PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Clinical efficacy and safety outcomes of bempedoic acid for LDL-C lowering therapy in patients at high cardiovascular risk: a systematic review and meta-analysis
AUTHORS	Lin, Yingfeng; Parco, Claudio; Karathanos, Athanasios; Krieger, Torben; Schulze, Volker; Chernyak, Nadja; Icks, Andrea; Kelm, Malte; Brockmeyer, Maximilian; Wolff, Georg

VERSION 1 – REVIEW

REVIEWER	Roever, Leonardo Federal University of Uberlândia, Brazil, Clinical Research - Cardiology
REVIEW RETURNED	30-May-2021

GENERAL COMMENTS	Six RCTs with a total of 3,956 patients and follow-ups of four to 52 weeks were identified. There was no difference in MACE (odds ratio (OR) 0.84; 95% confidence interval (CI) 0.61, 1.15), all-cause mortality (OR 2.37; CI 0.80, 6.99) and CV mortality (OR 1.66; CI 0.45, 6.04) for BA vs. placebo. BA showed beneficial trends for nonfatal MI (OR 0.57; CI 0.32, 1.00) and was associated with a lower risk of new-onset or worsening of DM (OR 0.68; CI 0.49, 0.94), but higher risk of gout (OR 3.29; CI 1.28, 8.46), and a trend for muscular disorders (OR 2.60; CI 1.15, 5.91) and worsening of renal function (OR 4.24; CI 0.98, 18.39). Bempedoic acid in high cardiovascular risk patients showed no significant effects on major cardiovascular outcomes in short-term follow-up. Include in article 1 - Compare and contrast your study with others in the most relevant world literature, particularly the recent literature. 2 - What new information is sufficient to modify existing clinical practice? 3 - What are the conclusions and implications for current practice, and particularly for future research that may have a significant impact on clinical decisions? 4 - What does this study add to the literature? 5 - At the end of the Discussion, under the subheading "Limitations," review the limitations of your study. 6 - At the end of the limitations, under the subheading " Future directions".

	7 - Conclusion Take special care to draw your conclusions only from your results and verify that your conclusions are firmly supported by your data 8– References Update

REVIEWER	Kurniawan, Andree Pelita Harapan University, Internal medicine
REVIEW RETURNED	03-Jul-2021

GENERAL COMMENTS	My Comments are 1. The introduction and methods have written well. 2. How about the quality of included studies? should be mentioned in the results 3. The included studies were too heterogenous in the study population: Interpretation the meta analysis results should be careful (more discussion about it) 4. How about the publication bias? and how about the GRADE validation? 5. The limitation should also be added about the included studies still limited in sample size. 6. In t conclusion should also be added: not only for long term data, however in the short term also still limited evidence to give recommendation. 7. In the discussion should be added: why the MACE not be affected? the role of Bempedoic acid? in the treatment of dyslipidemia..

VERSION 1 – AUTHOR RESPONSE

Reviewer 1, Dr. Leonardo Roever, Federal University of Uberlândia, Brazil
Reply: First of all, thank you very much for your valuable review of our manuscript. Your comments helped us to improve our work. Please find details below answering all of your questions.

1 - Compare and contrast your study with others in the most relevant world literature, particularly the recent literature.
Reply: Thank you. The process from the time of submission of our study was considerable, which is why the manuscript was not in the most updated state anymore. To account for this, we now updated our literature search, included relevant references and discussed results of other comparable meta-analyses investigating BA in contrast to our findings. Moreover, we compared results to other relevant trials investigating clinical outcomes of lipid-lowering (e.g. PCSK9-inhibitors or statins). Please refer to P 12 LL 29-31 and P 13 LL 1-2 of the revised manuscript for details.

2 - What new information is sufficient to modify existing clinical practice?
3 - What are the conclusions and implications for current practice, and particularly for future research that may have a significant impact on clinical decisions?
Reply: Thank you, we decided to answer your two questions together: Bempedoic acid is already an approved therapy in Europe (EMA) and the US (FDA) as an additional oral agent for its lipid-lowering potential, however its effects on clinical efficacy and safety outcomes thus far were unknown. Our study is, along with another recent publication with differing results [30], the first analysis of the currently available evidence base on these outcomes in patients at high cardiovascular risk. In short-

term follow-up no improvement in outcomes by administration of BA could be observed, however positive effects on diabetes and a trend for lower rates of MI suggest a beneficial potential. Trends of unfavourable effects on muscular disorders, renal function and gout sound a note of caution. Taken together, the current evidence base on BA in cardiovascular high risk patients regarding outcomes requires careful consideration by clinicians of patients comorbidities and underlying cardiovascular risk. There clearly are limitations mainly arising from the limited study follow-up duration, however these cannot be circumvented with the currently available evidence. We have updated the discussion section indicating limited evidence for bempedoic acid, a necessity of careful patient selection and for further research regarding clinical outcomes. You may find our adaptations in the revised manuscript (P 12 LL 16-22; P 13 LL 1-4, LL 13-16; P 14 LL 8-19).

4 - What does this study add to the literature?
Reply: Thank you for this important remark, and please also refer to our previous answer to your questions 2 and 3: We agree that novelty of our work was not clarified enough in the last version of the manuscript. In contrast to other meta-analyses we focussed on clinical outcomes rather than on lipid parameters only. Please find our more elaborate discussion in the discussion section of the revised manuscript (P 12 LL 16-22; P 13 LL 13-16).

5 - At the end of the Discussion, under the subheading "Limitations," review the limitations of your study.
Reply: Thank you, we agree that our study limitations were not transparent enough in the last version of our manuscript. We updated the ‘Limitations’ section at the end of our discussion and phrased it more appropriately (P 13 LL 29-30; P 14 LL 1-7):
“Meta-analysis is currently the only feasible way to explore clinical efficacy and safety of BA, however comes with a number of inherent limitations that arise from analyzing secondary or exploratory endpoints in these trials: Low event rates within limited follow-ups cause imprecise effect estimates leading to low-moderate certainty of consistency of estimated and true effects. Variation in length of follow-up may introduce bias; multiple testing bears additional risk. Additional limitations include trial heterogeneity in study co-medication (no statin vs. maximal tolerated statin, additional ezetimibe) and selection of patients regarding baseline cardiovascular risk and potential beneficial effects of lipid-lowering (patients with established ASCVD vs. patient at high cardiovascular risk). Generally, pooled sample size is still limited compared to other outcome trials in lipid-lowering therapy. Therefore, results of this meta-analysis are exploratory and should be interpreted with caution and evidence is limited to give a recommendation for treatment with BA.”

6 - At the end of the limitations, under the subheading " Future directions".
Reply: Thank you, this is important point. We created a new subheading ‘Future directions’ at the end of our discussion, discussing future implications of BA therapy for clinical aspects and research (P 14 LL 8-19).

7 – Conclusion: Take special care to draw your conclusions only from your results and verify that your conclusions are firmly supported by your data
Reply: Thank you. We rephrased our conclusion in the manuscript (P 14 LL 22-26) and abstract (P 2, LL 21) to reflect a more conservative interpretation of the data:
“Meta-analysis of bempedoic acid vs. placebo in patients at high cardiovascular risk showed no significant effects on major cardiovascular outcomes in short-term follow-up, despite significant reductions of LDL-C and other atherogenic lipid fractions. Unfavourable effects on muscular disorders, renal function, and the incidence of gout sound a note of caution. Hence, further studies with longer-term follow-up conducted in carefully selected populations are needed to clarify the risk/benefit ratio of this novel therapy.”

8– References

Reply: Thank you. We updated literature search and references up to November 1st 2021 and included new references listed below. See references section in manuscript (P 16 LL 11-12; P 17 LL 11-22, LL 36-37 LL).

4. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur J Prev Cardiol. 2021.
26. Cicero AFG, Fogacci F, Hernandez AV, et al. Efficacy and safety of bempedoic acid for the treatment of hypercholesterolemia: A systematic review and meta-analysis. PLoS Med. 2020;17(7):e1003121.
28. Bhagavathula AS, Al Matrooshi NO, Clark CCT, et al. Bempedoic Acid and Ezetimibe for the Treatment of Hypercholesterolemia: A Systematic Review and Meta-Analysis of Randomized Phase II/III trials. Clin Drug Investig. 2021;41(1):19-28.
29. Banach M, Duell PB, Gotto AM, Jr., et al. Association of Bempedoic Acid Administration With Atherogenic Lipid Levels in Phase 3 Randomized Clinical Trials of Patients With Hypercholesterolemia. JAMA Cardiol. 2020;5(10):1124-35.
30. Wang X, Zhang Y, Tan H, et al. Efficacy and safety of bempedoic acid for prevention of cardiovascular events and diabetes: a systematic review and meta-analysis. Cardiovasc Diabetol. 2020;19(1):128.
36. Fulcher J, O'Connell R, Voysey M, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet. 2015;385(9976):1397-405.
37. Azari S, Rezapour A, Omidi N, et al. Cost-effectiveness analysis of PCSK9 inhibitors in cardiovascular diseases: a systematic review. Heart Fail Rev. 2020;25(6):1077-88.

Reviewer 2, Dr. Andree Kurniawan, Pelita Harapan University:
Reply: We thank you very much for your thorough review of our manuscript. We have prepared this rebuttal answering all of your comments and have included a revised manuscript version. We hope you enjoy reading our next version.

1. The introduction and methods have written well.
Reply: Thank you, we appreciate that!

2. How about the quality of included studies? should be mentioned in the results
Reply: Thank you, you are right to ask for a quality assessment of studies. In the revised manuscript, we thus updated methods and results regarding quality of included studies, including a GRADE rating of certainty of results for primary outcomes and provided a table of rating results in supplementary materials (Supplementary Table 2). Please find changes in methods, results, and discussion section of the manuscript (P 4 LL 23-25; P 10 LL 1-8; P 13 L 1-4).

3. The included studies were too heterogenous in the study population: Interpretation the meta analysis results should be careful (more discussion about it)
Reply: Thank you. We agree that heterogeneity among populations of included studies is relevant and that’s an inherent limitation of our work. However, at the same time heterogeneity is a necessity, as there are no better data up to this point. All selected trials included patients requiring pharmacological lipid lowering and baseline LDL-C > 100 mg/dL indicating cardiovascular risk was elevated among all (to a different extent). In the revised manuscript, we included discussion about this limitation (P 13 LL 1-4, LL 8-9; P 14 LL 2-4).

4. How about the publication bias? and how about the GRADE validation?

Reply: Thank you. As recommended, we now performed a GRADE rating of certainty of results for primary outcomes and provided a table of rating results in supplementary materials (Supplementary Table 2). Certainty according to GRADE was low – moderate for primary outcomes. No relevant selection bias could be detected. Please find changes in methods (P 13 LL 23-25), results (P 10 LL 1-8), and limitiations (P 13 LL 29-30; P 14 LL 1-7) section of the revised manuscript.

5. The limitation should also be added about the included studies still limited in sample size.
Reply: Thank you. We agree that pooled sample size can be regarded as limited when compared to other outcome trials in lipid lowering therapy. We added this important aspect to limitations section of the discussion (P 14 LL 4-5).

6. In the conclusion should also be added: not only for long term data, however in the short term also still limited evidence to give recommendation.
Reply: Thank you. In the revised discussion section, we now clarified that available short-term data provide limited evidence for longer-term recommendations and further research is needed with regards to clinical outcomes and appropriate patient selection. Please find our adaptations in the revised manuscript (P 14 LL 5-7).

7. In the discussion should be added: why the MACE not be affected? the role of Bempedoic acid? in the treatment of dyslipidemia.
Reply: Thank you. MACE as an endpoint is difficult to judge after short-term follow-up, as accumulating events may need longer follow-up time to accrue. Additionally, MACE was only reported in 4 of the 6 included RCTs , which limited sample size and statistical power to detect differences. In our revised discussion section (P 12 LL 26-28), we now included neutral effects of bempedoic acid on MACE during the analyzed short-term follow-up.
Right now, there is approval of bempedoic acid for lipid-lowering therapy in Europe and the US, however the data regarding clinical outcomes are very sparse. Our meta-analysis is thus far our best guess to understand influence on outcomes. Bempedoic acid offers an alternative to advanced, non-oral and costly therapies (PCSK9 inhibitors, inclisiran) and may yet prove to show benefits for outcomes in upcoming phase 4 studies (e.g. CLEAR Outcomes). We incorporated this aspect into the new section “future directions” (P 14 LL 8-19).
We sincerely hope that this clarifies your remark appropriately.