

## Review Article

# The treatment efficacy of vitamin D3 for heart failure patients: a meta-analysis of randomized controlled trials

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**Abstract:** Introduction: The efficacy of vitamin D3 for heart failure remains controversial. We conducted a systematic review and meta-analysis to explore the impact of vitamin D3 on heart failure patients. Methods: We searched PubMed, EMBASE, Web of Science, EBSCO, and Cochrane library databases through September 2018 for randomized controlled trials (RCTs) assessing the effects of vitamin D3 versus placebo on heart failure. This meta-analysis is performed using a random-effect model. The primary outcome is a change in left ventricular ejection fraction (LVEF). Secondary outcomes include 6 minute walking test (6MWT) change, 25-hydroxyvitamin D (25(OH)D) change, brain natriuretic peptide (BNP), hospitalization rate and mortality. Results: Eight RCTs are included in the meta-analysis. Overall, compared with the control group for heart failure, vitamin D3 supplementation results in improvement in LVEF (MD=7.89; 95% CI=7.17 to 8.60;  $P<0.00001$ ), 6MWT change (MD=11.55; 95% CI=10.94 to 12.16;  $P<0.00001$ ) and 25(OH)D (MD=47.03; 95% CI=31.68 to 62.38;  $P<0.00001$ ), but has no significant effect on BNP (MD=-447.02; 95% CI=-1262.67 to 368.62;  $P=0.28$ ), hospitalization rate (RR=1.64; 95% CI=0.37 to 7.20;  $P=0.51$ ) and mortality (RR=1.12; 95% CI=0.77 to 1.64;  $P=0.55$ ). Conclusions: Vitamin D3 supplementation can provide some benefits for heart failure patients.

**Keywords:** Vitamin D3, heart failure, LVEF, randomized controlled trials, meta-analysis

## Introduction

Vitamin D deficiency is found to have an important association with many diseases such as hypertension, diabetes, atherosclerosis, and heart failure [1-3]. The possible role of vitamin D in protecting cardiac function may be explained by the complex relationship between heart and kidney, and the stimulation of vitamin D receptor is reported to have multiple positive effects such as an improvement in myocardial function through renin inhibition, parathyroid hormone (PTH) suppression and the improvement of calcium handling [4, 5].

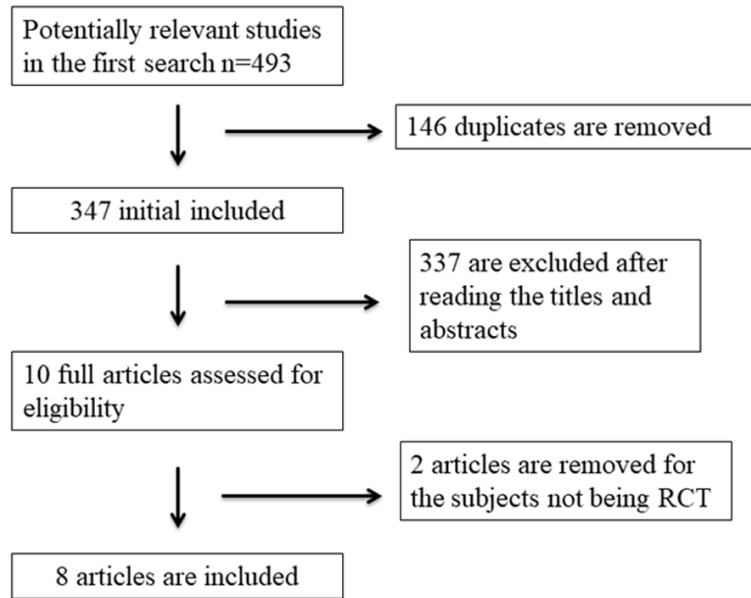
25-hydroxyvitamin D (25(OH)D) levels  $<75$  nmol/L are common in patients with heart failure and may be associated with an increased mortality risk [6-8]. The mortality risk of heart failure patients with 25(OH)D levels  $<25$  nmol/L is almost three fold greater compared to patients with 25(OH)D levels  $\geq 75$  nmol/L [9].

Vitamin D supplementation in normally recommended for osteoporosis [10]. Cholecalciferol is known as a non-active biological form of vitamin D. Vitamin D supplementation is reported to improve 25(OH)D levels, left ventricular ejection fraction (LVEF), and reduce mortality for heart failure patients [11-13].

However, the efficacy of vitamin D3 supplementation for heart failure patients has not been well established. Recently, several studies on the topic have been published, and the results are conflicting [10, 12-15]. We therefore perform a systematic review and meta-analysis of RCTs to investigate the efficacy of vitamin D3 versus placebo for heart failure.

## Materials and methods

Ethical approval and patient consent are not required because this is a systematic review and meta-analysis of previously published stud-



**Figure 1.** Flow diagram of study searching and selection process.

ies. The systematic review and meta-analysis are conducted and reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [16].

#### Search strategy and study selection

Two investigators independently searched the following databases (inception to September 2018): PubMed, EMBASE, Web of science, EBSCO, and Cochrane library databases. The electronic search strategy is conducted using the following keywords: 'vitamin D3' or 'cholecalciferol', and 'heart failure'. We also checked the reference lists of the screened full-text studies to identify other potentially eligible studies.

The inclusive selection criteria are as follows: (i) patients suffer from heart failure; (ii) intervention treatments are vitamin D3 versus placebo; (iii) study design is RCT.

#### Data extraction and outcome measures

We have extracted the following information: author, number of patients, age, sex, body mass index, New York Heart Association (NYHA) functional class and detail methods in each group etc. Data have been extracted independently by two investigators, and discrepancies are resolved by consensus. We also contacted the corresponding author to obtain any data when necessary.

The primary outcome is left ventricular ejection fraction (LVEF) changes. Secondary outcomes include 6 minute walking test (6MWT) change, 25hydroxyvitamin D (25(OH)D) change, brain natriuretic peptide (BNP), hospitalization rate and mortality.

#### Quality assessment in individual studies

Methodological quality of the included studies is independently evaluated using the modified Jadad scale [17]. There are 3 items for the Jadad scale: randomization (0-2 points), blinding (0-2 points), dropouts and withdrawals (0-1 points). The score of Jadad

Scale varies from 0 to 5 points. An article with Jadad score  $\leq 2$  is considered to be of low quality. A study is thought to be of high quality if the Jadad score  $\geq 3$  [18].

#### Statistical analysis

We estimate the mean difference (MD) with 95% confidence interval (CI) for continuous outcomes (LVEF, 6MWT change, 25(OH)D, and BNP) and risk ratio (RR) with 95% CIs for dichotomous outcomes (hospitalization rate and mortality). A random-effects model is used regardless of heterogeneity. Heterogeneity is reported using the  $I^2$  statistic, and  $I^2 > 50\%$  indicates significant heterogeneity [19]. Whenever significant heterogeneity is present, we search for potential sources of heterogeneity via omitting one study in turn for the meta-analysis or performing subgroup analysis. Publication bias is not evaluated because of the limited number ( $< 10$ ) of included studies. All statistical analyses are performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

#### Results

##### Literature search, study characteristics and quality assessment

A detailed flowchart of the search and selection results is shown in **Figure 1**. In total there were 493 potentially relevant articles are identified

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**Table 1.** Characteristics of included studies

| NO. | Author                     | Vitamin D3 group |  |            |  |                              |  | Control group |  |            |  |                              |                 | Follow up time | Jada scores |
|-----|----------------------------|------------------|--|------------|--|------------------------------|--|---------------|--|------------|--|------------------------------|-----------------|----------------|-------------|
|     |                            | Number           | Age (years)                              | Female (n) | Body mass index (kg/m <sup>2</sup> )           | NYHA functional class (I/II) | Methods  | Number        | Age (years)                              | Female (n) | Body mass index (kg/m <sup>2</sup> )           | NYHA functional class (I/II) | Methods         |                |             |
| 1   | Zittermann 2017, Germany   | 199              | 56 (48-62), median (interquartile range) | 33         | 27.8 (24.5-31.6), median (interquartile range) | 147/52                       | 4000 IU vitamin D daily                                      | 201           | 54 (48-60), median (interquartile range) | 35         | 27.8 (25.1-30.8), median (interquartile range) | 145/56                       | matched placebo | 3 years        | 5           |
| 2   | Turrini 2017, Italy        | 17               | 77±7                                     | 11         | 29±5.0   | 11/6                         | 300,000 U of oral cholecalciferol followed by 50,000 U/month | 16            | 79±7                                     | 9          | 28±5.0   | 11/5                         | matched placebo | 6 months       | 4           |
| 3   | Moretti 2017, USA          | 20               | 67±11                                    | 7          | 31±5   | -                            | 10,000 IU daily  | 20            | 65 ±16                                   | 6          | 28±5   | -                            | matched placebo | 6 months       | 4           |
| 4   | Witte 2016, UK             | 80               | 56.2±5.7                                 | 20         | -  | 5/16                         | 4,000 IU (100 µg) daily                                      | 83            | 52.4±6.5                                 | 18         | -  | 5/15                         | matched placebo | 1 year         | 4           |
| 5   | Dalbeni 2014, Italy        | 13               | 71.2                                     | 2          | 30.1   | total 10                     | 4000 IU/daily of cholecalciferol                             | 10            | 73.4                                     | 4          | 30.9   | total 7                      | matched placebo | 6 months       | 3           |
| 6   | Schroten 2013, Netherlands | 50               | 64.0±9.0                                 | 2          | -  | -                            | 2,000 IU oral VitD3 daily                                    | 51            | 63.5 ±11.1                               | 5          | -  | -                            | matched placebo | 6 weeks        | 3           |
| 7   | Boxer 2013, USA            | 31               | 65.8±10.6                                | 16         | 34.8±7.2                                       | 0/17                         | vitamin D3 50,000 IU weekly                                  | 33            | 66.0±10.4                                | 15         | 31.3±6.9                                       | 0/24                         | matched placebo | 6 months       | 5           |
| 8   | Schleithoff 2006, Germany  | 61               | 57 (53, 63), range                       | 9          | 26.0 (23.9, 29.0), range                       | -                            | 50 µg vitamin D3 daily                                       | 62            | 54 (50, 62), range                       | 12         | 25.4 (24.3, 28.4), range                       | -                            | matched placebo | 15 months      | 5           |

New York Heart Association: NYHA.

## Vitamin D3 for heart failure

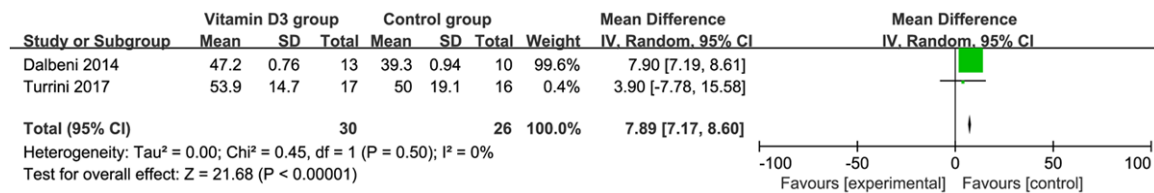


Figure 2. Forest plot for the meta-analysis of LVEF.

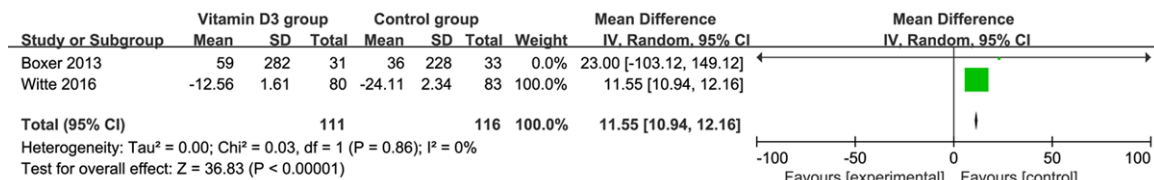


Figure 3. Forest plot for the meta-analysis of 6MWT change.

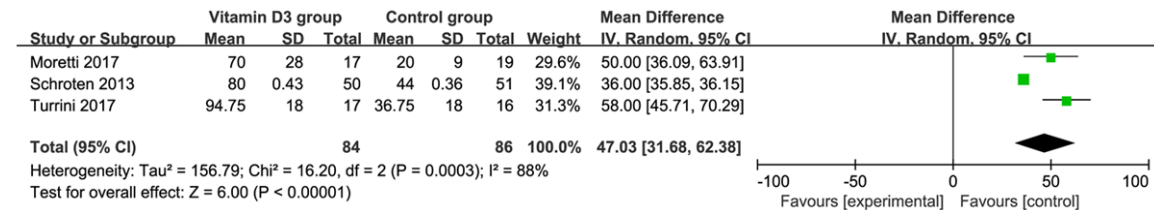


Figure 4. Forest plot for the meta-analysis of 25(OH)D (nmol/L).

initially. Finally, eight RCTs are included in the meta-analysis [10, 12-15, 20-22].

The baseline characteristics of the eight eligible RCTs in the meta-analysis are summarized in **Table 1**. The eight studies are published between 2006 and 2017, and the total sample size is 947 patients. The doses of vitamin D3 range from 2000 IU daily to 10,000 IU daily, and treatment duration varies from 6 weeks to 3 years, in the included RCTs.

Among the eight studies included here, two studies report LVEF [10, 12], two studies report 6MWT change [13, 21], three studies report 25(OH)D [10, 15, 20], two studies report BNP [10, 15], two studies report hospitalization rate [14, 21] and three studies report mortality [14, 20, 22]. Jadad scores of the eight included studies vary from 3 to 5, and all eight studies are considered to be high-quality ones according to the quality assessment.

### Primary outcome: LVEF

This outcome data is analyzed with the random-effect model, and the pooled estimate of

the two included RCTs suggested that compared to control group for heart failure, vitamin D3 is associated with significantly increased LVEF (MD=7.89; 95% CI=7.17 to 8.60;  $P < 0.00001$ ), with no heterogeneity among the studies ( $I^2=0\%$ , heterogeneity  $P=0.50$ ) (**Figure 2**).

### Sensitivity analysis

No heterogeneity is observed among the included studies for the primary outcome, and thus we do not perform sensitivity analysis via omitting one study in turn to detect the heterogeneity.

### Secondary outcomes

Compared to control group for heart failure patients, vitamin D3 can significantly improve 6MWT (MD=11.55; 95% CI=10.94 to 12.16;  $P < 0.00001$ ; **Figure 3**), and 25(OH)D (MD=47.03; 95% CI=31.68 to 62.38;  $P < 0.00001$ ; **Figure 4**), but shows no important impact on BNP (MD=-447.02; 95% CI=-1262.67 to 368.62;  $P=0.28$ ; **Figure 5**), hospitalization rate (RR=1.64; 95%

## Vitamin D3 for heart failure

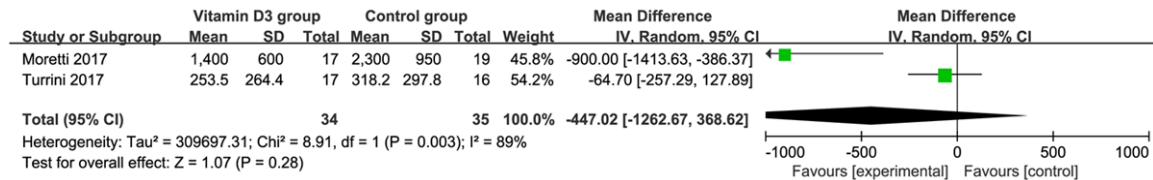


Figure 5. Forest plot for the meta-analysis of BNP (pg/ml).

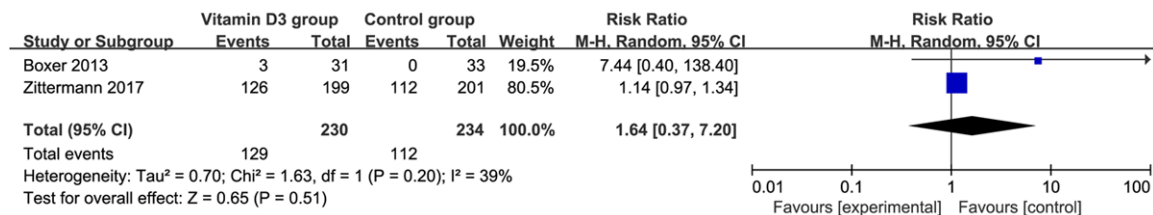


Figure 6. Forest plot for the meta-analysis of hospitalization rate.

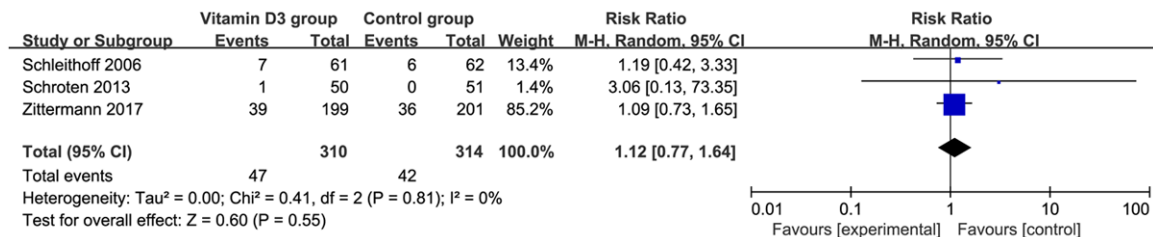


Figure 7. Forest plot for the meta-analysis of mortality.

CI=0.37 to 7.20;  $P=0.51$ ; **Figure 6**) and mortality ( $RR=1.12$ ; 95% CI=0.77 to 1.64;  $P=0.55$ ; **Figure 7**). Significant heterogeneity is observed for the analysis of 25(OH)D and BNP. There is low or no heterogeneity for the other analysis.

### Discussion

Heart failure patients may develop secondary hyperparathyroidism because of the renin-angiotensin-aldosterone system activation which is worsened by the combination of loop diuretics intake and low vitamin D level [23-26]. This metabolic impairment can result in the improvement in urinary and fecal calcium excretion which stimulates PTH production and maintains extracellular ionized calcium levels [27, 28]. Intracellular calcium overload and subsequent reactive oxygen species produce a pro-inflammatory state which induces myocardial remodeling and fibrosis [29]. Heart failure patients commonly suffer from vitamin D deficiency [30].

One RCT investigating the influence of cholecalciferol supplementation on functional, echocardiographic and hormonal parameters in patients with vitamin D deficiency and heart failure, reveals an improvement in 6MWT at 3 months, but no improvement in 6MWT at 6 months [10]. Other parameters including LVEF and BNP have strong connection with re-hospitalization and mortality [24]. However, our meta-analysis suggests that compared to control intervention for heart failure, vitamin D3 supplementation is associated with substantially improved LVEF, 6MWT and 25(OH)D, but has no significant impact on BNP, hospitalization rate and mortality. These inconsistencies may be caused by different baseline vitamin D levels, NYHA functional class of heart failure patients, various doses and duration of vitamin D3.

Optimal levels of cholecalciferol supplementation remain undefined. Previous studies have reported low doses of cholecalciferol adminis-



tered daily but with no changes in temporal vitamin D levels [21, 31]. The time required to reach normal vitamin D levels and whether those levels are maintained, remains unknown. In one study, patients are treated with a loading dose at baseline and a monthly maintenance dose, and normal levels of vitamin D in the treatment group for prolonged periods may partly explain why the improvement of functional parameters is observed at 3 months. In addition, PTH level should be an important index to correct the dosage of vitamin D. Patients can obtain a second loading dose during the study period [10].

This meta-analysis has several limitations. First, our analysis is based on only eight RCTs, and four of them have a relatively small sample size ( $n < 100$ ). Overestimation of the treatment effect is more likely in smaller trials compared with larger samples. Next, although there is no significant heterogeneity, the outcomes in our meta-analysis are not consistent, which may be caused by different baseline vitamin D levels, NYHA functional class of heart failure, doses and duration of vitamin D3 supplementation in each RCT. Finally, some unpublished and missing data may lead to bias for the pooled effect.

## Conclusion

Vitamin D3 can provide some benefits for heart failure patients.

## Disclosure of conflict of interest

None.

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