PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness of lipid-lowering therapy on mortality and major adverse cardiovascular event outcomes in patients undergoing percutaneous coronary intervention: a network meta-analysis of randomized controlled trials
AUTHORS	Deng, changjiang; Yan, Ju; Zheng, Ying-Ying; Wu, Ting-Ting; Pan, Ying; Hou, Xian-Geng; Wang, Si-Fan; Sirajidin, Subinur; Aimaitijiang, Mikereyi; Xie, Xiang

VERSION 1 – REVIEW

REVIEWER	Shinke, Toshiro Showa University, Division of Cardiology Department of Medicine
REVIEW RETURNED	05-Feb-2023

GENERAL COMMENTS	Thanks for giving me an opportunity to review the manuscript entitled 'Effectiveness of lipid-lowering therapy on mortality and major adverse cardiovascular event outcomes in patients undergoing percutaneous coronary intervention: a network meta-analysis of randomized controlled trials' by Deng CJ, et al. Overall statements were interesting but there exist some major critical points. Comments to the Author Major comments 1. Targeted goals of the current meta-analysis seems to be ambiguous. It has been repeatedly demonstrated that long-term optimal lipid-lowering therapy is effective in reducing long-term cardiovascular events. Did the authors try to the benefit of icosapent ethyl? 2. The standpoint that long-term application of statins bring potential side effects might not be acceptable in the current guideline directed medical treatment. Of course, we have to perform careful monitoring of side effects. 3. The authors stated all agents were considered to be applied with reasonable doses in this study. What was the retionale of reasonable doses? 4. The authors emphasis the advantage of EPA plus statins. The statistical comparison among the regimens seems not to be robust. Statistical review might be required. 5. The authors mentioned the powerful effect of PCSK9I on reducing LDL-C will increase the risk of intracranial hemorrhage. Please present data in the result and discuss the impact of hemorrhage on mortality. 6. This meta-analysis excluded studies on the preloading application of lipid-lowering drugs before PCI. PCI without

	preloaded lipid-lowering is not the routine clinical practice, so may weaken the value of current results.

REVIEWER	Shihara, Takayuki I Kansai Rosai Hospital, Cardiovascular Center
REVIEW RETURNED	05-Feb-2023

GENERAL COMMENTS	This article is interesting; however, I have some comments. 1. The discussion about PCSK9i was insufficient. The authors should do more discussion about the reason why PCSK9i plus statin reduced the risk of MACEs, but the risk of mortality remained unclear. 2. What is the clinical implication of this study? Judging from this study, what should we do additionally in terms of the lipid-lowering therapy for patients undergoing PCI? The authors should mention this point in the discussion section. 3. Limitations should be mentioned before the conclusion.

REVIEWER	Lee, Zhen-Vin University of Malaya Medical Centre, Cardiology Unit
REVIEW RETURNED	06-Feb-2023

GENERAL COMMENTS	Congratulations to the authors of the manuscript for the great effort. The manuscript however requires minor revision as there are some errors with regard to spelling and grammar.

REVIEWER	Jaiswal, Vikash AMA School of Medicine, Medicine
REVIEW RETURNED	28-May-2023

GENERAL COMMENTS	Effectiveness of lipid-lowering therapy on mortality and major adverse cardiovascular event outcomes in patients undergoing percutaneous coronary intervention: a network meta-analysis of randomized controlled trials Important area to investigate and here are some of my recommendations which i would like to see at the time of revisions. 1: Prospero registration(If not then kindly register it and add in methods section) 2: Include detail search strategy among all databases as an supplement and mention it in methods section. 3: Some of the included studies i see have Statin and some dont. So how will be the result not been biased. Same goes for control group where i see in the tables that some have statin in both arm and no alirocumab, or icosapent ethy. Please check all the studies once inclusion and exclusion criteria carefully. 4: In discussion i dont see any comparison with previous metas how it is different from old ones why those has been excluded?? Discussion must have comparison with all available meta analysis and original trails. So i would recommend to modify and update this as well

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Toshiro Shinke, Showa University
Comments to the Author:
BMJ Open
bmjopen-2022-070827
Thanks for giving me an opportunity to review the manuscript entitled 'Effectiveness of lipid-lowering therapy on mortality and major adverse cardiovascular event outcomes in patients undergoing percutaneous coronary intervention: a network meta-analysis of randomized controlled trials' by Deng CJ, et al. Overall statements were interesting but there exist some major critical points.

Comments to the Author

Major comments
1. Targeted goals of the current meta-analysis seems to be ambiguous. It has been repeatedly demonstrated that long-term optimal lipid-lowering therapy is effective in reducing long-term cardiovascular events. Did the authors try to the benefit of icosapent ethyl?
A: We have mentioned the benefit of icosapent ethyl in the passage (Results and Conclusion: EPA, especially icosapent ethyl, plus statins had a beneficial effect on reducing the risk of MACEs and mortality in post-PCI patients.)

2. The standpoint that long-term application of statins bring potential side effects might not be acceptable in the current guideline directed medical treatment. Of course, we have to perform careful monitoring of side effects.
A: We deeply agree with you that long-term application of statins should be performed careful monitoring of side effects. And in our passage, we
emphasized that PCSK9i plus statins was able to reduce the risk of MACEs, but the risk of mortality remained unclear, which should be more careful for the side effects of drug.

3. The authors stated all agents were considered to be applied with reasonable doses in this study. What was the retionale of reasonable doses?
A: In our manuscript, we analyzed many kinds of statin, such as simvastati、 rosuvastatin or atorvastatin. Like atorvastatin, whose reasonable dose is 10~20 mg/d. Retional doses for each drug are based on literature.

4. The authors emphasis the advantage of EPA plus statins. The statistical comparison among the regimens seems not to be robust. Statistical review might be required.
A: We used network meta-analysis to assess the benefits of different lipid-lowering regimens on the risk of MACEs and mortality in the post-PCI population. The references of relevant systematic reviews and meta-analyses were also searched to avoid omissions. The network meta-analysis refer to this literature(PMID: 34744709; DOI: 10.3389/fphar.2021.713007); In addition, two authors conducted literature retrieval independently, and any conflicts were resolved through discussion with the third author.

5. The authors mentioned the powerful effect of PCSK9I on reducing LDL-C will increase the risk of intracranial hemorrhage. Please present data in the result and discuss the impact of hemorrhage on mortality.
A: We are so sorry for the incorrect conclusion that the powerful effect of PCSK9I on reducing LDL-C will increase the risk of intracranial hemorrhage.There is a passage(DOI: 10.1161/str.52.suppl_1.p623)says that PCSK9i do not increase intracerebral hemorrhage(ICH) risk. PCSK9i may be a preferred lipid-lowering agent class in patients with elevated ICH risk, including

patients with intracerebral hemorrhage or multiple covert cerebral microbleeds.We have revised our manuscript.

6. This meta-analysis excluded studies on the preloading application of lipid-lowering drugs before PCI. PCI without preloaded lipid-lowering is not the routine clinical practice, so may weaken the value of current results.
A: We deeply agree with you that PCI without preloaded lipid-lowering may weaken the value of current results.We would improve our method for including studies on the preloading application of lipid-lowering drugs before PCI.

Reviewer: 2
Dr. Takayuki I shihara, Kansai Rosai Hospital
Comments to the Author:
This article is interesting; however, I have some comments.

1. The discussion about PCSK9i was insufficient. The authors should do more discussion about the reason why PCSK9i plus statin reduced the risk of MACEs, but the risk of mortality remained unclear.
A: Thanks for your opinions, we have revised our manuscript.
Alirocumab and evolumab are both proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i), which can increase the level of LDL receptor in the liver, thus improving the ability of the liver to bind LDL-C and reducing the level of peripheral LDL-C[61]. There was also a synergistic lipid-lowering pharmacological effect when PCSK9i was combined with statins that significantly reduced LDL-C and atherosclerosis event risk; however, there was still controversy regarding the mortality risk reduction[62]. It has been suggested that the powerful effect of PCSK9I on reducing LDL-C predisposes patients to hypocholesterolemia, which will not increase the risk of cerebral hemorrhage, PCSK9i may be a preferred lipid-lowering agent in patients with elevated ICH risk[63-65]. On the other hand, PCSK9i could not reduce serum inflammatory factors, suggesting that it may not reduce the risk of residual inflammation in the post-PCI population[66].

2. What is the clinical implication of this study? Judging from this study, what should we do additionally in terms of the lipid-lowering therapy for patients undergoing PCI? The authors should mention this point in the discussion section.
A: The clinical implication of this study is that there is a consensus on preloading high-dose statins to reduce MACEs in the perioperative period with PCI. However, there is still insufficient evidence for the continued application of lipid-lowering drugs to reduce the risk of long-term MACE and mortality. Our study will assess the benefits of different lipid-lowering regimens on the risk of MACEs and mortality in the post-PCI population by network meta-analysis.

3. Limitations should be mentioned before the conclusion.
A: Thanks for your opinions, we have revised our manuscript.

Reviewer: 3
Dr. Zhen-Vin Lee, University of Malaya Medical Centre
Comments to the Author:
Congratulations to the authors of the manuscript for the great effort. The manuscript however requires minor revision as there are some errors with regard to spelling and grammar.
A: Thanks for your opinions, we have revised our manuscript.

Reviewer: 4
Dr. Vikash Jaiswal, AMA School of Medicine
Comments to the Author:

Effectiveness of lipid-lowering therapy on mortality and major adverse cardiovascular event outcomes in patients undergoing percutaneous coronary intervention: a network meta-analysis of randomized controlled trials

Important area to investigate and here are some of my recommendations which i would like to see at the time of revisions.

1: Prospero registration(If not then kindly register it and add in methods section)
A: Thanks, we have added Prospero registration in methods section.

2: Include detail search strategy among all databases as an supplement and mention it in methods section.
A: Thanks for your opinions, we have added detail search strategy in our methods section of manuscript.

3: Some of the included studies i see have Statin and some dont. So how will be the result not been biased. Same goes for control group where i see in the tables that some have statin in both arm and no alirocumab, or icosapent ethy. Please check all the studies once inclusion and exclusion criteria carefully.
A: Thanks for your opinions, we carefully check all the studies once inclusion and exclusion criteria.We replenished our methods section of manuscript.

4: In discussion i dont see any comparison with previous metas how it is different from old ones why those has been excluded??
Discussion must have comparison with all available meta analysis and original trails. So i would recommend to modify and update this as well
A: Thanks for your opinions, we have revised our disscussion of manuscript.

Reviewer: 1
Competing interests of Reviewer: I understood and have nothing to disclose.

Reviewer: 2
Competing interests of Reviewer: I have nothing to disclose.

Reviewer: 3
Competing interests of Reviewer: None

Reviewer: 4
Competing interests of Reviewer: None

VERSION 2 – REVIEW

REVIEWER	Shinke, Toshiro Showa University, Division of Cardiology Department of Medicine
REVIEW RETURNED	05-Sep-2023

GENERAL COMMENTS	This manuscript has been well revised following the reviewer's comments. This reviewer would suggest it is ready for publication.

REVIEWER	Shihara, Takayuki I Kansai Rosai Hospital, Cardiovascular Center

REVIEW RETURNED	28-Aug-2023

GENERAL COMMENTS	Although I am not satisfied with the content of the discussion section, I have no additional comment.

REVIEWER	Jaiswal, Vikash AMA School of Medicine, Medicine
REVIEW RETURNED	10-Sep-2023

GENERAL COMMENTS	All my recommendations had been implemented and hence I recommend for acceptance. Thank you