PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effect of Vitamin D on Ventricular Remodeling in Heart Failure: A Meta-analysis of Randomized Controlled Trials.
AUTHORS	Zhao, Jindong; Jia, JingJing; Dong, PingShuan; Zhao, Di; Yang, XuMing; Li, DaoLin; Zhang, HuiFeng

VERSION 1 – REVIEW

REVIEWER	FABRIZIO TURRINI Cardiovascular Medicine, Department of Internal Medicine, Nuovo Ospedale Civile Sant'Agostino Estense Mdi Modena, Via Giardini 1355 - Baggiovara . Modena - Italy
REVIEW RETURNED	03-Dec-2017

GENERAL COMMENTS	The paper by Zhao et al is a meta-analysis of published studies regarding the effect among heart failure patients of vitamin D supplementation on left ventricular indexes of remodeling and systolic function. The issue of vitamin D effect on heart failure is of great clinical relevance. Paper is well written and analyses mainly studies with small sample size. It was found a significant increase in ejection fraction and a significant reduction in left ventricular end diastolic diameter. This result is encouraging and have great clinical interest but still far from practical implications. The main implication is to encourage further and deeper research. As mentioned by the authors heterogeneity is relevant. I do not find any major comment I do have minor observations 1. A limitation that should be mentioned in the manuscript is that the extent of detected improvement in remodelling parameters is close (if not below) to the range of inter or intra-observer variability of the echocardiographic method itself (if possible provide numbers) 2. The statement (page 4 line 28) “Result will help to guiding clinical medications” - is not appropriate has to be modified. 3. I strongly suggest to perform another subgroup analysis including studies with patients with reduced ejection fraction (for example Witte, Shedeed, Schleithoff) 4. Conclusions have to be re-thought: every study ends with the statement “larger studies are needed”…. I think that the scope of this meta-analysis is to find new clues and address the design of future research. In fact it could be claimed that a larger study with an heavier end point already exist: EVITA trial (Zittermann et al. Eur Heart Journal 2017) included four hundred patient treated and followed for 3 years without finding any effect on mortality. If the message of your work is that this is not the end of the story (then you need to cite this work!!) you have to argue why and how larger studies will re open this issue. Ejection fraction is probably the best

	surrogate end point in heart failure patients, that's the reason why your paper deserves attention. According to this perspective please clarify if different selection criteria are needed (for example ejection fraction, vitamin D threshold, PTH threshold….) or if different vitamin D dosages would be superior, or if more echocardiographic parameter needs to be evaluated…

REVIEWER	Melaine Priscila Fidélix School of Pharmaceutical Science, São Paulo State University-UNESP, Araraquara, SP, Brazil
REVIEW RETURNED	03-Jan-2018

GENERAL COMMENTS	It could be a little more discussed the plasma concentrations of vitamin D considered safe, so it would be easier to discuss which value to use for supplementation.

REVIEWER	Jason Oke University of Oxford, United Kingdom
REVIEW RETURNED	26-Jan-2018

GENERAL COMMENTS	The authors present a good systematic review with a clearly formulated research question. The analyses presented are appropriate and the conclusions drawn from the results are contrasted with the other literature around Vit d supplementation. There a tendency towards hyperbole (e.g. "Subgroup analysis also revealed a remarkably lowered LVEDD in adults" but in general, the conclusions are balanced. General criticisms. The authors have made a good but not exhaustive search of the literature. For example, there has been no hand searching of journals and searching for unpublished literature. The locating of one or two extras studies can be crucial with a fairly small review. Search strategy (in terms of words) seems appropriate but a content specialist may be a better judge of whether any important terms have been missed. Can they confirm a HF specialist has reviewed this? I think the authors could do more to explain whether a 2.31mm decrease in LVEDD equates to patient benefit. i.e. I think this is particularly important as vit D supplementation doesn't seem to improve more obvious HF outcomes such as LVEF or more patient-orientated outcomes like exercise tolerance (according to the Jiang review). What will this mean for HF patients their short or long-term outcomes. I don't think this will be missed by the editorial review but the quality of English in this paper is not high. E.g. "Make a retrieval of PubMed, EMbase, CNKI, Cochrane library and WEB SCINENCE" "the main factor leading to economic loss due to its characterized by bad prognosis" In their defence, English is probably not their first language but the readability of the paper could be improved with some input from a skilled writer.

	Specific comments on methods: In the Data analysis and synthesis section it say that “RevMan5.3 software was employed for data analysis, with risk ratio (RR) and 95% C.I used for binary variables.” But all analyses presented are in mean differences continuous measures and so there is no need for this sentence. There was no mention of how the variance/Std.dev of change in mean difference is derived – is this calculated automatically in RevMan? I don’t know if RevMan does this because I don’t use this software – some description of how this is calculated (even if it is done automatically in RevMan) would be useful for people wanting to replicate their work.

VERSION 1 – AUTHOR RESPONSE

Responds to the reviewer’s comments:

Reviewer #1: Prof. TURRINI
Response to comment: (Please state any competing interests or state ‘None declared’: None declared)
Disclosure of conflict of interest
None.
Funding
This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.
(Reported on page 23).
1. Response to comment: (A limitation that should be mentioned in the manuscript is that the extent of detected improvement in remodelling parameters is close (if not below) to the range of inter or intra-observer variability of the echocardiographic method itself (if possible provide numbers)
Response: Thanks for the kind suggestion of Prof. TURRINI and we have modified the limitation of the study according to the suggestion.
Although all trials included in this study are RCTs, there are still many limitations in this study: 1) because the current studies found that vitamin D has a weak and uncertain effect on ventricular remodelling and cardiac function in patients with HF and cannot improve exercise tolerance or reduce cardiac mortality, additional large-scale clinical studies are needed. Future research needs to focus on whether different vitamin D dosages would be superior; in addition, different selection criteria need to be defined (for example, ejection fraction, vitamin D threshold, PTH threshold, etc.) and additional echocardiographic parameters, the 6MWD and cardiovascular mortality need to be evaluated; 2) this study exhibits heterogeneity, and age stratification and whether there is reduced ejection fraction may be sources of clinical heterogeneity according to the subgroup analysis; 3) different recommended dosages of vitamin D are reported in different trials, which may affect study results; therefore, additional trials are required to explore the relationship between vitamin D dosage and effect; 4) the conclusions need to be interpreted with caution, as the extent of detected improvement in the remodelling parameters is close to the range of the inter- or intra-observer variability of the echocardiographic method itself. The baseline vitamin D level of patients and the follow-up duration may affect the study results, and except for Dalbeni et al [27], whom have mentioned that no change in therapy was made during follow-up, other studies have not reported adjustments in HF medication. Therefore, whether the weak improvement in the remodelling parameters from vitamin D are attributed to other HF drugs is unclear.
About “the range of inter or intra-observer variability of the echocardiographic method itself”, we refer to the Ultrasonic Diagnosis (third edition), medicine teaching material edited by the government (Enacted by the Department of Health of China in 2013), detailed data of Axial Resolution is 1mm,

when 3~3.5MHz ultrasonic probe being used. But an Echocardiography specialist confirmed the data is 3mm. Because the differences, we cannot confirm the specific numerical. We are very sorry.
2. Response to comment: (The statement (page 4 line 28) “Result will help to guiding clinical medications” - is not appropriate has to be modified.)
Response: We fully agree with Prof. TURRINI and we have modified the statement according to the suggestion. “The results suggest that vitamin D may be utilized as adjunctive heart failure medication in heart failure patients with an underlying lack of or insufficiency in vitamin D.”
3. Response to comment: (I strongly suggest to perform another subgroup analysis including studies with patients with reduced ejection fraction (for example Witte, Shedeed, Schleithoff)
Response: We thank Prof. TURRINI for the valuable comments. As suggested, another subgroup analysis has now been performed.
According to patients with or without reduced ejection fraction, subgroup analyses were performed. Vitamin D supplementation was effective at reducing the LVEDD in patients with reduced ejection fraction (patients with reduced ejection fraction: heterogeneity $\chi 2$, $P = 0.07$, $I2 = 62\%$; MD=-3.11mm, 95% CI: -5.67- -0.55, $P = 0.02$; patients without reduced ejection fraction: heterogeneity $\chi 2$, $P = 0.76$, $I2 = 0\%$; MD=-0.91mm, 95% CI: -2.76- 0.94, $P = 0.34$) (Figure 7). In addition, vitamin D supplementation was effective at increasing the LVEF in patients with reduced ejection fraction (patients with reduced ejection fraction: heterogeneity $\chi 2$, $P = 0.02$, $I2 = 73\%$; MD=6.21%, 95% CI: 2.01- 10.41, $P = 0.004$; patients without reduced ejection fraction: heterogeneity $\chi 2$, $P = 0.002$, $I2 = 80\%$; MD=2.74%, 95% CI: -1.96- 7.45, $P = 0.25$) (Figure 8).
4. Response to comment: (Conclusions have to be re-thought: every study ends with the statement “larger studies are needed”…. I think that the scope of this meta-analysis is to find new clues and address the design of future research. In fact it could be claimed that a larger study with an heavier end point already exist: EVITA trial (Zittermann et al. Eur Heart Journal 2017) included four hundred patient treated and followed for 3 years without finding any effect on mortality. If the message of your work is that this is not the end of the story (then you need to cite this work!!) you have to argue why and how larger studies will re open this issue. Ejection fraction is probably the best surrogate end point in heart failure patients, that’s the reason why your paper deserves attention. According to this perspective please clarify if different selection criteria are needed (for example ejection fraction, vitamin D threshold, PTH threshold….) or if different vitamin D dosages would be superior, or if more echocardiographic parameter needs to be evaluated…)
Response: We thank the Prof. TURRINI for the constructive suggestions to improve this manuscript. We have re-written the limitation and conclusions.
Although all trials included in this study are RCTs, there are still many limitations in this study: 1) because the current studies found that vitamin D has a weak and uncertain effect on ventricular remodelling and cardiac function in patients with HF and cannot improve exercise tolerance or reduce cardiac mortality, additional large-scale clinical studies are needed. Future research needs to focus on whether different vitamin D dosages would be superior; in addition, different selection criteria need to be defined (for example, ejection fraction, vitamin D threshold, PTH threshold, etc.) and additional echocardiographic parameters, the 6MWD and cardiovascular mortality need to be evaluated; 2) this study exhibits heterogeneity, and age stratification and whether there is reduced ejection fraction may be sources of clinical heterogeneity according to the subgroup analysis; 3) different recommended dosages of vitamin D are reported in different trials, which may affect study results; therefore, additional trials are required to explore the relationship between vitamin D dosage and effect; 4) the conclusions need to be interpreted with caution, as the extent of detected improvement in the remodelling parameters is close to the range of the inter- or intra-observer variability of the echocardiographic method itself. The baseline vitamin D level of patients and the follow-up duration may affect the study results, and except for Dalbeni et al [27], whom have mentioned that no change in therapy was made during follow-up, other studies have not reported adjustments in HF medication. Therefore, whether the weak improvement in the remodelling parameters from vitamin D are attributed to other HF drugs is unclear.

In conclusion, this study shows that supplementation of vitamin D inhibit myocardial remodelling in patients with HF and improve their cardiac function. Vitamin D may be utilized as adjunctive HF medication for HF patients with an underlying lack of or insufficiency in vitamin D. This result is encouraging and of great clinical interest but still far from practical implications. The main implication is to encourage further research.
EVITA trial studied the effect of vitamin D on all-cause mortality in HF. However, this study was not included because the data were not suitable for this study. Zittermann et al found that a daily vitamin D dose of 4,000IU did not reduce mortality in patients with advanced HF. However, it is worth noting that the primary endpoint was all-cause mortality and not cardiovascular mortality. This study mainly focused on the influence of vitamin D on ventricular remodelling and the ejection fraction. Even though these changes cannot reduce mortality in patients with HF, they may have other effects that improve the life quality and exercise tolerance of patients.
We thank Prof. TURRINI for the positive comments of our work and the constructive suggestions to improve this manuscript.

Reviewer #2: Prof. Melaine Priscila Fidélix
Response to comment: (Please state any competing interests or state ‘None declared’: None declared)
Disclosure of conflict of interest
None.
Funding
This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.
(Reported on page 23).
1. Response to comment: (It could be a little more discussed the plasma concentrations of vitamin D considered safe, so it would be easier to discuss which value to use for supplementation.)
Response: This is indeed an important suggestion and we have included more discussed on this aspect in the manuscript.
Vitamin D toxicity is based not only on the dosing but also on circulating 25OHD levels. The Institute of Medicine [35] has set the dosage for vitamin D at 4,000IU daily for healthy adults, and the Endocrine Society [36] has set a dosage of 10,000IU daily for patients who are at risk of having circulating 25OHD levels <50 nmol/L. The Institute of Medicine [35] considers circulating 25OHD levels below 30 nmol/L as deficient, levels between 30 and 49.99 nmol/L as inadequate, levels between 50 and 125 nmol/L as adequate, and levels above 125 nmol/L as potentially harmful.
Special thanks Prof. Melaine Priscila Fidélix for the good comments.

Reviewer #3: Prof. Oke
Response to comment: (Please state any competing interests or state ‘None declared’: None declared)
Disclosure of conflict of interest
None.
Funding
This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.
(Reported on page 23).
1. Response to comment: (The authors present a good systematic review with a clearly formulated research question. The analyses presented are appropriate and the conclusions drawn from the results are contrasted with the other literature around Vit d supplementation. There a tendency towards hyperbole (e.g. "Subgroup analysis also revealed a remarkably lowered LVEDD in adults" but in general, the conclusions are balanced.)

Response: We thank Prof. Oke for the excellent summary and appreciate the constructive feedback Prof. Oke has provided. We have toned down and re-written the conclusions of Abstract、Result and Discussion according to the suggestion.
In conclusion, this study shows that supplementation of vitamin D inhibit myocardial remodelling in patients with HF and improve their cardiac function. Vitamin D may be utilized as adjunctive HF medication for HF patients with an underlying lack of or insufficiency in vitamin D. This result is encouraging and of great clinical interest but still far from practical implications. The main implication is to encourage further research.
2. Response to comment: (The authors have made a good but not exhaustive search of the literature. For example, there has been no hand searching of journals and searching for unpublished literature. The locating of one or two extras studies can be crucial with a fairly small review. Search strategy (in terms of words) seems appropriate but a content specialist may be a better judge of whether any important terms have been missed. Can they confirm a HF specialist has reviewed this?)
Response: Thanks for Prof. Oke's valuable comments. We found that we have many inadequacies in our current work. According to the Prof. Oke's suggestion, the Search Strategy has been consulted by a HF specialist and a librarian and been further improvement. Grey literature was also retrieved in Opengrey and ProQuest. The reference lists of identified articles and the bibliographies of original articles were also reviewed. An example of the full search strategy of Medline/PubMed has provided as a supplementary file. (supplementary file 1)
3. Response to comment: (I think the authors could do more to explain whether a 2.31mm decrease in LVEDD equates to patient benefit. i.e. I think this is particularly important as vit D supplementation doesn't seem to improve more obvious HF outcomes such as LVEF or more patient-orientated outcomes like exercise tolerance (according to the Jiang review). What will this mean for HF patients their short or long-term outcomes.)
Response: We thank the Prof. Oke for the constructive suggestions to improve this manuscript. We do more to explain this question according to the criticisms.
This study mainly focused on the influence of vitamin D on ventricular remodelling and the ejection fraction. Even though these changes cannot reduce mortality in patients with HF, they may have other effects that improve the life quality and exercise tolerance of patients.
In conclusion, this study shows that supplementation of vitamin D inhibit myocardial remodelling in patients with HF and improve their cardiac function. Vitamin D may be utilized as adjunctive HF medication for HF patients with an underlying lack of or insufficiency in vitamin D. This result is encouraging and of great clinical interest but still far from practical implications. The main implication is to find new clues and address the design of future research.
A recent meta-analysis [44] also reported that vitamin D supplementation could not improve the LVEF (WMD: 4.11%, 95% CI: -0.91 to 9.12, P =0.11) and 6-minute walk distance (6MWD) (WMD: 8.90 m, 95% CI: -48.47 to 66.26, P =0.76) in the treatment of chronic HF. In contrast, this study included three other studies, two of which showed a positive effect from vitamin D supplementation. The present studies have not shown that vitamin D supplementation can improve the 6MWD among patients [26,30,45,46]; thus, our meta-analysis did not evaluate this parameter. There are probably many factors that affect exercise tolerance, such as physical condition, obesity, habits, and environment, and these confounding factors may obscure the weak force from the remodelled ventricle.
4. Response to comment: (I don't think this will be missed by the editorial review but the quality of English in this paper is not high. E.g.)
Response: We are very sorry for our incorrect writing and we have used the American Journal Experts (AJE) to proofread the manuscript. The certificate has been submitted as a supplementary file. (supplementary file 2)
5. Response to comment: (Specific comments on methods:
In the Data analysis and synthesis section it say that "RevMan5.3 software was employed for data analysis, with risk ratio (RR) and 95% C.I used for binary variables." But all analyses presented are in mean differences continuous measures and so there is no need for this sentence.)

Response: We are thankful to Prof. Oke for this comment. Following the Prof. Oke's suggestion, we have removed this sentence in manuscript.

6. Response to comment: (There was no mention of how the variance/Std.dev of change in mean difference is derived – is this calculated automatically in RevMan? I don't know if RevMan does this because I don't use this software – some description of how this is calculated (even if it is done automatically in RevMan) would be useful for people wanting to replicate their work.)

Response: This is a good point, and we will be pleased to do some description considering the Prof. Oke's suggestion.

According to the Cochrane Handbook, 16.1.3 Missing standard deviations, 16.1.3.2 Imputing standard deviations for changes from baseline: Note that the mean change in each group can always be obtained by subtracting the final mean from the baseline mean even if it is not presented explicitly. However, the information in this table does not allow us to calculate the standard deviation of the changes. We cannot know whether the changes were very consistent or very variable. Some other information in a paper may help us determine the standard deviation of the changes. If statistical analyses comparing the changes themselves are presented (e.g. confidence intervals, standard errors, t values, P values, F values) then the techniques described in Chapter 7 (Section 7.7.3) may be used. The specific methods have provided as a supplementary file. (supplementary file 3)

When there is not enough information available to calculate the standard deviations for the changes, they can be imputed. When change-from-baseline standard deviations for the same outcome measure are available from other studies in the review, it may be reasonable to use these in place of the missing standard deviations.

The following alternative technique may be used for imputing missing standard deviations for changes from baseline (Follmann 1992, Abrams 2005). Here we describe (1) how to calculate the correlation coefficient from a study that is reported in considerable detail and (2) how to impute a change-from-baseline standard deviation in another study, making use of an imputed correlation coefficient. Note that the methods in (2) are applicable both to correlation coefficients obtained using (1) and to correlation coefficients obtained in other ways (for example, by reasoned argument). An alternative to these methods is simply to use a comparison of final measurements, which in a randomized trial in theory estimates the same quantity as the comparison of changes from baseline.

The Cochrane Handbook has been submitted as a supplementary file. (supplementary file 4).

We very much appreciate the overall comments of Prof. Oke and the constructive suggestions to improve this manuscript.

VERSION 2 – REVIEW

REVIEWER	Fabrizio Turrini Azienda Ospedaliera Universitaria Modena
REVIEW RETURNED	18-Mar-2018

GENERAL COMMENTS	I found corrections exhaustive with respect to observations made

REVIEWER	Jason Oke Nuffield Department of Primary Care Health Sciences, University of Oxford
REVIEW RETURNED	19-Mar-2018

GENERAL COMMENTS	The authors have worked hard on responding to my criticisms and those of the other authors. I would like to make one further comment on the issue of standard deviation of change measures from baseline. The authors have responded by quoting directly from the Cochrane Handbook. This is fine but it is not clear what method they have used and to what

	extent they have had to "impute" standard deviations, if at all. This is important as the Handbook states that " These methods should be used sparingly, because one can never be sure that an imputed correlation is appropriate (correlations between baseline and final values will, for example, decrease with increasing time between baseline and final measurements, as well as depending on the outcomes and characteristics of the participants). An alternative to these methods is simply to use a comparison of final measurements, which in a randomized trial in theory estimates the same quantity as the comparison of changes from baseline." page 165 Can the authors add a comment in the results section, stating how many of the std deviations were fully reported in the original papers and whether they had to impute any, and what method was used if they were.

VERSION 2 – AUTHOR RESPONSE

Responds to the reviewer's comments:

Reviewer #1: Prof. TURRINI

Response: We thank Prof. TURRINI for the positive comments. Taken together, we deeply appreciate the reviewer for supports of this manuscript.

Reviewer #3: Prof. Oke

Response to comment: (the issue of standard deviation of change measures from baseline)

Response: We are sorry for not detailed enough to response the issue clearly, and we would further respond Prof. Oke's comment.

Combining the characteristics of the studies included in our meta-analysis, we consulted The Chinese Cochrane Center, and both they and we consider that to compare of change from baseline of each research can better reflect the influences caused by the intervening measures than compare of final values. This is because that the baseline date of each studies is not exactly parallel, and is thus not necessarily comparable.

16.1.3.2 Imputing standard deviations for changes from baseline

(the Cochrane Handbook page 165)

(1) Calculating a correlation coefficient from a study reported in considerable detail

Where either the baseline or final standard deviation is unavailable, then it may be substituted by the other, providing it is reasonable to assume that the intervention does not alter the variability of the outcome measure. Assuming the correlation coefficients from the two intervention groups are similar, a simple average will provide a reasonable measure of the similarity of baseline and final measurements across all individuals in the study.

(2) Imputing a change-from-baseline standard deviation using a correlation coefficient

Detailed Procedure

1. The standard deviations for changes from baseline of Witte et al [30] could be directly calculated by using the RevMan software (see supplementary file 1). And the Corr of Witte et al [30] were imputed by using the aforesaid formula (1). Corr（LVEF）=0.6/Corr (LVEDD) =0.7.

2. The standard deviations for changes from baseline of Dalbeni et al [27] could be directly calculated by using the RevMan software. And the Corr of Dalbeni et al [27] were imputed by using the aforesaid formula (1). Corr（LVEF）=0.6/Corr (LVEDD) =0.6.

3. The standard deviations for changes from baseline were reported in Boxer et al [32].

4. The standard deviations for changes from baseline of Schleithoff et al [28] could be directly calculated by using the RevMan software. And the Corr of Schleithoff et al [28] were imputed by using the aforesaid formula (1). Corr（LVEF）=0.6/Corr (LVEDD) =0.8.

5. The standard deviations for changes from baseline were not reported in Turrini et al [26].

6. The standard deviations for changes from baseline were not reported in Qu et al [31].

7. The standard deviations for changes from baseline were not reported in Shedeed [29]

The standard deviations for changes from baseline on the LVEF were reported in four studies [27,28,30,32]. According to the Cochrane Handbook, the Corr were imputed by averaging the Corr of those four studies, and further imputed the standard deviations for changes from baseline for other studies [26,31,29] by using the aforesaid formula (2). The sensitivity analysis was conducted on condition that Corr =0.5, no changes were found in the conclusion.

The standard deviations for changes from baseline on the LVEDD were reported in three studies [27,28,30]. According to the Cochrane Handbook, the Corr were imputed by averaging the Corr of those three studies, and further imputed the standard deviations for changes from baseline for other studies [26,29] by using the aforesaid formula (2). The sensitivity analysis was conducted on condition that Corr =0.5, 0.6, 0.8, no changes were found in the conclusion.

We add a comment in the results section:

The standard deviations for changes from baseline on the LVEF were reported in four studies [27,28,30,32]. According to the Cochrane Handbook, the Corr were imputed by averaging the Corr of those four studies, and further imputed the standard deviations for changes from baseline for other studies [26,31,29].

The standard deviations for changes from baseline on the LVEDD were reported in three studies [27,28,30]. According to the Cochrane Handbook, the Corr were imputed by averaging the Corr of those three studies, and further imputed the standard deviations for changes from baseline for other studies [26,29].