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Peer Review File

Effects of Sacubitril/valsartan on Hypertensive Heart Disease: the REVERSE-LVH Randomized Phase 2 Trial

Corresponding Author: Professor Calvin Chin

This manuscript has been previously reviewed at another journal. This document only contains information relating to versions considered at Nature Communications.

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #2

(Remarks to the Author)
Thank you to the authors for their explanation. I am unfortunately unconvinced based upon the arguments put forth by the authors.

ECV is calculated based on Hct, native, and post contrast T1 times. It is a percentage calculation based on the above variables. Clearly, S-V is not affecting native or post contrast T1 times. If there was an effect of S-V on interstitial fibrosis, one of these values would be affected. The figures the authors make are misleading, suggesting that ECV is somehow a fraction of interstitial volume compared to overall myocardial volume. This is not the case. As such, I continue to disagree with the authors in their interpretation of their results.

Reviewer #3

(Remarks to the Author)
Thanks for addressing my prior comments; I'm satisfied with the responses and edits.

Reviewer #4

(Remarks to the Author)
Revised manuscript studying the effects of sacubitril/valsartan vs. valsartan on interstitial volume assessed with MRI.

I think the author have adequately addressed the concerns about the use of interstitial volume (or ECV) vs. ECV fraction.

I generally agree with most of the conclusions of the study. The findings are relatively novel and clinically relevant (with the possible exception of a few claims that I mention below). The finding of independent effects from change in BP is important.

I have a few other significant concerns. Inclusion of patients previously treated with ACEI/ARB doesn't make sense. First, it would potentially bias against the ACEI/ARB as patients still had LVH despite this treatment (i.e, had already "failed" this treatment and thus would not be expected to respond if reinitiated). Second, 2 weeks is far too short of a washout for any changes in ECV (i.e., whatever was there from the initial treatment would still be there after 2 weeks, and thus impossible to discern how well the drug actually worked). This could potentially be dealt with by showing us changes in those previously treated with ACEI/ARB (i.e. a sensitivity analysis) and adjusting for prior ACEI/ARB use in the covariate analysis (not just adjusting for BP).
Need a comment on whether a 2.5 ml change in interstitial volume is clinically meaningful (the difference between ARNI and ARB groups).

Unless there were changes in body weight, there is no need to index to BSA in this trial.

The change in ESTIMATED LV filling pressure from MRI of 0.9 mmHg is very small and I think it is an overstatement to say

that there was improvement in diastolic functon(stated in several places).

In the introduction, the authors state that diffuse interstitial fibrosis evolves to replacement fibrosis. I don't believe this is true very often unless there is coexisting ischemic heart disease.

I don't understand the statement in the discussion about improvement in systolic after longer durations of treatment. This seems irrelevant to this study and is highly speculative without supporting data.

Version 1:

Reviewer comments:

Reviewer #4

(Remarks to the Author)
The responses are satisfactory.

RESPONSE TO REVIEWERS' COMMENTS

Effects of Sacubitril/valsartan on Hypertensive Heart Disease: The REVERSE-LVH Randomized Phase 2 Trial

NCOMMS-24-84273-T

We thank the Reviewers for their comments and are pleased that the Editorial board is willing to consider our re-submission. We have provided a point-by-point response to each of the issues raised. All changes have been highlighted in yellow in the revised manuscript. We believe that our manuscript has been substantially improved by these revisions and hope that the Editors and Reviewers will now consider it suitable for publication in the *Nature Communications*.

REVIEWER COMMENTS

Reviewer #2 (Remarks to the Author):

Thank you to the authors for their explanation. I am unfortunately unconvinced based upon the arguments put forth by the authors.

ECV is calculated based on Hct, native, and post contrast T1 times. It is a percentage calculation based on the above variables. Clearly, S-V is not affecting native or post contrast T1 times. If there was an effect of S-V on interstitial fibrosis, one of these values would be affected. The figures the authors make are misleading, suggesting that ECV is somehow a fraction of interstitial volume compared to overall myocardial volume. This is not the case. As such, I continue to disagree with the authors in their interpretation of their results.

As noted in our previous response, compartmental analyses using the ECV fraction are not unique and are, in fact, recommended to evaluate treatment effects on both the interstitial and myocyte compartments, as illustrated in our earlier figure. While we understand that we may not be able to fully address the Reviewer's concerns, we have made further efforts to strengthen the manuscript. Specifically, we have now included additional data on circulating cardiac biomarkers—NT-proBNP and high-sensitivity troponin T.

Compared to valsartan, sacubitril/valsartan was associated with a significant reduction from baseline to 52 weeks in NT-proBNP (effective treatment ratio: 0.72; 95% CI: 0.54 to 0.91; P=0.006) and in high-sensitivity troponin T (effective treatment ratio: 0.83; 95% CI: 0.69 to 0.99; P=0.005).

Reviewer #3 (Remarks to the Author):

Thanks for addressing my prior comments; I'm satisfied with the responses and edits.

Reviewer #4 (Remarks to the Author):

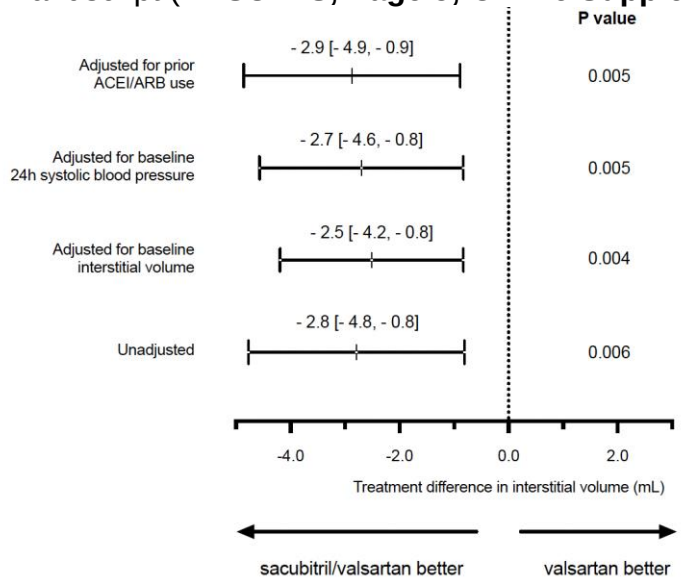
Revised manuscript studying the effects of sacubitril/valsartan vs. valsartan on interstitial volume assessed with MRI.

I think the author have adequately addressed the concerns about the use of interstitial volume (or ECV) vs. ECV fraction.

I generally agree with most of the conclusions of the study. The findings are relatively novel and clinically relevant (with the possible exception of a few claims that I mention below). The finding of independent effects from change in BP is important.

I have a few other significant concerns. Inclusion of patients previously treated with ACEI/ARB doesn't make sense. First, it would potentially bias against the ACEI/ARB as patients still had LVH despite this treatment (i.e, had already "failed" this treatment and thus would not be expected to respond if reinitiated). Second, 2 weeks is far too short of a washout for any changes in ECV (i.e., whatever was there from the initial treatment would still be there after 2 weeks, and thus impossible to discern how well the drug actually worked). This could potentially be dealt with by showing us changes in those previously treated with ACEI/ARB (i.e. a sensitivity analysis) and adjusting for prior ACEI/ARB use in the covariate analysis (not just adjusting for BP).

We thank the Reviewer for the suggestion. We have performed sensitivity analyses and observed no treatment interaction with prior ACEI/ARB use (P=0.967). Furthermore, the reduction of interstitial volumes remained greater in the sacubitril/valsartan group compared to valsartan alone after accounting for prior ACEI/ARB use (see figure below). We have now included these additional data in the revised manuscript (**RESULTS, Page 5; Online Supplemental Data Figure 3**).



Need a comment on whether a 2.5 ml change in interstitial volume is clinically meaningful (the difference between ARNI and ARB groups).

We acknowledged the clinical significance of observed effect size remains uncertain. This limitation is discussed in the revised manuscript (Discussion, Page 11).

Unless there were changes in body weight, there is no need to index to BSA in this trial.

There were no changes in body weight at the start and end of the study. In response to the Reviewer's suggestion, we revised the results to present absolute changes in the cardiac MRI parameters.

The change in ESTIMATED LV filling pressure from MRI of 0.9 mmHg is very small and I think it is an overstatement to say that there was improvement in diastolic function (stated in several places).

We thank the Reviewer for the comment. In addition to the reduction in estimated LV filling pressure, left atrial size—a surrogate marker of diastolic function—was also reduced, favoring sacubitril/valsartan (−18.3 ± 16.6 mL vs. −8.6 ± 13.6 mL; P = 0.006). These findings are further supported by reductions in circulating cardiac biomarkers, which have now been included in the revised manuscript.

However, we acknowledge that while these results are encouraging, the clinical significance of these findings is currently unknown. We have revised the manuscript accordingly to present these observations with appropriate caution. We hope these changes are more acceptable.

In the introduction, the authors state that diffuse interstitial fibrosis evolves to replacement fibrosis. I don't believe this is true very often unless there is coexisting ischemic heart disease.

In response to the Reviewer's comments, we have amended it to read "Its pathophysiology is accompanied by an expansion in extracellular volume (ECV) due to accumulation of extracellular matrix components and collagen deposition throughout the myocardium – diffuse interstitial fibrosis. This type of fibrosis typically develops gradually and is initially reversible"

I don't understand the statement in the discussion about improvement in systolic after longer durations of treatment. This seems irrelevant to this study and is highly speculative without supporting data.

We thank the reviewer for the comment. We have removed this sentence to avoid confusion.