Journal of Clinical Question

Decision Letter (JCQ-2025-0030)

From: [redacted]
To:
CC:
BCC:

Subject: Journal of Clinical Question - Decision on Manuscript ID JCQ-2025-0030

Body: 1-Oct-2025

Dear Professor Lv:

Manuscript ID JCQ-2025-0030 entitled "Cholesteryl Ester Transfer Protein Inhibitors for Dyslipidemia in Cardiovascular Risk Patients: A Systematic Review and Meta-Analysis" which you submitted to the Journal of Clinical Question, has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter.

The reviewer(s) have recommended publication, but also suggest some minor revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s)' comments and revise your manuscript.

To submit your revised manuscript, follow the below steps.
1. Access to https://mc.manuscriptcentral.com/jcq and log into the site.
2. Click "Author" at the top left of the screen at "Home" page.
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4. Click "create a revision" on the manuscript you are going to revise.
5. The system creates your revision manuscript form. Provide your comments about the revised points at the response field, fill in on each field step by step as same as you did for the original submission, and submit your revised manuscript.
IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.
Your manuscript number has been appended to denote a revision.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Please also highlight the changes to your manuscript within the document by using the track changes mode in MS Word or by using bold or colored text.

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When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) in the space provided. You can use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Because we are trying to facilitate timely publication of manuscripts submitted to the Journal of Clinical Question, your revised manuscript should be uploaded as soon as possible. If it is not possible for you to submit your revision in a reasonable amount of time, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to the Journal of Clinical Question and I look forward to receiving your revision.

Sincerely,
Richard Isaacs
Journal of Clinical Question

[Editor's Comments]
Associate Editor
Comments to the Author:
1. Check grammar and flow for minor errors.
2. Ensure all abbreviations are defined on first use in both abstract and main text.
3. Add ORCID IDs for authors if available

[Reviewer(s)' Comments]
Reviewer: 1

Comments to the Author
To begin with, congratulations on completing a fascinating systematic review and meta-analysis (SRMA) and crafting an article that aligns well with PRISMA guidelines.
here are few suggestions
1. Methodology written well soundly, The exact search strategy can be added
2. The result section on MACE, line 185- "acetrapib was associated with a significantly
reduced risk of MACE" Its not appropriate as OR is 92 with CI of range upto 98, when applied as RR the upper limit of CI goes upto 0.99 which almost nullifies the effect.
3.Again this statement is not appropriate "Evacetrapib was associated with a significantly reduced risk of all-cause mortality again 95% CI: 0.82–1.00" as the upper limit of CI is 1 which reflect zero advantage

Reviewer: 2

Comments to the Author
This systematic review and meta-analysis by Zhang et al. examines the efficacy and safety of cholesteryl ester transfer protein inhibitors (CETPi) in adults with dyslipidemia and elevated cardiovascular risk. The authors synthesized data from seven randomized controlled trials (n = 77,762) evaluating major CETPi agents, including anacetrapib, obicetrapib, dalcetrapib, evacetrapib, and torcetrapib. The review concludes that anacetrapib demonstrates potential clinical benefit, while newer agents such as obicetrapib show promising lipid effects warranting further investigation in outcome-driven trials.

Major Comments
1.The discussion effectively summarizes the lipid effects of CETPi but should better contextualize the disconnect between lipid changes and clinical outcomes. Expanding on the concept of HDL functionality—particularly cholesterol efflux capacity and anti-inflammatory effects—would enhance understanding of why HDL elevation does not necessarily yield cardiovascular protection.Furthermore, clarifying which patient populations (e.g., those with residual risk despite statins and PCSK9 inhibitors) might benefit most from CETPi would increase the manuscript's clinical relevance.
2. Substantial heterogeneity ($I^2 > 90\%$) was reported in lipid outcomes. The authors are encouraged to conduct subgroup or meta-regression analyses to explore sources of heterogeneity (e.g., agent generation, baseline lipid levels, trial duration).Since torcetrapib had known off-target toxicity, presenting results excluding early-generation agents could help isolate the true class effect of CETP inhibition.
3. Future Research DirectionsThe discussion section would benefit from a more detailed projection of ongoing and future CETPi trials, especially Phase III studies of obicetrapib. Including expected endpoints, population characteristics, and potential design improvements over previous trials would provide readers with a forward-looking perspective.Moreover, recommending functional HDL biomarkers for future research (e.g., cholesterol efflux capacity, apoA-I turnover) would add depth to the mechanistic outlook.

Minor Comments
1.Clarify whether the search date "July 10, 2025" refers to the last database update.
2. Maintain consistency between "CETPi" and "CETP inhibitors."
3. Standardize lipid reporting units (e.g., consistently use mg/dL or % change).
4. Verify uniform use of statistical abbreviations (CI, OR, MD).
5. Emphasize that no language restrictions were applied to the search (currently mentioned but could be clearer).
6. Minor stylistic edits could improve readability (e.g., simplify "demonstrated more encouraging results" to "showed more favorable results").
7. Ensure that all abbreviations (MACE, HDL-C, LDL-C, etc.) are defined upon first mention.

Date Sent: 1-Oct-2025

Journal of Clinical Question

Author's Response to Decision Letter for (JCQ-2025-0030)

Cholesteryl Ester Transfer Protein Inhibitors for Dyslipidemia in Cardiovascular Risk Patients: A Systematic Review and Meta-Analysis

Dear Editor and Reviewrs,

We sincerely thank the Associate Editor and Reviewers for their constructive feedback and valuable insights, which have helped improve the quality and clarity of our manuscript. We have carefully revised the paper according to all comments. Detailed responses to each point are provided below.

Editor's Comments
1. Check grammar and flow for minor errors.
Response: Thank you for this comment. The manuscript has been thoroughly proofread, and minor grammatical and stylistic issues have been corrected to enhance overall flow and readability.
2. Ensure all abbreviations are defined on first use in both abstract and main text.
Response: Thank you for this suggestion. All abbreviations (e.g., MACE, HDL-C, LDL-C, OR, CI, RR, etc.) have been defined at their first mention in both the abstract and main text to ensure clarity and consistency.
3. Add ORCID IDs for authors if available
Response: Thank you for this recommendation. ORCID IDs for all authors have been added where available.

Reviewer: 1
1. Methodology written well soundly, The exact search strategy can be added
Response: We appreciate this valuable comment. A detailed description of the search strategy has been added to the Supplementary Material (Table S1) to enhance transparency and reproducibility.

2. The result section on MACE, line 185- "acetrapib was associated with a significantly reduced risk of MACE" Its not appropriate as OR is 92 with CI of range upto 98, when applied as RR the upper limit of CI goes upto 0.99 which almost nullifies the effect.
Response: Thank you for this observation. The statement has been revised to more accurately reflect statistical precision as follows: “Figure 1 displays the results for MACE. Anacetrapib was associated with a statistically significant reduction in the risk of MACE (OR: 0.92; 95% CI: 0.86–0.98; p = 0.01; I^2 = 0%). However, the 95% CI was close to the null value, suggesting that the effect size was modest.”

3.Again this statement is not appropriate "Evacetrapib was associated with a significantly reduced risk of all-cause mortality again 95% CI: 0.82–1.00" as the upper limit of CI is 1 which reflect zero advantage
Response: Thank you for this comment. We agree and have revised the statement as follows:
“Figure 2 presents the outcomes for all-cause mortality. Evacetrapib was associated with a statistically significant reduction in the risk of all-cause mortality (OR: 0.83; 95% CI: 0.82–1.00; p = 0.04). However, the 95% CI approached the null value, indicating that the magnitude of the effect was not robust.”

Reviewer: 2
Major Comments
1. The discussion effectively summarizes the lipid effects of CETPi but should better contextualize the disconnect between lipid changes and clinical outcomes. Expanding on the concept of HDL functionality—particularly cholesterol efflux capacity and anti-inflammatory effects—would enhance understanding of why HDL elevation does not necessarily yield cardiovascular protection.Furthermore, clarifying which patient populations (e.g., those with residual risk despite statins and PCSK9 inhibitors) might benefit most from CETPi would increase the manuscript’s clinical relevance.
Response: Thank you for this insightful suggestion. The discussion has been expanded to include HDL functionality (e.g., cholesterol efflux capacity and anti-inflammatory properties) and to better address the disconnect between HDL-C elevation and cardiovascular outcomes. The following content has been added:
“Earlier-generation CETPi, such as torcetrapib, initially generated enthusiasm due to their striking effects on HDL-C but ultimately failed to improve clinical outcomes. The ILLUMINATE trial demonstrated not only a lack of efficacy but also increased cardiovascular risk, largely attributed to off-target effects such as hypertension and elevated aldosterone levels.”
“Elevating HDL-C may exert anti-inflammatory effects through enhanced reverse cholesterol transport and other pleiotropic mechanisms, thereby reducing cardiovascular disease risk.”
“Clinicians should remain cautious and consider CETPi investigational until further outcome data are available.”

2. Substantial heterogeneity (I^2 > 90%) was reported in lipid outcomes. The authors are encouraged to

conduct subgroup or meta-regression analyses to explore sources of heterogeneity (e.g., agent generation, baseline lipid levels, trial duration). Since torcetrapib had known off-target toxicity, presenting results excluding early-generation agents could help isolate the true class effect of CETP inhibition.
Response: Thank you for the constructive comment. We acknowledge the high heterogeneity observed in lipid outcome analyses. Subgroup analyses were conducted according to the different CETP inhibitors. However, sensitivity analyses were not feasible due to the limited number of studies per agent. We have added the following discussion:
"Because the included RCTs varied in design, follow-up duration, and outcome definitions, these factors may have contributed to heterogeneity. Sensitivity analyses were not feasible given the limited number of studies available for each agent. Nevertheless, considering the heterogeneity of trial outcomes and the lack of consistent cardiovascular benefit, routine clinical use cannot yet be recommended."

3. Future Research Directions The discussion section would benefit from a more detailed projection of ongoing and future CETPi trials, especially Phase III studies of obicetrapib. Including expected endpoints, population characteristics, and potential design improvements over previous trials would provide readers with a forward-looking perspective. Moreover, recommending functional HDL biomarkers for future research (e.g., cholesterol efflux capacity, apoA-I turnover) would add depth to the mechanistic outlook.
Response: Thank you for this excellent suggestion. The discussion has been expanded as follows:
"In the TANDEM trial, a fixed-dose combination of obicetrapib and ezetimibe achieved an approximately 50% LDL-C reduction over 12 weeks in such patients. The ongoing PREVAIL trial will determine whether this LDL-C lowering translates into fewer cardiovascular events. However, given the mixed outcomes of prior CETPi studies and limited evidence of event reduction, routine clinical use remains premature. Future studies should assess not only lipid changes but also HDL functionality, such as particle composition, cholesterol efflux, and anti-inflammatory properties, to better predict cardiovascular benefit."

Minor Comments
1.Clarify whether the search date "July 10, 2025" refers to the last database update.
Response: Thank you for noting this. The text has been clarified to indicate that this date refers to the last database update.

2. Maintain consistency between "CETPi" and "CETP inhibitors."
Response: Thank you for this suggestion. The term "CETP inhibitors (CETPi)" is now used consistently throughout the manuscript.

3. Standardize lipid reporting units (e.g., consistently use mg/dL or % change).
Response: Thank you for pointing this out. Lipid parameters are now reported consistently in mg/dL or as percentage change, depending on the outcome, for clarity and readability.

4. Verify uniform use of statistical abbreviations (CI, OR, MD).
Response: Thank you for the comment. As also addressed in the Editor's comment, all statistical abbreviations have been standardized and verified throughout the manuscript.

5. Emphasize that no language restrictions were applied to the search (currently mentioned but could be clearer).
Response: Thank you for the suggestion. This clarification has been strengthened in the Methods section.

6. Minor stylistic edits could improve readability (e.g., simplify "demonstrated more encouraging results" to "showed more favorable results").
Response: Response: Thank you for this helpful feedback. Several sentences have been simplified, including the revision of "demonstrated more encouraging results" to "showed more favorable results."

7. Ensure that all abbreviations (MACE, HDL-C, LDL-C, etc.) are defined upon first mention.
Response: Thank you for this reminder. This has been completed as per the Editor's earlier comment.

We once again thank the Associate Editor and Reviewers for their thoughtful and constructive feedback, which has greatly improved the clarity, rigor, and overall quality of our manuscript. All comments have been carefully addressed, and corresponding revisions have been implemented. We believe the revised version presents a clearer and more comprehensive analysis of CETP inhibitors and their clinical implications.
We appreciate your time and consideration and look forward to your favorable assessment of our revised manuscript.
Sincerely,
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