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Review

Vitamin D Status, Supplementation and Cardiovascular Disease

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Abstract. *This review was conducted to assess the dose–response relationship between vitamin D and cardiovascular disease (CVD) outcomes in humans: Prospective cohort studies indicate a multivariable-adjusted non-linear increase in CVD events at levels of circulating 25-hydroxyvitamin D [25(OH)D] of less than 50 nmol/l. However, Mendelian randomization studies do not support these findings. Although meta-analyses of randomized controlled trials (RCTs) do not rule out small beneficial vitamin D effects on surrogate parameters of CVD risk, such as arterial stiffness, at vitamin D doses equivalent to 1,000-5,333 IU daily, other meta-analyses of RCTs show no reduction in CVD events by vitamin D supplementation. Notably, some cohort studies and a recent RCT provide evidence for harmful effects of vitamin D on CVD outcomes at 25(OH)D levels in excess of 100 nmol/l. In conclusion, more studies in individuals with a deficient 25(OH)D level (i.e. <30 nmol/l) are needed, but caution is necessary regarding supplementation with vitamin D doses achieving a 25(OH)D level which exceeds 100 nmol/l.*

Vitamin D is an essential substance for humans. Generally, such substances show a U-shaped association of oral intake with their biological response, with deleterious effects on body functions not only at toxic doses but also at deficient doses (1).

Data from experimental animals indeed support the assumption of a U-shaped association between vitamin D and bodily functions, including a biphasic vitamin D effect on the cardiovascular system (1, 2). However, the level of scientific evidence for extrapolating data to humans from experimental animals is low (Figure 1). The present review article, therefore, aimed to summarize data in humans in order to answer the question of whether vitamin D should be recommended for prevention of CVD, thereby also considering potentially harmful effects of vitamin D. The review focuses on prospective cohort studies, randomized controlled trials (RCTs) and, when available, meta-analyses of these types of studies, as well as Mendelian randomization studies. Special attention regarding CVD outcomes is paid to the association with level of circulating 25-hydroxyvitamin D [25(OH)D] and vitamin D dosing.

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Search Strategy

A systematic literature search in PubMed was performed without language restrictions for relevant publications released until the end of May 2017. The following search terms were used: 'vitamin D' or 'vitamin D supplementation' or 'vitamin D administration' or 'cholecalciferol' or '25-hydroxyvitamin D' or 'Mendelian randomization' and 'cardiovascular disease (CVD)' or 'heart failure' or 'hypertension' or 'cardiovascular mortality' or 'myocardial infarction' or 'stroke'. Personal collections of articles on this topic, as well as references from selected articles were also used to extend the search. Some articles are not cited due to space limitations.

Dietary Reference Values for Vitamin D

Based on circulating 25(OH)D, which is the generally accepted indicator of vitamin D status, the North American Institute of Medicine (IOM) (3) has classified levels of 50 to 125 nmol/l as adequate (divide by 2.496 to convert into ng/ml), between 30 and 49.99 nmol/l as inadequate and levels below 30 nmol/l as deficient, whereas levels in excess of 125 nmol/l are classified as potentially harmful. The IOM also recommends an age-dependent daily vitamin D dose of 600 to 800 IU in healthy adults to guarantee an adequate vitamin D status even if skin synthesis of vitamin D is very low. The recommended oral intakes are based on a threshold level of

50 nmol/l for an adequate 25(OH)D level in blood and focus on bone health. Similar recommendations for adults (800 IU daily in the absence of skin synthesis of vitamin D) have been released by some European nutrition societies (4). In line with these recommendations, a systematic review of RCTs (5) has demonstrated that depending on age and body weight, adults would on average need a daily vitamin D dose of 200 to 720 IU for an increment in circulating 25(OH)D from 25 to 50 nmol/l. Moreover, these official recommendations are confirmed by a trial demonstrating that a daily vitamin D supplement of 800 IU is able to achieve a 25(OH)D level of 50 nmol/l in the circulation in almost all female adults of childbearing age in winter (6). With respect to vitamin D toxicity, the IOM (3) and the European Food Safety Authority (7) have set the no observed adverse effect level at 10,000 IU daily and, using a safety factor of 2.5, the upper tolerable intake level at 4,000 IU daily. The IOM and the European nutrition societies do not recommend vitamin D for preventing CVD. Likewise, the Endocrine Society recommends vitamin D only for maintaining musculoskeletal health (8). However, in its guidelines to clinicians, the Endocrine Society recommends a target 25(OH)D level of 75 nmol/l and a daily vitamin D dose of up to 2,000 IU (8). Notably, the aforementioned systematic review (5) demonstrated that for an increment in circulating 25(OH)D to 75 nmol/l the average dose, age and body weight-dependently, would be up to 3,360 IU, indicating that higher target levels for circulating 25(OH)D increase the required oral vitamin D intake exponentially (5). Moreover, it has been demonstrated that a daily vitamin D dose of 3,800-5,000 IU is necessary to attain a circulating 25(OH)D concentration greater than 75 nmol/l in almost all adults (9). The Endocrine Society has set the upper tolerable intake level at 10,000 IU daily and from their Clinic Practice Guideline (8) it can indirectly be assumed that they consider levels of 75 up to 250 nmol/l 25(OH)D as adequate and those exceeding 250 nmol/l as potentially harmful.

Cohort Studies on Vitamin D and CVD Risk

A recent meta-analysis of prospective cohort studies published dose-response relationships between circulating levels of 25(OH)D and CVD outcomes (10). Data were based on 34 studies with more than 180,000 participants. The dose-response relationship showed a nonlinear increase of the multivariable-adjusted risk of CVD events at 25(OH)D levels below 50 nmol/l but no further decrease in the risk of CVD events at higher levels, *i.e.* between 50 and 137.5 nmol/l. Regarding CVD mortality, this meta-analysis showed a continuous decrease in the relative risk from 25(OH)D levels of 12.5 nmol/l up to the highest recorded value, which was 100 nmol/l. Surprisingly, however, the meta-analysis did not include two very large observational studies (11, 12): The study by Dror *et al.* reported data based on over 400,000 Israeli health service members and showed a progressive increase in the relative risk of a composite of acute coronary syndrome and mortality at 25(OH)D levels below 50 nmol/l and a low risk at levels between 50 and 90 nmol/l (11). Nonetheless, the risk increased significantly again at levels exceeding 90 nmol/l, indicating an inverse J-shaped association between circulating 25(OH)D level and clinical outcome. Such an inverse J-shaped association was also reported in almost 250,000 individuals from the Copenhagen general practice sector, with the lowest CVD-associated mortality at circulating 25(OH)D levels of between 50 and 100 nmol/l (12). In these two very large cohort studies, the total number of patients with a 25(OH)D level greater than 100 nmol/l was small. Grant argues that the association between CVD events and a high 25(OH)D level may be due to vitamin D supplement use because of physician advise to take extra vitamin D supplements due to having a vitamin D-deficiency-associated disease (13). However, this would at least be an indication for the ineffectiveness of vitamin D supplement use in the clinical setting. Moreover, a U-shaped association between major cardiac and cerebrovascular events and a circulating 25(OH)D level of 20 to 120 nmol/l has also been demonstrated in cardiac surgical patients (14), although there was no evidence that the high 25(OH)D levels were due to vitamin D supplement use (15). Altogether, it is noteworthy that observational vitamin D studies cannot prove causality, and even multivariable adjustment cannot solve the problem of residual confounding (16). Therefore, RCTs are the only appropriate way to demonstrate the role of vitamin D in CVD health.

Randomized Controlled Trials

Biochemical CVD risk markers. Dyslipoproteinemia is a well-established risk factor for CVD (17). It has been proposed from experimental studies that vitamin D determines the cholesterol level through regulating bile acid synthesis from cholesterol, influencing vascular calcification, suppressing the renin–angiotensin–aldosterone system, and inhibiting foam cell formation (17). Nevertheless, the outcomes of those evaluating associations of vitamin D with serum lipids have to be investigated in RCTs. In 2012, Wang *et al.* performed a meta-analysis on the effect of vitamin D on the lipid profile (18). Based on seven RCTs with 1,346 individuals aged 18 to 80 years, it was concluded that vitamin D supplementation does not reduce but in fact increases the LDL-cholesterol level. The pooled estimate of effect for vitamin D supplementation on LDL-cholesterol was 3.23 mg/dl [95% confidence interval (CI)=0.55 to 5.90 mg/dl]. No statistically significant effects for vitamin D supplementation were observed for total cholesterol, HDL-cholesterol and triglycerides [differences in means were 1.52 mg/dl (95%CI=−1.42 to 4.46 mg/dl), −0.14 mg/dl (95%

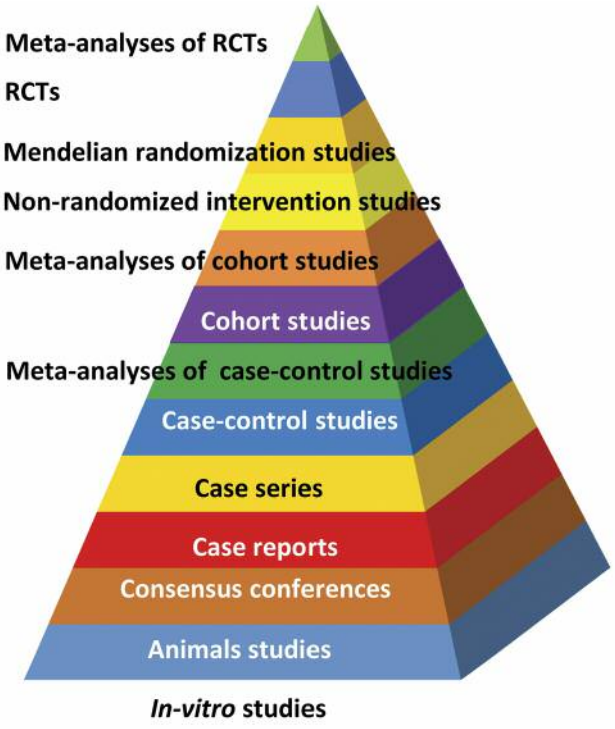

Figure 1. *Hierarchy of scientific evidence. RCTs, Randomized controlled trials.*

CI=–0.99 to 0.71 mg/dl) and –1.92 mg/dl (95% CI=–7.72 to 3.88 mg/dl), respectively]. The inspection of seven additional RCTs 2 years later did not substantially change the findings based on the aforementioned meta-analysis (18). It was therefore concluded that for definitive answers to be given, large, well-designed RCTs need to be conducted (17). These RCTs should be performed in vitamin D-deficient individuals of populations which have hyperlipidemia as an inclusion criterion. It was also suggested that until such studies have been performed, recommendations for vitamin D supplementation should not change (17).

CVD is often associated with inflammatory processes. Regarding markers of inflammation, such as C-reactive protein (CRP), the results of the meta-analysis of 10 trials involving a total of 924 participants showed that vitamin D supplementation significantly reduced the level of circulating high-sensitivity (hs)-CRP level by 1.08 mg/l (95% CI=–2.13-–0.03 mg/l), with evidence of heterogeneity. Subgroup analysis suggested a higher reduction of 2.21 mg/l (95% CI=–3.50-–0.92 mg/l) among participants with baseline hs-CRP level of 5 mg/l or higher (19). However, this meta-analysis may have been subject to a selection bias, since a study demonstrating null effects of vitamin D on hs-CRP (20) was not included in the meta-analysis. Moreover, evidence is accumulating that inflammation is not a major risk factor for CVD (21).

Surrogate clinical parameters. Data concerning the effect of vitamin D on surrogate parameters of CVD risk can be helpful for estimating the potential of vitamin D in avoiding clinical CVD events such as myocardial infarction or stroke. Hypertension and arterial stiffness are among such surrogate parameters of CVD risk.

In 2015, a meta-analysis incorporating individual patient data from 27 RCTs (3092 participants) came to the conclusion that vitamin D supplementation is ineffective as an agent for lowering blood pressure (22). The mean difference in systolic and diastolic blood pressure between individuals assigned to vitamin D and those receiving placebo was –0.5 (95% CI=–1.2 to 0.4) mmHg and 0.2 (95% CI=–0.3-0.7) mmHg, respectively. In 2016, Veloudi *et al*. investigated the effect of vitamin D dose on blood pressure according to trial duration in 36 RCTs (23). Duration of the included studies ranged from 5 weeks to more than 7 years, and the calculated daily vitamin D dose ranged between 30 IU (administered as alphacalcidol) and 6,575 IU. Only eight out of the 36 studies reported a significant benefit of vitamin D on blood pressure. None of these studies lasted longer than 6 months, and no dose-response relationship was established. The majority of the eight studies with beneficial vitamin D effects were performed in the 1980s using activated vitamin D (alphacalcidol), or vitamin D bolus doses equivalent to 6,575 IU daily. Another systematic review and meta-analysis came to the conclusion that vitamin D supplementation had no effect on systolic or diastolic blood pressure in populations with non-chronic kidney disease (24).

A meta-analysis of RCTs on arterial stiffness reported non-significant reductions in pulse-wave velocity (standardized mean difference=–0.10 m/s, 95% CI=–0.24-0.04 m/s) and augmentation index (standardized mean difference=–0.15%; 95% CI=–0.32-0.02%), the latter being a measure of the enhancement of central aortic pressure, by vitamin D supplementation in the range of 1,000 to 5,700 IU/day (25). Out of the18 studies included, 11 had a mean 25(OH)D level of less than 50 nmol/l, four of between 50 and 75 nmol/l, and two greater than 75 nmol/l at recruitment, whereas one study provided no 25(OH)D data. The aforementioned review by Veloudi *et al*. included nine studies on carotid-femoral pulse-wave velocity in their analysis (23). Duration of the included studies ranged between 2 and 12 months, and the calculated daily vitamin D dose ranged between 1,644 IU and 6,575 IU. Only one out of the nine studies (calculated daily dose 2,005 IU) showed a beneficial effect.

Collectively, results on surrogate parameters indicate, at best, a tendency towards a small beneficial effect on arterial stiffness.

CVD outcomes. Elamin *et al*. summarized data about the effect of vitamin D supplementation on myocardial infarction and stroke (26). The daily vitamin D dose of the seven included studies ranged between 300 and 1,000 IU. In the four studies where baseline 25(OH)D data were available, the concentrations were less than 60 nmol/l, less than 30 nmol/l, or on average 46 or 54 nmol/l, respectively. The relative risk of myocardial infarction and stroke was 1.02 (95% CI=0.93-1.13) and 1.05 (95% CI=0.88-1.25), respectively. In a more recent meta-analysis, Bolland *et al*. (27) included four additional studies together with the seven studies of the meta-analysis by Elamin *et al*. (26) to assess the effect of vitamin D on myocardial infarction or ischemic heart disease and stroke or cerebrovascular disease. These additional studies had baseline 25(OH)D levels of 38, 48, 53 and 72 nmol/l , respectively, and vitamin D doses of 400, 800, and 1,100 IU daily, or 500,000 once a year (equivalent to 1,340 IU daily). Results were similar to the data by Elamin *et al*. (26) and did not differ substantially in subgroup analyses of trials using vitamin D supplements alone or in combination with calcium administration. The meta-analysis by Bolland *et al*. (27) provided evidence that vitamin D supplementation does not alter the relative risk of CVD events by 15% or more. In line with these data, a very recent large RCT on elderly individuals with a mean baseline 25(OH)D level of 64 nmol/l failed to demonstrate a significant effect of a monthly vitamin D bolus of 100,000 IU for 3.34 years on incident CVD and death (primary endpoint) [hazard ratio (HR)=1.02, 95% CI=0.87-1.20], nor on myocardial infarction, angina, heart failure, hypertension, arrhythmias, arteriosclerosis, stroke, and venous thrombosis (secondary endpoints) (28). The findings of this RCT also supported the results of a meta-analysis that indicated no significant effect of vitamin D supplementation on heart failure events (29).

CVD mortality. The most important clinical endpoint with respect to CVD events is CVD mortality. In a Cochrane review of vitamin D supplementation for prevention of mortality in adults (30), vitamin D3 use did not reduce CVD mortality (RR=0.98, 95% CI=0.90 to 1.07). Results are based on 10 trials covering 47,267 individuals. The vitamin D doses were equivalent to 400-1340 IU daily, with one exception using 100,000 IU daily.

Mendelian Randomization Studies

Some may argue that lifelong adequate vitamin D status is necessary to prevent CVD events efficiently. According to this claim, vitamin D supplement use may be ineffective, even if the study duration is several years, if vitamin D supplements are used primarily in elderly patients with already pre-existing CVD risk. However, Mendelian randomization can contribute to solving this problem. This study approach takes advantage of lifelong differences in vitamin D status attributable to genetic variants in single nucleotide polymorphisms and is therefore not confounded by lifestyle factors (Figure 2). A Danish approach used an observational study design together with a Mendelian randomization analysis to assess the association of circulating 25(OH)D with CVD outcome (31, 32). The approach took into account that synthesis of 25(OH)D is influenced by polymorphisms in 7-dehydrocholesterol reductase and hepatic cytochrome P450 family 2 subfamily R member 1 (*CYP2R1*, also known as vitamin D-25-hydroxylase). Data indicate significantly higher observational multivariable-adjusted HRs for a 25-nmol/l decrease in 25(OH)D for ischemic heart disease (HR=1.07, 95% CI=1.01-1.13) and myocardial infarction (HR=1.16, 95% CI=1.06-1.27), whereas the odds ratios (ORs) for a genetically associated 25 nmol/l decrease were not significantly associated with ischemic heart disease (OR=0.98, 95% CI=0.76-1.26) or myocardial infarction (OR=1.15, 95% CI=0.83-1.59) (31). With respect to CVD mortality, the OR for an observational multivariable-adjusted reduction of 25(OH)D concentration by 20 nmol/l was 1.13 (95% CI=1.03 to 1.24) but was 0.77 (95% CI=0.55 to 1.08) for a genetically determined reduction by 20 nmol/l (32). In a Mendelian randomization study on blood pressure including up to 108,173 individuals from 35 studies (33), each 10% increase in genetically determined 25(OH)D concentration was associated with a significant reduction of 0.29 mm Hg in diastolic blood pressure, a significant reduction of 0.37 mm Hg in systolic blood pressure, and an 8.1% reduced odds of hypertension, indicating that in the long term, vitamin D might have a small, but significantly beneficial effect on

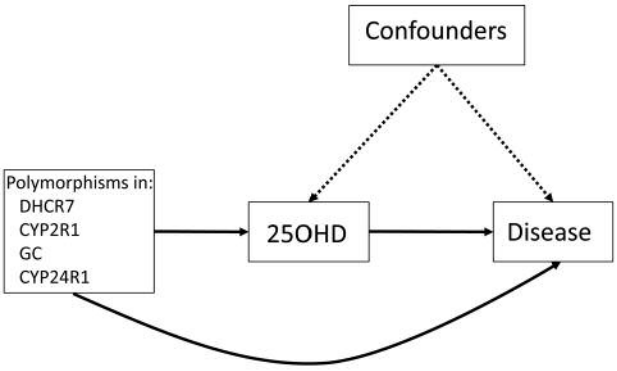

Figure 2. *Schematic representation of Mendelian randomization analysis. 25(OH)D, 25-hydroxyvitamin D; DHCR7, 7-dehydrocholesterol-reductase; CYP2R1, cytochrome P450 family 2 subfamily R member 1 (vitamin D-25-hydroxylase); GC, group-specific globulin (identical to vitamin D-binding protein); CYP24A1, cytochrome P450 family 24 subfamily A member 1 (vitamin D-24-hydroxylase).*

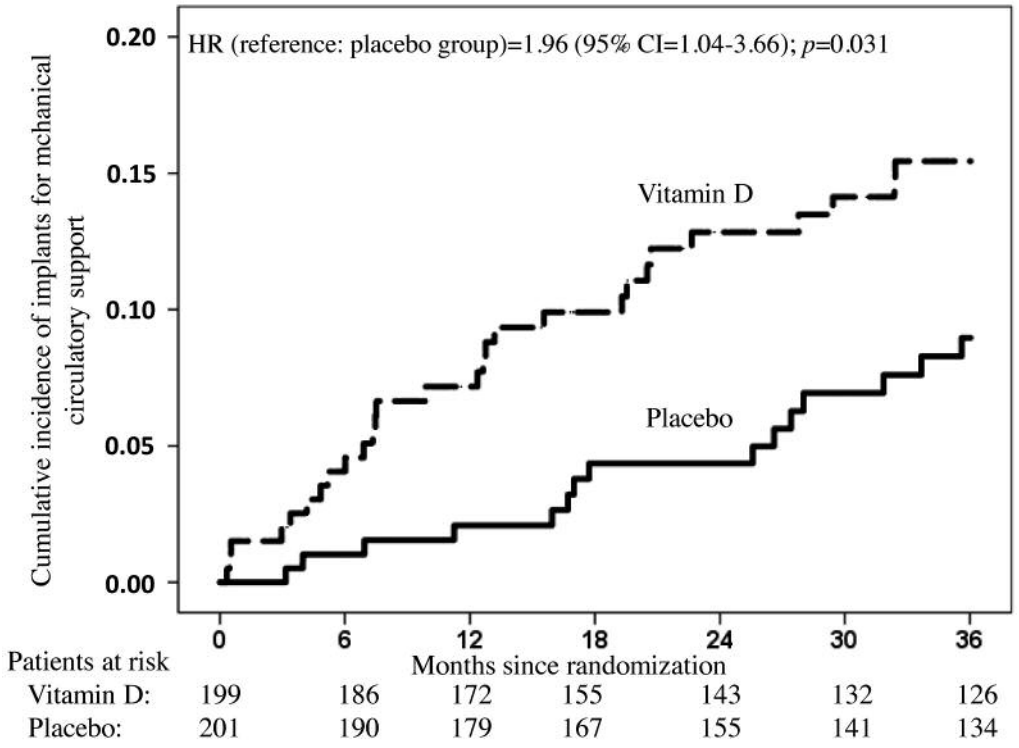

Figure 3. *Requirement for mechanical circulatory support implants in patients with advanced heart failure receiving supplement of 4,000 IU vitamin D_3 daily for 3 years by study [unpublished data from the EVITA trial (34)]. HR: Hazard ratio; CI: confidence interval.*

blood pressure. However, as indicated by the Mendelian randomization studies on myocardial infarction, ischemic heart disease, and CVD mortality (31, 32), this effect obviously does not translate into a reduced risk of CVD events. Therefore, results from the Mendelian randomization approach generally support the null effect of vitamin D supplement use on CVD events demonstrated by RCTs. Data also support the assumption that no premature conclusions should be drawn based solely on observational data.

Potentially Harmful Vitamin D Effects on CVD Outcomes in Humans

As mentioned before, several cohort studies have reported an increased risk of CVD events at a circulating 25(OH)D level greater than 100 nmol/l (11, 12, 14). Although the aforementioned recently published large and long-lasting RCT by Scragg *et al*. (28) found no significant effect of vitamin D on CVD outcome, another recent RCT on advanced heart failure (EVITA trial) provided further evidence for adverse effects of vitamin D in patients with CVD (34): In the EVITA trial, a daily vitamin D3 supplement of 4,000 IU for 3 years resulted in a greater need for mechanical implants for circulatory support (Figure 3). This relationship was only present in patients with an initial circulating 25(OH)D concentration of 30 nmol/l or more (34). This group also achieved in-study 25(OH)D levels greater than 100 nmol/l, whereas 25(OH)D levels remained below 100 nmol/l in those with a level of less then 30 nmol/l. Since the need for mechanical circulatory support was only a secondary endpoint in that study, a chance finding cannot be definitively ruled out. However, the effect was also related to an elevated plasma calcium level: The incidence of hypercalcemia (plasma calcium >2.75 mmol/l) was 6.2% and 3.1% in the vitamin D-treated and placebo groups, respectively (p=0.192). Moreover, vitamin D supplementation resulted in a significant increase in plasma calcium, although the mean calcium level still remained within the reference range (34). The number of individuals with an in-study plasma calcium level above 2.6 mmol/l was significantly higher in the group assigned to vitamin D than in the group assigned to placebo (Figure 4). Notably, long-term results of the effect of vitamin D on plasma calcium are very limited. According to the IOM, there continues to be large uncertainty about the progressive health effects of regular ingestion of even moderately high amounts of vitamin D in the long term (3). In the EVITA trial, the vast majority of participants had an initial

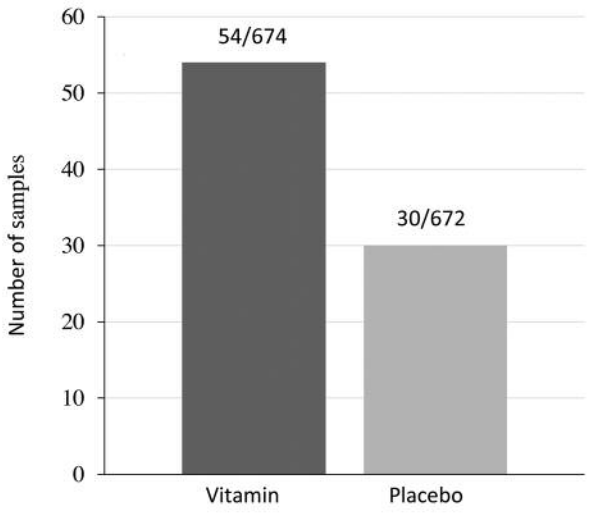

Figure 4. *Number of blood samples with a plasma calcium level >2.6 mmol/l in patients with advanced heart failure supplemented with 4,000 IU vitamin D_3 daily for 3 years by study [unpublished data from the EVITA trial (34)]. The difference between groups was significant (p=0.009).*

estimated glomerular filtration rate (eGFR) value less than 90 ml/min/1.73 m^2 and a decrease in in-study eGFR value, indicating renal decline. Impaired kidney function is considered to contribute to the loss of homeostatic control of serum calcium concentration and may thus influence the cutoff point defining toxicity of vitamin D and calcium (3). Paticularly, the Atherosclerosis Risk in Communities study reported that a high plasma calcium level was independently associated with greater risk of incident heart failure (35). In that study, heart failure incidence was lowest at a calcium level of 2.25 mmol/l and increased progressively up to 2.75 nmol/l. Moreover, a meta-analysis of observational data indicated a statistically positive association between serum calcium and CVD (36).

Notably, besides the EVITA trial (34), several other studies using vitamin D doses of 4,000 to 5,000 IU vitamin D daily reported in-study levels of 25(OH)D greater than 100-125 nmol/l in a substantial proportion of individuals (37-39).

Conclusion

RCTs provide the highest level of scientific evidence. Data from various RCTs and meta-analyses of RCTs on vitamin D supplementation and CVD outcomes are available. Although data do not rule out small beneficial effect of vitamin D on arterial stiffness, no reduction in CVD events or CVD mortality were demonstrated. Mendelian randomization studies support the findings of RCTs regarding CVD events. In the majority of RCTs, the baseline 25(OH)D levels were below 75 nmol/l and around 40 to 60 nmol/l. In the future, however, more RCTs in individuals with a deficient initial 25(OH)D level (*i.e.* <30 nmol/l) are needed to investigate whether or not vitamin D-deficient individuals benefit from use of vitamin D supplement. These studies should adhere to the official dietary reference values for vitamin D of 800 IU daily. Caution is necessary regarding long-term supplementation with vitamin D achieving 25(OH)D levels in excess of 100 nmol/l, especially in the clinical setting.

In summary, there is currently no convincing evidence for a reduction in CVD events through vitamin D supplement use.

References

1 Zittermann A: Vitamin D and cardiovascular disease. Anticancer Res *34*: 4641-4648, 2014.

2 Zittermann A: The biphasic effect of vitamin D on the musculoskeletal and cardiovascular system. Int J Endocrinol *2017*: 3206240, 2017.

3 Ross AC, Taylor CL, Yaktine AL, Del Valle HB; Institute of Medicine of the National Academies, Food and Nutrition Board: Dietary reference intakes calcium vitamin D: Committee to review dietary reference intakes for Vitamin D and calcium. Washington, D.C: The National Academies Press, 2010.

4 Deutsche Gesellschaft für Ernährung, Österreichische Gesellschaft für Ernährung, Schweizerische Gesellschaft für Ernährungsforschung, Schweizerische Vereinigung für Ernährung. Referenzwerte für die Nährstoffzufuhr 1. Aufl Neustadt an der Weinstraße: Neuer Umschau Buchverlag; 2013. (5. Korrigierter Nachdruck).

5 Zittermann A, Ernst JB, Gummert JF, Börgermann J: Vitamin D supplementation, body weight and human serum 25-hydroxyvitamin D response: a systematic review. Eur J Nutr *53*: 367-374, 2014.

6 Pilz S, Hahn A, Schön C, Wilhelm M and Obeid R: Effect of two different multimicronutrient supplements on vitamin D status in women of childbearing age: a randomized trial. Nutrients *9*: pii: E30, 2017.

7 European Food Safety Authority: Scientific opinion on the tolerable upper intake level of vitamin D: EFSA J10:2813, 2012.

8 Holick MF, Binkley NC, Bischoff-Ferrari HA and Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM; Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab *96*: 1911-1930, 2011.

9 Aloia JF, Patel M, Dimaano R, Li-Ng M, Talwar SA, Mikhail M, Pollack S and Yeh JK: Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration. Am J Clin Nutr *87*: 1952-1958, 2008.

10 Zhang R, Li B, Gao X, Tian R, Pan Y, Jiang Y, Gu H, Wang Y, Wang Y and Liu G: Serum 25-hydroxyvitamin D and the risk of cardiovascular disease: dose-response meta- analysis of prospective studies. Am J Clin Nutr *105*: 810-819, 2017.

11 Dror Y, Giveon SM, Hoshen M, Feldhamer I, Balicer RD and Feldman BS: Vitamin D levels for preventing acute coronary syndrome and mortality: evidence of a nonlinear association. J Clin Endocrinol Metab *98*: 2160-2167, 2013.

12 Durup D, Jørgensen HL, Christensen J, Tjønneland A, Olsen A, Halkjær J, Lind B, Heegaard AM and Schwarz P: A reverse J-shaped association between serum 25-hydroxyvitamin D and

cardiovascular disease mortality: The CopD Study. J Clin Endocrinol Metab *100*: 2339-2346, 2015.
13 Grant WB: Alternate explanations for the observed U-shaped 25(OH)D-mortality rate relation. Comment in response to the article by Zittermann *et al*. (Eur Heart J *34*: 1358-1364, 2013). https://academic.oup.com/eurheartj/article/34/18/1358/505800#usercomments.
14 Zittermann A, Kuhn J, Dreier J, Knabbe C, Gummert JF and Börgermann J: Vitamin D status and the risk of major adverse cardiac and cerebrovascular events in cardiac surgery. Eur Heart J *34*: 1358-1364, 2013.
15 Zittermann A, JF Gummer and J Börgermann: Future studies are needed. Response to comment by Grant regarding the article by Zittermann *et al*. (Eur Heart J *34*: 1358-1364, 2013) https://academic.oup.com/eurheartj/article/34/18/1358/505800#usercomments.
16 Jorde R: RCTS are the only appropriate way to demonstrate the role of vitamin D in health. J Steroid Biochem Mol Biol pii: S0960-0760(17)30128-0, 2017.
17 Challoumas D: Vitamin D supplementation and lipid profile: What does the best available evidence show? Atherosclerosis *235*: 130-139, 2014.
18 Wang H, Xia N, Yang Y and Peng DQ: Influence of vitamin D supplementation on plasma lipid profiles: a meta-analysis of randomized controlled trials. Lipids Health Dis *11*: 42, 2012.
19 Chen N, Wan Z, Han SF, Li BY, Zhang ZL and Qin LQ: Effect of vitamin D supplementation on the level of circulating high-sensitivity C-reactive protein: a meta-analysis of randomized controlled trials. Nutrients *6*: 2206-2216, 2014.
20 Zittermann A, Frisch S, Berthold HK, Götting C, Kuhn J, Kleesiek K, Stehle P, Koertke H and Koerfer R: Vitamin D supplementation enhances the beneficial effects of weight loss on cardiovascular disease risk markers. Am J Clin Nutr *89*: 1321-1327, 2009.
21 Kaplan H, Thompson RC, Trumble BC, Wann LS, Allam AH, Beheim B, Frohlich B, Sutherland ML, Sutherland SD, Stieglitz J, Rodriguez DE, Michalik DE, Rowan CJ, Lombardi GP, Bedi R, Garcia AR, Min JK, Narula J, Finch CE, Gurven M and Thomas GS: Coronary atherosclerosis in indigenous South American Tsimane: a cross-sectional cohort study. Lancet *389*: 1730-1739, 2017.
22 Beveridge LA, Struthers AD, Khan F, Jorde R, Scragg R, Macdonald HM, Alvarez JA, Boxer RS, Dalbeni A, Gepner AD, Isbel NM, Larsen T, Nagpal J, Petchey WG, Stricker H, Strobel F, Tangpricha V, Toxqui L, Vaquero MP, Wamberg L, Zittermann A, Witham MD; D-PRESSURE Collaboration: Effect of vitamin D supplementation on blood pressure: a systematic review and meta-analysis incorporating individual patient data. JAMA Intern Med *175*: 745-754, 2015.
23 Veloudi P, Jones G and Sharman JE: Effectiveness of vitamin D supplementation for cardiovascular health outcomes. Pulse *4*: 193-207, 2017.
24 Qi D, Nie X and Cai J: The effect of vitamin D supplementation on hypertension in non-CKD populations: A systemic review and meta-analysis. Int J Cardiol *227*: 177-186, 2017.
25 Rodríguez AJ, Scott D, Srikanth V and Ebeling P: Effect of vitamin D supplementation on measures of arterial stiffness: a systematic review and meta-analysis of randomized controlled trials. Clin Endocrinol *84*: 645-657, 2016.
26 Elamin MB, Abu Elnour NO, Elamin KB, Fatourechi MM, Alkatib AA, Almandoz JP, Liu H, Lane MA, Mullan RJ, Hazem A, Erwin PJ, Hensrud DD, Murad MH and Montori VM: Vitamin D and cardiovascular outcomes: a systematic review and meta-analysis. J Clin Endocrinol Metab *96*: 1931-1942, 2011.
27 Bolland MJ, Grey A, Gamble GD and Reid IR: The effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes: a trial sequential meta-analysis. Lancet Diabetes Endocrinol *2*: 307-320, 2014.
28 Scragg R, Stewart AW, Waayer D, Lawes CMM, Toop L, Sluyter J, Murphy J, Khaw KT and Camargo CA Jr.: Effect of monthly high-dose vitamin D supplementation on cardiovascular disease in the vitamin D assessment study: a randomized clinical trial. JAMA Cardiol *2*: 08-616, 2017.
29 Ford JA, MacLennan GS, Avenell A, Bolland M, Grey A, Witham M; RECORD Trial Group: Cardiovascular disease and vitamin D supplementation: trial analysis, systematic review, and meta-analysis. Am J Clin Nutr *100*: 746-755, 2014.
30 Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Wetterslev J, Simonetti RG, Bjelakovic M and Gluud C: Vitamin D supplementation for prevention of mortality in adults. Cochrane Database Syst Rev *1*: CD007470, 2014.
31 Brøndum-Jacobsen P and Benn M, Afzal S and Nordestgaard BG: No evidence that genetically reduced 25-hydroxyvitamin D is associated with increased risk of ischaemic heart disease or myocardial infarction: a Mendelian randomization study. Int J Epidemiol *44*: 651-661, 2015.
32 Afzal S, Brøndum-Jacobsen P and Bojesen SE and Nordestgaard BG: Genetically low vitamin D concentrations and increased mortality: Mendelian randomisation analysis in three large cohorts. BMJ *349*: g6330, 2014.
33 Vimaleswaran KS, Cavadino A, Berry DJ; LifeLines Cohort Study investigators, Jorde R, Dieffenbach AK, Lu C, Alves AC, Heerspink HJ, Tikkanen E, Eriksson J, Wong A, Mangino M, Jablonski KA, Nolte IM, Houston DK, Ahluwalia TS, van der Most PJ, Pasko D, Zgaga L, Thiering E, Vitart V, Fraser RM, Huffman JE, de Boer RA, Schöttker B, Saum KU, McCarthy MI, Dupuis J, Herzig KH, Sebert S, Pouta A, Laitinen J, Kleber ME, Navis G, Lorentzon M, Jameson K, Arden N, Cooper JA, Acharya J, Hardy R, Raitakari O, Ripatti S, Billings LK, Lahti J, Osmond C, Penninx BW, Rejnmark L, Lohman KK, Paternoster L, Stolk RP, Hernandez DG, Byberg L, Hagström E, Melhus H, Ingelsson E, Mellström D, Ljunggren O, Tzoulaki I, McLachlan S, Theodoratou E, Tiesler CM, Jula A, Navarro P, Wright AF, Polasek O; International Consortium for Blood Pressure (ICBP); Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium; Global Blood Pressure Genetics (Global BPGen) consortium; Hayward C, Wilson JF, Rudan I, Salomaa V, Heinrich J, Campbell H, Price JF, Karlsson M, Lind L, Michaëlsson K, Bandinelli S, Frayling TM, Hartman CA, Sørensen TI, Kritchevsky SB, Langdahl BL, Eriksson JG, Florez JC, Spector TD, Lehtimäki T, Kuh D, Humphries SE, Cooper C, Ohlsson C, März W, de Borst MH, Kumari M, Kivimaki M, Wang TJ, Power C, Brenner H, Grimnes G, van der Harst P, Snieder H, Hingorani AD, Pilz S, Whittaker JC, Järvelin MR and Hyppönen E: Association of vitamin D status with arterial blood pressure and hypertension risk: a Mendelian randomisation study. Lancet Diabetes Endocrinol *2*: 719-729, 2014.

34 Zittermann A, Ernst JB, Prokop S, Fuchs U, Dreier J, Kuhn J, Knabbe C, Birschmann I, Schulz U, Berthold HK, Pilz S, Gouni-Berthold I and Gummert JF, Dittrich M and Börgermann J: Effect of vitamin D on all-cause mortality in heart failure (EVITA): a 3-year randomized clinical trial with 4,000 IU vitamin D daily. Eur Heart J *38*: 2279-2286, 2017.

35 Lutsey PL, Alonso A, Michos ED, Loehr LR, Astor BC, Coresh J and Folsom AR: Serum magnesium, phosphorus, and calcium are associated with risk of incident heart failure: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Clin Nutr *100*: 756-764, 2014.

36 Reid IR, Gamble GD and Bolland MJ: Circulating calcium concentrations, vascular disease and mortality: a systematic review. J Intern Med *279*: 524-540, 2016.

37 Heaney RP, Davies KM, Chen TC, Holick MF and Barger-Lux MJ: Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. Am J Clin Nutr *77*: 204-210, 2003.

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