Yes

Table 2 (continued)

Author, Year	Country, WHO Region	Aim	Design, Population	n	Age (y)	Gender (Male%, female %)	Intervention/ Investigation	Observation	Significant Association
Vatakencherry et al. (2019) [35]	India, South-East Asia	To analyze the relationship between vitamin D and HTN in South Indian patients visiting a tertiary care facility for a health checkup.	Cross sectional, Participants attending a health check up in a period of 3 months.	520	20–60	64.8% 35.2%	HTN was determined to present if at least one of the following three conditions was met: SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or usage of antihypertensive medications. The peripheral venous blood samples (2 ml) were taken from each participant to determine their vitamin D levels.	Prevalence of HTN=86.2%, VDD=78.8%, vitamin D Insufficiency=8.1% and vitamin D sufficiency=13.1%. Prevalence of severe and mild–moderate VDD in hypertensive patients were 77% and 8.7%, respectively and in non-hypertensive's 22.2% and 13.9%, respectively. Prevalence of vitamin D insufficiency and sufficiency in hypertensive patients was 6% and 8.3%, respectively and in non-hypertensive's were 20.8% and 43.1%, respectively ($p<0.001$). Among hypertensive's, mean vitamin D level in people with severe deficiency was 4.44 ± 1.50 and among non-hypertensive's, mean vitamin D level in people with severe deficiency was 5.50 ± 1.12 ($p<0.005$).	Yes
Liang et al. (2018) [36]	China, Western Pacific	To examine the relationship between serum 25(OH) D levels and HTN, as well as the risk factors for HTN in children.	case–control, Students at elementary schools.	164	9.81	50.16% 49.84%	The participant's BP was monitored on 3 separate occasions using an OMRON arm-style electronic sphygmomanometer while seated and then 3 cc of venous blood was drawn, and vitamin D was assessed using HPLC. A 25(OH) D level of < 50 nmol per litre was used to identify VDD.	The serum vitamin A level in hypertensive subjects was not significantly different compared to control, but the serum25(OH) D level was significantly lower in HTN subjects compared to control (38.22 ± 12.00umol/L vs. 43.28 ± 12.33 umol/L, $p=0.02$). In comparison with the control group, the level of 25(OH) D receptors was lower in HTN children ($p=0.003$).	Yes

HTN Hypertension, *RCT* Randomised control trial, *C- cohort* cholecalciferol group, *P- cohort* placebo group, *IU* International unit, *PTH* Parathyroid hormone, *LDL* Low Density Lipoprotein, *25(OH) D* 25-hydroxyvitamin D, *BP* Blood pressure, *SBP* Systolic Blood pressure, *ANCOVA* analysis of covariance, *DBP* Diastolic Blood pressure, *MAP* Mean Arterial Blood pressure, *NA* Not Applicable, *DM* Diabetes Mellitus, *LFT* Liver Function Test, *CRP* C-reactive protein, *ALP* Alkaline phosphatase, *ALT* alanine transaminase, *HPLC* high-performance liquid chromatography, *VDD* Vitamin D Deficiency

Navarro-Valverde et al. [52] conducted a randomized control trial in which they demonstrated that only 1 had major adverse cardiovascular event in the group who received 25(OH)D3 compared to 5 in the control group ($p = 0.66$) and 28.6% of patients with 25(OH)D levels ≤ 50 nmol/L experienced major adverse cardiovascular events compared to 0% of patients with level > 50 nmol/L ($p = 0.037$).

Lee et al. [53] have also demonstrated that 106 out of the 339 individuals who had plaque also had lower levels of 25(OH)D ($p = 0.0316$). On the contrary, the study by Aslanabadi et al. [54] indicated that vitamin D did not significantly affect the cardiac biomarker ($p = 0.417$). Still, the mean change in Creatine Kinase-Myoglobin Binding between 8 and 24 h ($p = 0.048$) and hs- C-reactive protein ($p = 0.045$) was significantly in favor of the vitamin D group. In addition, Sajjadieh et al. [55] did not find any association between vitamin D serum levels and coronary artery calcification, and the study by López-Bautista et al. [56] did not find any independent relationship between VDD and CAD occurrence among the Mexican Population. A study by Rokni et al. [57] suggested that 25(OH)D may be a risk factor for CAD but needs further investigation.

Most studies cited above in Table 3 supported that lower vitamin D levels is associated with an increased risk of CAD, and supplementation with vitamin D may help reduce major adverse cardiovascular events. However, this needs to be explored further in a larger clinical trial.

Association of Vitamin D with AF

Prevalence of AF

AF is the most common persistent arrhythmia that significantly impacts overall morbidity and mortality. According to estimates, after age 40, the risk of AF increases by up to 26%, and AF may cause 10% to 15% of all strokes, with a 1.9-fold increase in mortality [58, 59]. Although it is not a lethal arrhythmia, it can lower the quality of life, elevate the likelihood of cardiac mortality, and lead to stroke. Epidemiological research on AF has found that the condition's prevalence is underestimated. The major causes are the failure to diagnose paroxysmal AF and the lack of interest in treating silent AF patients. The prevalence of AF is anticipated to increase over time as the population's age structure changes, the proportion of elderly people rises, and other risk factors, including HTN, diabetes, and CV disease, increase [60].

Relationship Between Vitamin D and AF

It is established that an inflammatory state is closely correlated to AF. IL-10 production can be increased by vitamin D, whereas IL-6, IL-12, interferon, and tumor necrosis factor-alpha production can be decreased. This relationship creates a cytokine spectrum that helps reduce inflammation [60]. It is also hypothesized that cardiac remodeling driven by RAAS axis activation may enhance the risk of AF [61]. The activity of the RAAS is modulated by vitamin D. Oxidative stress and inflammation brought on by activated RAAS may both result in AF [58].

Low plasma 25(OH)D3 levels may cause the RAAS to become more active, whereas RAAS suppression can delay the development of AF. Vitamin D is a negative endocrine modulator of RAAS. Patients with Vitamin D insufficiency fail to suppress RAAS, making preventing AF more challenging [61]. High fibroblast growth factor 23 levels prevent 1-α hydroxylase activity and reduce vitamin D3 synthesis [60]. Chen et al. [62] demonstrated a consistent association between high circulating fibroblast growth factor 23concentrations and AF. Another pathophysiology attempt at an explanation focuses on how parathyroid hormones interact with vitamin D to affect electrolytes, particularly calcium but phosphate and magnesium. Unbalanced electrolytes may be causative in the onset of AF [63••].

Relationship Between Genetically Predisposed VDD and AF

Chan et al. [64] attempted to establish a relationship between low levels of vitamin D and AF in a case–control study on subjects recruited from a Chinese clinical cohort of patients with stable coronary artery disease. A total of 12 Single Nucleotide Polymorphisms involved in the vitamin D mechanistic pathways from prior genome-wide association studies were studied, and a composite Genetic Risk Score (GRS) (linear continuous: 0–8) was constructed based on the summation method described previously in the literature.

The Vitamin D Genetic Risk Score (points 0–8) generated from the 4 Single Nucleotide Polymorphisms involved in the Vitamin D-binding protein)/group-specific component was strongly predictive of serum 25(OH)D [$p = 0.52$, 95% CI: 0.294–0.742; $p < 0.001$], and this relationship persisted even after adjustment for confounders (age, gender, BMI, smoking, HTN, diabetes mellitus, systolic/diastolic BP, triglycerides, low-density lipoprotein / high-density lipoprotein cholesterol, creatinine, etc.) [64].

Genetic exposure to vitamin D was independently associated with a reduced risk of AF. Categorically, those with genetically deprived vitamin D status, as denoted by a low Genetic Risk Score (0–3), had an excess AF risk of 85% compared to those with a high Genetic Risk Score (4–8). This evidence suggests that VDD might have an important role in AF development [64].

Table 3 Recent studies on Association of Vitamin D and Coronary Artery Disease (CAD)

Author, Year	Country, WHO Region	Aim	Design, Population	n	Age (y)	Gender (Male%, female %)	Intervention/ Investigation	Observation	Significant Association
Dziedzic et al. (2022) [46••]	Poland, European Region	To evaluate the association between 25(OH) D serum levels and the stage of CAD in Polish male subjects.	Prospective, Polish male Cardiac patients.	669	65 ± 11	100%, 0%	In subjects, the stage of CAD and blood levels of 25(OH) D was determined. Additionally, subjects with a history of MI were examined for any variations in 25(OH) D levels in comparison to those with stable CAD.	Patients with single-, double-, or triple-vessel disease showed significantly lower 25(OH) D levels than patients without major coronary lesions (median, 17 vs. 15 ng/mL; p 0.01). When MI was determined to be the cause of the then-current hospitalization in comparison to stable CAD, as well as in patients with a history of MI, significantly lower levels of 25(OH) D were evident; all these cases had lower levels of 25(OH) D in comparison to individuals with no such history.	Yes
Verdoia et al. (2021) [47•]	Italy, European Region	To estimate the impact of vitamin D levels on the long-term results in patients suffering from CAD undergoing PCI.	Prospective, Patients undergoing coronary angiography and PCI	705	1: 67.8 ± 11.1 2: 66.6 ± 10.8 3: 67.5 ± 10.4	1: 72.7%,27.3% 2: 84.3%,15.7% 3: 75.8%,24.2%	At check-in, Vitamin D level was measured. The threshold for severe deficiency was set at 10 ng/ml. The overall mortality rate was to be observed. Cardiovascular mortality, recurrent ACS, or serious cardiovascular events at the longest follow-up time were secondary objectives.	Lower levels of Vitamin D were associated with more severe coronary disease (p = 0.001), previous CABG (p < 0.001), lower ejection fraction (p = 0.02), acute presentation (p = 0.04). MACE (adjusted HR [95%CI] = 1.32[1.07–1.63], p = 0.01) and the composite of death and MI (adjusted HR [95%CI] = 1.3[1.03–1.65], p = 0.03) were significantly associated with VDD (7.6% vs. 2.9% vs. 0.4%). Patients with DM, CKD, and age all had a similarly increased risk.	Yes

Table 3 (continued)

Author, Year	Country, WHO Region	Aim	Design, Population	n	Age (y)	Gender (Male%, female %)	Intervention/ Investigation	Observation	Significant Association
Ismail et al. (2021) [48]	Egypt, Eastern Mediterranean Region	To find the relation between vitamin D2, D3, its metabolites and ACS in patients undergoing coronary angiography.	Case control, Patients with ACS undergoing coronary angiography and matched controls	123	> 18	Cases- 78.1%,21.9% Control- 76%, 24%	History, physical examination, interview with the patients, ECG, echocardiography, and diagnostic coronary angiography was done and then blood samples were taken in 24 h of admitting the study participants to measure Vitamin D levels.	Statistics of the study showed that ACS patients had lower levels of vitamin D and metabolites than the controls. Low levels of 25(OH) D and 1,25(OH)2 D were found to be significant predictors of the development of ACS, along with high total cholesterol, and low levels of high-density lipoprotein cholesterol, according to multivariate regression analysis. It was also interesting to note that neither vitamin D2 nor D3 was able to predict ACS ($p > 0.05$).	Yes
Xu et al. (2020) [50]	China, Western Pacific Region	To assess the link between CAD and vitamin D levels in PM women.	Case Control, Female patients undergoing coronary angiography for evaluation of CAD and age-matched controls.	212	> 50	0%, 100%	Serum 25(OH) D concentrations were assessed and classified as optimal (serum 25(OH) D: ≥ 20 ng/mL), insufficient (serum 25(OH) D: 10 to < 20 ng/mL), and deficient (serum 25(OH) D: < 10 ng/mL) in subjects and from age-matched controls.	CAD was found in 26.3% patients with appropriate vitamin D levels, 31.8% patients with insufficient Vitamin D levels, and 52.8% of patients with Vitamin D deficit. According to multivariate regression analysis the risk of developing CAD was increased with decreasing Vitamin D level (OR = 2.891; 95% confidence range = 1.459–7.139, p .001).	Yes
Sajjadieh et al. (2020) [55]	Iran, Eastern Mediterranean Region	To find out the relationship between Vitamin D serum level and CAC.	Cross sectional, Patients who were referred for performing CTA.	67	56.6 ± 10.9	60%, 40%	Spearman correlation used to assess the link connecting vitamin D and CAC.	Vitamin D levels and CAC were not correlated (Spearman coefficient = 0.03, p = 0.805).	No

Table 3 (continued)

Author, Year	Country, WHO Region	Aim	Design, Population	n	Age (y)	Gender (Male%, female %)	Intervention/ Investigation	Observation	Significant Association
Norouzi et al. (2019) [51]	Iran, Eastern Mediterranean Region	To evaluate further by investigating the association between serum vitamin D levels and the extent and severity of premature coronary artery involvement.	Case–control, Patient diagnosed with CAD with coronary angiography as case group and matched controls.	732	41–50	Cases-52%,48% Control-44.1%,55.9%	Blood samples were taken from each participant after angiography to measure serum levels of 25(OH) D. The patients were then categorized into three groups according to their serum 25(OH) D concentration.	In both groups, the mean serum levels of 25(OH) D were found to be 13.12 ± 11.13 and 18.28 ± 8.34 ($p = 0.036$) respectively. In the case group, those with HTN ($p = 0.018$), a family history of CVD ($p = 0.016$), and aspirin usage ($p = 0.036$) had significantly lower mean serum vitamin D levels. Patients in the case group had an average Gensini score of 45.02 ± 23.62, with men having a higher average score ($p = 0.022$). The Gensini score and the serum vitamin D levels had a marginally significant negative connection ($p = 0.001$ & $R = -0.543$). The mean Gensini score did not differ substantially ($p > 0.05$) between patients with inadequate vitamin D levels (47.02 ± 22.78), insufficient levels (26.0 ± 21.72), and adequate levels (39.0 ± 43.84).	Yes
Aslanabadi et al. (2018) [54]	Iran, Eastern Mediterranean Region	To study the role of vitamin D in preventing myocardial injury following elective PCI.	RCT, Patient planned to have an elective PCI.	106	18–80	44.11%, 55.89%	12 h before PCI, the intervention group received 300,000 IU of vitamin D orally, while the control group did not receive any vitamin D.	Following PCI, 20 patients (42%) in the control group and 18 patients (34.6%) in the intervention group both had an increase in CK-MB ($p = 0.417$). Furthermore, in the control and intervention groups, the proportion of patients with an increase in cTnI was 4 patients (8%) and 2, respectively ($p = .419$) showing that the level of cardiac biomarkers did not alter significantly. However, the mean difference in CK-MB between 8 and 24 h was substantially lower ($p = 0.048$) in the vitamin D group.	Yes

Table 3 (continued)

Author, Year	Country, WHO Region	Aim	Design, Population	n	Age (y)	Gender (Male%, female %)	Intervention/ Investigation	Observation	Significant Association
Navarro-Valverde et al. (2018) [52]	Spain, European Region	To assess how 25(OH) D3 therapy affects patients with non-ST elevation ACS after undergoing PCI.	RCT, Patients with non-ST-elevation ACS, CAD and percutaneous revascularization	41	70.6 ± 6.3	75.6%, 24.4%	Patients were given the conventional treatment plus 25(OH) D3 supplementation or the standard treatment alone at random. At the conclusion of the 3-month follow-up period, MACE were assessed.	In the supplemented group, one MACE was found compared to five in the control group (p = 0.66). At the conclusion of the research, 28.6% of patients with 25(OH) D levels 50 nmol/L experienced MACE, compared to 0% of patients with 25(OH) D > 50 nmol/L (RR: 1,4; p = .037).	No
Rokni et al. (2018 [57]	Iran, Eastern Mediterranean Region	To compare the serum levels of the vitamin 25(OH) D, phosphate, and calcium in people with proven CAD by angiography and healthy people in a sample group in northeastern Iran.	Case–control CAD patients and healthy subjects with no symptoms of CAD.	566	20–80	53%, 47%	Subjects were split into two research groups based on the results of their angiograms: those with > 50% stenosis of one or more coronary arteries and those with 50% stenosis. The serum 25(OH) D levels and anthropometric measurements were taken.	When compared to the control participants (16.4 ± 9.5 ng/ml), it was found that crude serum 25(OH) D concentrations were considerably higher in the Angio- (21.6 ± 11.8 ng/ml) and Angio + (21.3 ± 10.2 ng/ml) groups. (p < 0.001) In comparison to the control group, the serum 25(OH) D concentration in the Angio- and Angio + groups were considerably greater (p < 0.001).	Yes
Lee et al. (2017) [53]	South Korea, East Asia Region	To examine the relation between the existence of coronary artery plaque and vitamin D among participants who were not previously diagnosed with CAD.	Retrospective, Participants who underwent CCTA along with blood test for serum 25(OH) D level during a routine medical check-up.	339	45–67	85.8%, 66.5%	Participants received CCTA and a blood test to measure their serum 25(OH) D level. After overnight fasting, blood was taken in the morning, then concentrations of serum 25(OH) D, were determined and recorded.	It was found that 106 of the 339 total individuals had coronary artery plaques. (17.7 ± 7.72 ng/mL vs. 19.6 ± 7.12 ng/mL, p = 0.0316), the serum 25(OH) D level of the group with plaque was lower than that of the group without the plaque.	Yes

Table 3 (continued)

Author, Year	Country, WHO Region	Aim	Design, Population	n	Age (y)	Gender (Male%, female %)	Intervention/ Investigation	Observation	Significant Association
López-Bautista et al. (2017) [56]	Mexico, Region of Americas	To assess the independent association between VDD (VDD) and CAD (CAD) in Mexican adult population.	Case control, Patients with established CAD and matched control subjects.	500	53 ± 6.1	82.4%, 17.6%	Chemiluminescence assay was used to measure 25(OH) D levels.	It was found that the control group had a considerably higher rate of 25(OH) D deficiency (21.2 vs. 16%). Analysis using multiple logistic regression did not reveal a connection between VDD and CAD (OR: 1.37).	*No*

CAD Coronary artery disease, *MI* Myocardial Infarction, *PCI* Percutaneous coronary intervention, *ACS* Acute coronary syndrome, *CABG* Coronary artery bypass graft, *MACE* Major adverse cardiovascular events, *CI* Confidence interval, *DM* Diabetes mellitus, *CKD* Chronic kidney disease, *HDL* High density lipoprotein, *PM* Post-menopausal, *ECG* Electrocardiogram, *OR* Odds Ratio, *CAC* Coronary artery calcification, *CTA* Computed tomography angiography, *HTN* Hypertension, *CVD* Cardiovascular disease, *RCT* Randomised control trial, *IU* International unit, *CK-MB* Creatine Kinase-Myoglobin Binding, *cTnI* cardiac Troponin I, *CCTA* Coronary computed tomographic angiography, *VDD* Vitamin D Deficiency, *25(OH) D* 25-hydroxyvitamin D

Relationship Between Vitamin D Status and 1-α-hydroxylase in AF

Nikolova et al. [65], in a prospective observational study, evaluated the vitamin D status and the expression of 1-α-hydroxylase (CYP27B1) in peripheral blood mononuclear cells in patients with CVD (HF and AF specifically) in an attempt to reveal possible relationships with CVD risk factors. A significant decrease in 25(OH)D levels was found in the AF-group (29–56 ± 11.76 ng/ml, P = 0.044) vs. controls (37.36 ± 15.10 ng/ml), with an increase in coronary artery calcium score. In addition, a significant decrease was also seen in BMI, abdominal obesity, and duration of HTN for both controls and cases (HF and AF patients).

In this study, the analysis of the (CYP27B1) gene expression in peripheral blood mononuclear cells revealed a tendency for downregulation (p = 0.07) in HF and AF patients and increased coronary calcium accumulation. This concept not only implies a significant association between serum 25(OH)D levels and the incidence of AF and HF but also lays the foundation for further studies on 1-α-hydroxylase gene (CYP27B1) expression in peripheral blood mononuclear cells to be used as a reliable biomarker for CV pathology [65].

Relationship Between Vitamin D Levels and Incident AF & Postoperative Atrial Fibrillation (POAF)

Cerit et al. [58] observed subjects who underwent CABG surgery to assess the relationship between Vitamin D and the development of POAF. They noted that although there was a significant negative correlation between Vitamin D and left atrial diameter, Vitamin D level was not an independent predictor for POAF. A succeeding study by Cerit et al. [59] demonstrated that while no significant difference in terms of POAF was noted between patients with taking oral vitamin D supplements and those that did not, i.e. control group; (p = 0.538), those without vitamin D deficiency had a significant advantage from vitamin D supplementation to reduce the incidence of POAF (p = 0.02).

In a large retrospective study by Turin et al. [61], where 47,083 patients were included to establish a relationship between VDD and incident AF in the setting of RAAS inhibition, a significant association between vitamin D levels and the incidence of AF was observed. The major observational finding was that VDD patients in the angiotensin-converting enzyme inhibitor/angiotensin receptor blocker receiving group had an increased rate of AF. An investigation by Kara et al. [66] suggests that vitamin D supplementation reduced the probability of developing POAF by 0.24 times (p = 0.034) in patients with VDD. In contrast, patients who acquired POAF had greater vitamin D concentrations and took vitamin D supplements more frequently, according to research by Ohlrogge et al. [63••], which determined that

Table 4 Recent studies on Association of Vitamin D and Atrial fibrillation (AF)

Author, Year	Country, WHO Region	Aim	Design, Population	n	Age (y)	Gender (Male%, female%)	Intervention/ Investigation	Observation	Significant Association
Ohlrogge et al. (2022) [63••]	Germany, European Region	To study the relationship between vitamin D and POAF.	Prospective Cohort, Patients undergoing CABG with support of heart–lung machine at University Heart and Vascular Centre Hamburg.	201	66.6	84.6%, 15.4%	Baseline data collection, review of EMR, blood taken and stored before surgery. Post-operative data collected from questionnaires, discharge report and EMR. All participants' ECG analyzed by 2 investigators and third cardiologist for discrepancies. 25(OH) D measured.	Patients who developed POAF had higher vitamin D concentrations and took supplementations more often.	Yes
Nikolova et al. (2021) [65]	Bulgaria, European region	To study the vitamin D status in CVD patients and to reveal possible relationships with CVD risk factors.	Prospective, Patients who were admitted at the Cardiology Clinics of the University Hospital -Varna between October 2018 and January 2020	93	62 ± 12	35.48%, 64.5%	Vitamin D status was assessed by measurement of 25(OH) D using liquid chromatography with mass detection. Gene expression of the regulatory enzyme of vitamin D metabolism, 1-alpha-hydroxylase (CYP27B1), was evaluated by two-step real-time qPCR. Coronary artery calcium scans were performed and coronary artery calcium scoring.	Serum 25(OH) D levels of the controls were higher than those of the CVD-patients (37.36 ± 15.10 ng/mL vs. 27.70 ± 11.80 ng/mL, $p = 0.008$). The vitamin D status worsened with the severity of CVD pathology: significant decrease of 25(OH) D levels was found in the AF-group (29.56 ± 11.76 ng/mL, $p = 0.044$) and HF-group (24.47 ± 11.61 ng/mL, $p = 0.003$) vs. controls (37.36 ± 15.10 ng/mL). A significant reduction in circulating vitamin D levels with the increase of CACS ($p = 0.007$) was also observed. Significant positive relationship ($p = 0.041$) between serum 25(OH) D levels and CYP27B1 gene expression.	Yes

Table 4 (continued)

Author, Year	Country, WHO Region	Aim	Design, Population	n	Age (y)	Gender (Male%, female%)	Intervention/ Investigation	Observation	Significant Association
Kara et al. (2020) [66]	Turkey, European region	This study aimed to investigate the preventive effects of a high-dose vitamin D administered preoperatively on POAF occurrence in patients with insufficient or deficient serum vitamin D levels who underwent CABG.	Retrospective Cohort, Patients who had vitamin D deficiency or insufficiency during the preoperative evaluation	116	64 to 76	75% 25%	In the treatment group, patients with vitamin D deficiency were administered 300.000 IU vitamin D orally and those with vitamin D insufficiency 150.000 IU 48 h preoperatively.	The ratio of POAF occurrences found in the treatment and control groups were 12.07% and 27.59%, respectively. Vitamin D treatment was found to reduce the risk of POAF development by 0.24 times ($p = 0.034$).	Yes
Turin et al. (2018) [61]	USA, Region of Americas	This study seeks to determine the relationship between vitamin D deficiency and incident AF and characterize this relationship in the setting of RAAS inhibition.	Retrospective Cohort, Patients who received 25(OH) D lab testing in clinical care at Loyola University Medical Centre from Dec 2003 to Feb 2016.	47,083	< 50 to > 70	26.5%, 73.4%	25(OH) D was measured using a quantitative CLIA in 53% of patients and with LC–MS in the remaining 47% and presence of AF was determined by ICD-9 code data along with the date of diagnosis.	Patients in the AI group were less likely to have incident AF compared to the NAI group before and after adjustment for 25(OH) D level, and there was a trend for higher incident AF in the 25(OH) D deficiency population that did not reach statistical significance.	No
Chan et al. (2017) [64]	Hong Kong, Western Pacific Region	To show low vitamin D level is associated with AF and may be implicated in its pathogenesis.	Case-Control, Chinese clinical cohort of patients with stable CAD	1175	68–79	80.4%, 19.53%	SNPs of vitamin D mechanistic pathways and serum 25(OH) D levels were studied in an age- and gender-matched case–control study. Twelve SNPs involved in the vitamin D mechanistic pathways were studied. A GRS (0–8) was constructed from SNPs associated with serum 25(OH) D as a proxy to lifelong vitamin D - deficient state.	All 4 SNPs involved in the VBP/GC were significantly associated with serum 25(OH) D in control subjects without AF. Vitamin D GRS (points 0–8) generated from the 4 SNPs involved in the VBP/GC was strongly predictive of serum 25(OH)D. Genetic polymorphisms of VBP/GC found closely linked to serum 25(OH) D levels were associated with AF. Aggregated genetic vitamin D exposure, as reflected by the vitamin D GRS composed from SNPs of VBP/GC was significantly associated with reduced risk of AF.	Yes

Table 4 (continued)

Author, Year	Country, WHO Region	Aim	Design, Population	n	Age (y)	Gender (Male%, female%)	Intervention/ Investigation	Observation	Significant Association
Cerit et al. (2018) [59]	Cyprus, European Region	To study the relationship between pre-operative vitamin D supplementation and development of POAF.	RCT, Patients who underwent on-pump CABG surgery.	328	67 -77	52.3% 47.7%	Prevalence of vitamin D insufficiency and deficiency was calculated among the study population and assigned to receive either oral vitamin D (50.000 IU) (treatment group; n=40 insufficiency patients, n=28 deficiency patients) or not 48 h before CABG surgery and followed up during hospitalization process with respect to new-onset POAF.	The occurrence of POAF was not significantly different among treatment and control groups in patients with vitamin D insufficiency (31% vs. 33%, P=0.538). There was a significant difference between these two groups in occurrence of POAF in patients with VDD (18% vs. 29%, P=0.02).	Yes
Cerit et al. (2017) [58]	Cyprus, European Region	To study the relationship between vitamin D and the development of POAF after CABG.	Retrospective Cohort, Patients who underwent on-pump CABG surgery	128	67 –77	87.5%, 12.5%	Patients were monitored using a heart- rhythm monitor and daily ECG recordings were obtained during hospital stay.	41 out of 128 patients (32%) developed POAF.	*No*

POAF Post operative atrial fibrillation, *CABG* Coronary artery bypass graft, *EMR* Electronic medical records, *ECG* Echocardiogram, *25(OH) D* 25-hydroxyvitamin D, *CVD* Cardiovascular disease, *AF* Atrial fibrillation, *HF* Heart failure, *CACS* Coronary artery calcium score, *PCR* Polymerization chain reaction, *CABG* Coronary artery bypass graft, *IU* International unit, *RAAS* Renin Angiotensin Aldosterone System, *CLIA* Chemiluminescent immunoassay, *LC-MS* Liquid chromatography-mass spectrometry, *AI* Angiotensin inhibitor group, *NAI* Non- angiotensin inhibitor group, *CAD* Coronary Artery Disease, *SNPs* Single nucleotide polymorphisms, *GRS* Genetic Risk Score, *VBP/GC* Vitamin-binding protein/Group specific component, *VDD* Vitamin D Deficiency, *ECG* Electrocardiogram

using vitamin D supplements could increase the incidence of POAF (p = 0.034, OR = 5.03).

(The studies demonstrating an association between vitamin D and AF have been shown in Table 4. Further research is also needed on this topic to conclude because the findings of the various studies conducted in the recent past have needed to be more consistent.

Conclusion

Being the leading cause of morbidity and mortality, cardiovascular disease risk factors such as vitamin D levels have much potential based on recent evidence through interventional and observational studies. A significant association, along with the mechanism of association between vitamin D and cardiovascular disease entities, including heart failure, hypertension, coronary artery disease, and atrial fibrillation, has been documented in the literature. Although most studies have been reported in the context of vitamin D and heart failure, with literature even detailing the effect of vitamin D on the quality of life of heart failure patients and a predictor for risk of hospitalization, a definitive clinical recommendation has yet to be made. Indeed, a conclusive role of vitamin D in impacting overall cardiovascular disease remains to be established through future research.

Abbreviations CVD: Cardiovascular disorder; CV: Cardiovascular; VDD: Vitamin D deficiency; 25(OH)D: Serum 25-hydroxyvitamin D; VDR: Vitamin D receptor; 1,25(OH)2D: 1,25-Dihydroxyvitamin D; BP: Blood pressure; CAD: Coronary artery disease; HF: Heart failure; HTN: Hypertension; AF: Atrial fibrillation; RAAS: Renin-angiotensin-aldosterone system; PTH: Parathyroid hormone; IL: Interleukin; HR: Hazard ratio; OR: Odds ratio; POAF: Post-operative atrial fibrillation

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Data Availability The authors declare that data supporting the findings of this study are available within the article.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflict of interest associated with this publication.

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- • Of importance
- •• Of major importance

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