Author's response to reviews

Title: Effect of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on Cardiovascular events in Patients with Heart Failure: A meta-analysis of randomized controlled trials

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Author’s response to reviews:

Reviewer Comments to Author:

Reviewer: 1

Comments to the Author

The article is well written, setup looks sound in the underlying statistical work and proces. English is okay, some minor revision of sentences. I would advice to let the work be checked by an official translator. The conclusion is wrong. Proof is given for the fact that ACEI is better than placebo, and ACB not. No direct proof is given for the conclusion between ACEI and ARB. The proof for the ACEI against PLACEBO are all articles older than 20 years. The other comparisons don't give a difference. The effect in Figure 5 is driven by the differences in therapy versus
placebo. If the placebo group was taken out, no effect would be seen. More interesting is the fact that ARB doesn't give a positive effect versus placebo. Recommend to rewrite the conclusion about ACEI being superior than ARB. Do an statistical analyses when the positive effect of ACEI versus placebo is seen (starting with the oldest and adding newer article and the effect on RR) how many patients are treated with placebo without extra benefit!!

Focus on the fact that there is no positive effect versus placebo from ARB.

1. English is okay, some minor revision of sentences. I would advice to let the work be checked by an official translator.

Thank you for the suggestion. We have sent the manuscript to a native English speaker. He has modified the paper where you can see from the manuscript.

2. The conclusion is wrong. Proof is given for the fact that ACEI is better than placebo, and ACB not. No direct proof is given for the conclusion between ACEI and ARB. The proof for the ACEI against PLACEBO are all articles older than 20 years. The other comparisons don't give a difference. The effect in Figure 5 is driven by the differences in therapy versus placebo. If the placebo group was taken out, no effect would be seen. More interesting is the fact that ARB doesn't give a positive effect versus placebo. Recommend to rewrite the conclusion about ACEI being superior than ARB.

Conclusions: In HF patients, ACEIs, but not ARBs reduced all-cause mortality and cardiovascular deaths. Thus, ACEIs should be considered as first-line therapy to limit excess mortality and morbidity in this population.

3. Do an statistical analyses when the positive effect of ACEI versus placebo is seen (starting with the oldest and adding newer article and the effect on RR) how many patients are treated with placebo without extra benefit!!

Thank you for the suggestions. The data can be found from the table below. But, there is no newer RCTs on effect of ACEI versus placebo. The authors' response letter has been included as a supplementary file.

4. Focus on the fact that there is no positive effect versus placebo from ARB.

We agree with this reviewer’s suggestion and add this point in the discussion part (Page 10). And in the CHARM-Alternative trial, candesartan did not reduce all-cause mortality in HF patients, but reduced the risk of CV death or HF hospitalization by 23% (p =0.0004). The Val-Heft study showed the same results. These may due to the negative effect of ARBs on heart failure, which could be mediated through a vasoconstrictor-induced increase in blood pressure or a direct effect on cardiac and vascular tissues. So, more related studies are expected to conducted in this area.
Reviewer: 2

Comments to the Author:

I think your meta-analysis is very interesting. However, I would like to make a small observation from a practical issue: in the "meta-regression" section you have compared captopril versus enalapril. It would be interesting if you could do this again adding lisinopril and ramipril, since these drugs are currently more used than captopril.

Thank you for your nice comments. We fully agree with this reviewer’s viewpoint. We have added this point in Page 9 (Result part: Meta-regression). In our study, thirty-two trials (n=39,254) compared ACEIs with various control therapies (13 arms (n=10,134) compared ACEIs 2-6, 23-30 with placebo treatment; 10 arms (n=8,714) in which the comparator was active treatment 7-8, 31-38; and 9 arms (n=20,406) compared ACEIs with ARBs 9-12, 14, 39-42). Of all these studies, only one study compared Ramipril with placebo and two studies compared lisinopril with placebo/active drugs. So, we didn’t do meta-regression of these two drugs. But, you can see the results in Figure 5.