PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of Aspirin Use on Clinical Outcomes in Patients With Vasospastic Angina: A Systematic Review and Meta-analysis
AUTHORS	lin, yaowang; chen, yang; yuan, jie; Qin, Haiyan; dong, shaohong; chen, qiuling

VERSION 1 – REVIEW

REVIEWER	Fabien Picard Hopital Cochin, Cardiologie
REVIEW RETURNED	14-Feb-2021

GENERAL COMMENTS	I read with interest the manuscript of Lin et al on the impact of aspirin use on clinical outcomes in patients with vasospastic angina. They performed a systematic review and meta analysis on the impact of aspirin in patients who experienced vasospastic angina and had no significant coronary artery stenosis. This study included 6 studies (4 propensity matched, 1 retrospective and 1 prospective chorots) comprising 3661 patients. They found no difference on outcomes in patients receiving aspirin or not. The authors should be congratulated for their effort in studying an understudied disease. The manuscript respect meta analysis standards. The manuscript could benefit from language editing. I have few comments: Major comments: - In their abstract, the authors talk about lower incidence of MI, higher cardiac death, etc. Please just describe the results: no difference in MACE, MI and cardiac death. This is what the results shows. The very large confidence intervals associated with the results highlight the impossibility to say anything about tendencies. - Same comments for the results and discussion paragraph. - MACE definition: Please state why the authors chose these variables for MACE (cardiac death, acute coronary syndrome, and hospitalization due to unstable angina, percutaneous coronary intervention, symptomatic arrythmia in heart failure, appropriate implantable cardioverter-defibrillator (ICD), and shock). I understand that this was the cumulation of all endpoints described in MACE in the different trials. Nevertheless, this cannot be used like that as some patients might have experienced ICD shock not being reported in the first second third fourth, fifth studies, etc. Standardization of clinical endpoints is of major importance. Please use a more standard definition of MACE and use only the data which are accessible. Minor comments: - Search strategy: do not say various search engines, just state which research databases you used to retrieve the articles

	- Please be more precise on the exact terms used to retrieve data. We should be able to get the exact same number of publications using the same words. - "Two investigators, namely, Lin and Chen, extracted the study data, which have been presented in Table 1". Please state how discrepencies were resolved. - The authors can discuss the recent findings on aspirin in primary prevention patients to parallel with patients with VSA. - One of the problem is that patients with 40% stenosis are deemed to be VSA patients without coronary stenosis but might benefit from aspirin. Please discuss that in the limitations/discussion - Please be more tempered on conclusion - Figures: please indicates which way goes aspirin better

REVIEWER	Marcel Beijk Amsterdam UMC Locatie AMC, Cardiology
REVIEW RETURNED	15-Feb-2021

GENERAL COMMENTS	This meta-analysis evaluates the efficacy of aspirin to prevent cardiovascular disease in vasospastic angina (VSA) patients. Four propensity-matched cohorts, one retrospective analysis, and one prospective multicenter cohort were included in the meta-analysis and the incidence of MACE with follow-up of 1–5 years was investigated. The main finding was that aspirin use was found to have no significant effect on reducing MACE, myocardial infarction, and cardiac death in VSA. A tendency of higher risk of MACE and cardiac death was recognized, but not that of myocardial infarction. The manuscript would likely benefit from professional English editing. Comments: The paper has several major limitations that need clarification for the readers to be able to interpreted the results of this meta-analysis especially which patients were analyzed: 1. The authors should provide insight in how many patients had undergone provocation testing for coronary vasospasm. I assume a substantial amount of patients were diagnosed only based on symptoms. 2. The authors should give insight if only patients with epicardial coronary vasospams were included or also patient with microvascular dysfunction. 3. How many patient included in the meta-analysis had presence of coronary artery disease? As those patients do have an indication for aspirin. Shouldn't these patient be excluded from the meta-analysis? 4. The incidence of the secondary endpoints are very low and to reach a statistical significant difference many patients should be included. VSA patients are often presented at an emergency department with chest pain. Did the authors evaluate hospitalizations for chest pain? Introduction: - The terms MINOCA and INOCA are interchangeable. It is preferred to use INOCA. - What about ANOCA? - What do the authors mean with endothelial dysfunction? Microvessel disease? Data analysis and subgroup study: - 'MACE has been described as cardiac death, acute coronary

syndrome, and hospitalization due to unstable angina, percutaneous coronary intervention, symptomatic arrhythmia in heart failure, appropriate implantable cardioverter-defibrillator (ICD), and shock.' Was this definition applied for this meta-analysis? If so, why did the authors include symptomatic arrhythmia in heart failure for this meta-analysis in the primary endpoint? Were patients with pre-existent heart failure included?
- 'In the case of high heterogeneity (I2 > 50%), subgroup analysis was carried out.' What subgroup analysis did the authors perform?

Results:
- 'All studies except five studies provided the secondary endpoint, with follow-up durations ranging from 1 to 5 years (Table 1)'. What do the authors mean by this, did only one study (1 out of 6) report secondary endpoints? If so, then there is no meta-analysis to be performed for the secondary endpoints. I guess the authors mean that only five studies provided outcomes for secondary endpoint analysis.

Discussion
- 'Coronary artery spasm (CAS) appeared to play a significant role in the pathogenesis of ischemic heart disease, besides acute coronary syndromes (ACS) or chronic coronary syndromes (CCS)'. Where to do the authors refer to?
- 'A common mechanism by which myocardial infarction (MI) or MINOCA manifests by thrombus formation.' This is not a complete sentence.

Figure 1:
- To provide more insight in the included studies, the authors should summarize the reasons for exclusion of the 2414 articles.

Figure 3:
- which subgroup was analyzed?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Fabien Picard, Hopital Cochin
Comments to the Author:
I read with interest the manuscript of Lin et al on the impact of aspirin use on clinical outcomes in patients with vasospastic angina.
They performed a systematic review and meta analysis on the impact of aspirin in patients who experienced vasospastic angina and had no significant coronary artery stenosis. This study included 6 studies (4 propensity matched, 1 retrospective and 1 prospective chorots) comprising 3661 patients. They found no difference on outcomes in patients receiving aspirin or not. The authors should be congratulated for their effort in studying an understudied disease. The manuscript respect meta analysis standards. The manuscript could benefit from language editing.
Response: Thank you for your insight review of my paper. We have revised the paper thoroughly to ensure their corrections, and this manuscript has been re-edited and proofread by a professional editor with Medjaden Bioscience Limited recently.
I have few comments:
Major comments:
- In their abstract, the authors talk about lower incidence of MI, higher cardiac death, etc. Please just describe the results: no difference in MACE, MI and cardiac death. This is what the results shows. The very large confidence intervals associated with the results highlight the impossibility to say anything about tendencies.

Response: First of all, we should apologize for the mistake generated by the previous version of the manuscript. We have revised the sentence in the abstract with your kind advice.

- Same comments for the results and discussion paragraph.

Response: We have revised the sentence in the abstract with your kind advice.

- MACE definition: Please state why the authors chose these variables for MACE (cardiac death, acute coronary syndrome, and hospitalization due to unstable angina, percutaneous coronary intervention, symptomatic arrythmia in heart failure, appropriate implantable cardioverter-defibrillator (ICD), and shock). I understand that this was the cumulation of all endpoints described in MACE in the different trials. Nevertheless, this cannot be used like that as some patients might have experienced ICD shock not being reported in the first second third fourth, fifth studies, etc. Standardization of clinical endpoints is of major importance. Please use a more standard definition of MACE and use only the data which are accessible.

Response: MACE and MI have been defined differently in the included articles. Ascribe to lack of original data, no standard definition of MACE is accessible. Accordingly, we have addressed this as one of the limitations.

Minor comments:

- Search strategy: do not say various search engines, just state which research databases you used to retrieve the articles

 Response: We have revised as your kind suggestion.

- Please be more precise on the exact terms used to retrieve data. We should be able to get the exact same number of publications using the same words.

 Response: We have revised as your kind suggestion.

- "Two investigators, namely, Lin and Chen, extracted the study data, which have been presented in Table 1". Please state how discrepencies were resolved.

 Response: We have revised as your kind suggestion. The study data was independently extracted by two investigators, namely, Lin and Chen, using pre-defined extraction forms and conflict was resolved by a third reviewer.

- The authors can discuss the recent findings on aspirin in primary prevention patients to parallel with patients with VSA.

 Response: We have revised as your kind suggestion. We have added ARRIVE and ASCEND studies in the introduction section.

- One of the problem is that patients with 40% stenosis are deemed to be VSA patients without coronary stenosis but might benefit from aspirin. Please discuss that in the limitations/discussion

 Response: We have revised as your kind suggestion and added this in the limitation section.

- Please be more tempered on conclusion

 Response: We have revised as your kind suggestion.

- Figures: please indicates which way goes aspirin better

 Response: We have revised as your kind suggestion.

Reviewer: 2

Dr. Marcel Beijk, Amsterdam UMC Locatie AMC

Comments to the Author:

This meta-analysis evaluates the efficacy of aspirin to prevent cardiovascular disease in vasospastic angina (VSA) patients. Four propensity-matched cohorts, one retrospective analysis, and one prospective multicenter cohort were included in the meta-analysis and the incidence of MACE with follow-up of 1–5 years was investigated. The main finding was that aspirin use was found to have no significant effect on reducing MACE, myocardial infarction, and cardiac death in VSA. A tendency of higher risk of MACE and cardiac death was recognized, but not that of myocardial infarction.

The manuscript would likely benefit from professional English editing.

Response: Thank you for your insight review of my paper. We have revised the paper thoroughly to ensure their corrections, and this manuscript has been re-edited and proofread by a professional editor with Medjaden Bioscience Limited recently.

Comments:

The paper has several major limitations that need clarification for the readers to be able to interpreted the results of this meta-analysis especially which patients were analyzed:

1. The authors should provide insight in how many patients had undergone provocation testing for coronary vasospasm. I assume a substantial amount of patients were diagnosed only based on symptoms.

Response: 4 studies underwent coronary provocation test, except for 1 study (Seong-Sik Cho, 2019) receiving ECG provocation test.

2. The authors should give insight if only patients with epicardial coronary vasospams were included or also patient with microvascular dysfunction.

Response: All the patients with epicardial coronary vasospams diagnosed by provocation test were included in this study.

3. How many patient included in the meta-analysis had presence of coronary artery disease? As those patients do have an indication for aspirin. Shouldn't these patient be excluded from the meta-analysis?

Response: Patients with significant stenosis (≥ 50%) were excluded in this meta-analysis.

4. The incidence of the secondary endpoints are very low and to reach a statistical significant difference many patients should be included. VSA patients are often presented at an emergency department with chest pain. Did the authors evaluate hospitalizations for chest pain?

Response: Thank you for insight review of my paper. Previous Asian studies of patients have showed that the prevalence of CAS is around 40-50% in patients with angina and 57% in patients with ACS (Hung MJ, etc. AM J CARDIOL. 2006). In non-obstructive coronary arteries (MINOCA) patients, the positive of provocative test is about 46% (Montone RA, etc. EUR HEART J. 2018). Further studies evaluating hospitalizations for chest pain are required to improve the diagnosis of CAS.

Introduction:

- The terms MINOCA and INOCA are interchangeable. It is preferred to use INOCA.

Response: We have deleted MINOCA in the introduction section with your suggestion.

- What about ANOCA?

Response: Thank you for review of my manuscript. We have checked carefully and no ANOCA was found in the manuscript

- What do the authors mean with endothelial dysfunction? Microvessel disease?

Response: Endothelial dysfunction is commonly associated with decreased NO bioavailability, which tends to affect more CAS patients than CAD.

Data analysis and subgroup study:

- 'MACE has been described as cardiac death, acute coronary syndrome, and hospitalization due to unstable angina, percutaneous coronary intervention, symptomatic arrhythmia in heart failure, appropriate implantable cardioverter-defibrillator (ICD), and shock.' Was this definition applied for this meta-analysis? If so, why did the authors include symptomatic arrhythmia in heart failure for this meta-analysis in the primary endpoint? Were patients with pre-existent heart failure included?

Response: The definition of MACE was applied for this meta-analysis. we should apologize for the mistake generated by the previous version of the manuscript. The correct definition of MACE included symptomatic arrhythmia, no heart failure.

- 'In the case of high heterogeneity (I2 > 50%), subgroup analysis was carried out.' What subgroup analysis did the authors perform?

Response: MACE incidence: OR = 0.90, 95% CI: 0.55–1.68, p = 0.829, I2 = 82.2% . The subgroup analysis of MACE: OR = 1.09, 95% CI: 0.81–1.47, I2 = 0%.

Results:

- 'All studies except five studies provided the secondary endpoint, with follow-up durations ranging from 1 to 5 years (Table 1)'. What do the authors mean by this, did only one study (1 out of 6) report secondary endpoints? If so, then there is no meta-analysis to be performed for the secondary endpoints. I guess the authors mean that only five studies provided outcomes for secondary endpoint analysis.

Response:Thank you for your insight review of my manuscript. We have revised the sentence carefully with your direction.

Discussion

- 'Coronary artery spasm (CAS) appeared to play a significant role in the pathogenesis of ischemic heart disease, besides acute coronary syndromes (ACS) or chronic coronary syndromes (CCS)'. Where to do the authors refer to?

Response: Coronary artery spasm (CAS) appeared to play a significant role in the pathogenesis of ischemic heart disease including acute coronary syndromes (ACS) and chronic coronary syndromes (CCS).

- 'A common mechanism by which myocardial infarction (MI) or MINOCA manifests by thrombus formation.' This is not a complete sentence.

Response: A common mechanism by which myocardial infarction (MI) or MINOCA manifests by platelet aggregation, which leads to coronary thrombus formation.

Figure 1:

- To provide more insight in the included studies, the authors should summarize the reasons for exclusion of the 2414 articles.

Response: We have revised the Figure 1 with your suggestion.

Figure 3:

- which subgroup was analyzed?

Response: Figure 3 was the subgroup of MACE。

VERSION 2 – REVIEW

REVIEWER	Fabien Picard Hopital Cochin, Cardiologie
REVIEW RETURNED	10-Jun-2021

GENERAL COMMENTS	I read the reply and the new version of the manuscript. Unfortunately, some points still need to be addressed - There still are some language mistake and I wonder how was language editing performed - In the abstract, the authors are still talking about tendencies: "Aspirin use was tended to be linked with lower incidence of myocardial infarction (OR = 0.62, 95% CI: 0.09–4.36, p = 0.615, I2 = 73.8%) and higher incidence of cardiac death (OR = 1.73, 95% CI: 0.61–4.94, p = 0.444, I2 = 0%) during follow-up, but with no significant difference between-group." there is no statistical relationship and no tendency - Still same thing for results and discussion

REVIEWER	Marcel Beijk Amsterdam UMC Locatie AMC, Cardiology
REVIEW RETURNED	03-Jun-2021

GENERAL COMMENTS	Still, the manuscript could benefit from language editing. The comments raised by the reviewers are not adequately addressed. Moreover, some answers are incorrect. Example: Comment made by the reviewer: 3. How many patient included in the meta-analysis had presence of coronary artery disease? As those patients do have an indication for aspirin. Shouldn't these patient be excluded from the meta-analysis? Response: Patients with significant stenosis (≥ 50%) were excluded in this meta-analysis. Remark by the reviewer: Kim, et al (2013) had a cut of value of <70% stenosis to exclude patients.

Reviewer: 2

Dr. Marcel Beijk, Amsterdam UMC Locatie AMC

Comments to the Author:

Still, the manuscript could benefit from language editing.

Response: Thank you for your insightful review of our manuscript. We have revised the paper thoroughly to ensure language corrections. This manuscript has been edited and by a professional editor at *Medjaden* Bioscience Limited.

The comments raised by the reviewers are not adequatly addressed. Moreover, some answers are incorrect.

Example:

Comment made by the reviewer: 3. How many patient included in the meta-analysis had presence of coronary artery disease? As those patients do have an indication for aspirin. Shouldn't these patient be excluded from the meta-analysis? Response: Patients with significant stenosis (≥ 50%) were excluded in this meta-analysis. Remark by the reviewer: Kim *et al.* (2013) had a cut of value of < 70% stenosis for excluding patients.

Response: Thank you for your insightful review of our manuscript. According to the study by Kim *et al.* (2013), insignificant coronary artery stenosis was defined as less than 70% stenosis in one or more epicardial coronary arteries. Among the included patients, very few had stenosis between 50% to 70%, and this population should benefit from aspirin. However, the use of aspirin is still not linked with lower incidence of MACE. We added Figure 3A as subgroup study of MACE (excluded Kim. 2013) demonstrating this finding.

Reviewer: 1

Dr. Fabien Picard, Hopital Cochin

Comments to the Author:

I read the reply and the new version of the manuscript.

Unfortunately, some points still need to be addressed

- There still are some language mistake and I wonder how was language editing performed

Response: Thank you for your insightful review of our manuscript. We have revised the paper thoroughly to ensure language corrections. This manuscript has been edited and by a professional editor at *Medjaden* Bioscience Limited.

- In the abstract, the authors are still talking about tendencies: "Aspirin use was tended to be linked with lower incidence of myocardial infarction (OR = 0.62, 95% CI: 0.09–4.36, p = 0.615, I2 = 73.8%) and higher incidence of cardiac death (OR = 1.73, 95% CI: 0.61–4.94, p = 0.444, I2 = 0%) during follow-up, but with no significant difference between-group." there is no statistical relationship and no tendency

- Still same thing for results and discussion

Response: We apologize for these mistakes in the previous version of the manuscript. We have revised the sentence in the abstract, result and discussion accordingly

VERSION 3 – REVIEW

REVIEWER	Fabien Picard Hopital Cochin, Cardiologie
REVIEW RETURNED	28-Jun-2021

GENERAL COMMENTS	All the comments have been adressed

REVIEWER	Marcel Beijk Amsterdam UMC Locatie AMC, Cardiology
REVIEW RETURNED	28-Jun-2021

GENERAL COMMENTS	I have read the reply and the revised manuscript. - still the language could be improved. - overall the manuscript is weak regarding the accuracy in the text, description of included meta-analysis, description of patients characateristics, and the lack on information about the safety (bleeding events).

VERSION 3 – AUTHOR RESPONSE

Reviewer: 1

Dr. Fabien Picard, Hopital Cochin

Comments to the Author:

All the comments have been addressed

Reviewer: 2

Dr. Marcel Beijk, Amsterdam UMC Locatie AMC

Comments to the Author:

I have read the reply and the revised manuscript.

- still the language could be improved.

Response: We apologize for these language mistakes in the previous version of the manuscript. We have revised the paper thoroughly to ensure language corrections. This manuscript has been edited and by a professional editor, a native English speaking colleague at *Medjaden* Bioscience Limited.

- overall the manuscript is weak regarding the accuracy in the text, description of included meta-analysis, description of patients characaceristics, and the lack on information about the safety (bleeding events).

Response: Thank you for your insightful review of our manuscript. We have started to rigorously conducted a randomized controlled study to further confirm the result of this meta-analysis.