

**Re: World Journal of Diabetes (Manuscript ID: 52045)**

**Title: Long-term effect of clopidogrel in patients with and without diabetes: A systematic review and meta-analysis of randomized controlled trials**

Please find our point-by-point responses to each of the reviewers' comments and suggestions below, which we feel have helped to substantially improve the work. The major revisions described below have been marked in red in the revised manuscript. We appreciate the editor and reviewers' thorough work in reviewing our manuscript, and hope that our corrections will meet with your approval. Thank you very much for your helpful comments and suggestions.

**Response to Reviewer #1:**

**Comment 1:**

A major problem I found in this manuscript is the level of usage of English language. Few examples of bad usage of English Language: Abstract: First Line: Diabetic patients were reported..... Core Tip The evidence derived .....the effect of clopidogrel is weaken with the present of diabetes is still..... As far as we know.....by the presence of diabetes Introduction Subgroup data .....diabetes weaken the effect of clopidogrel on recurrent cardiovascular events and all-cause death..... The poor usage of English Language as shown above and in some parts of the manuscript, made some parts of the manuscript not to be

properly understood. Authors are therefore advised to edit their entire manuscript for English Language, perhaps making use of a native English speaker.

**Response:**

We apologize for the unclear descriptions in the original manuscript. We have carefully revised the relevant paragraphs. In addition, we used the editorial service of a professional English-language editing company (Edanz Group Ltd., <http://www.edanzediting.com>) to improve the language of our manuscript. We hope you agree that the language is now acceptable. The following figure is the editing certification provided by a native English-speaking science editor.



## Certificate of Editing

Edited provisional title  
Long-term effect of clopidogrel in patients with and without diabetes:  
A systematic review and meta-analysis of randomized controlled  
trials

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Date Completed  
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While this certificate confirms the authors have used Edanz's editing services, we cannot guarantee that additional changes have not been made after our edits.

**Comment 2:**

Abstract: Going by the title and the aim of this review 'to systematically evaluate the efficacy of clopidogrel in treating acute coronary or ischemic stroke among diabetic

and non-diabetic patients', it would have been nice if a group that received clopidogrel alone was included in the study.

**Response:**

Thanks for your comments. We agree with you that if we can include a group that received clopidogrel alone in this meta-analysis might provide more information for authors. However, as aspirin is the first choice antiplatelet therapy for patients with ischemic cardiovascular disease according to current guidelines, few randomized controlled trials were performed to compare the efficacy of clopidogrel alone with blank placebo or aspirin alone.

**Comment 3:**

The year range the authors covered in the literature search from the indexing data bases was not stated in the abstract.

**Response:**

Thanks. According to your suggestion, we have added the year range of the literature search in the abstract (**Page 3, Line 7**).

**Comment 4:**

The use of the word 'diabetics' as seen in the abstract and in different parts of the manuscript should be corrected as it is no longer an acceptable terminology. Suggest to correct it to 'people with diabetes mellitus'.

**Response:**

Accepted. "Diabetics" throughout this manuscript has been corrected to "patients with diabetes mellitus".

**Comment 5:**

L11 and L16, p values of 0.26 and 0.74 (at an alpha value of 0.05 that was set as the threshold for statistical significance) cannot be considered to be significant. Authors are advised to recheck.

**Response:**

Thank you for this comment. We are sorry for this confusion. Actually, 0.26 and 0.74 are the *P* values for the heterogeneity statistics ( $I^2$ ), which indicate no evidence of heterogeneity across trials in our meta-analyses. In the revised manuscript, the *P* values for HRs have been added in the Abstract and the Results, and we hope the description is clear and understandable (**Page 3, Lines 17 to 19; Page 10, Lines 4 to 6, and Lines 18-19**).

**Comment 6:**

Introduction Page 8, Undefined abbreviations such as: 'HR' and 'CI' should be written in full before abbreviating them for clarity of presentation. Again, P values of 0.26 and 0.74 cannot be considered to be statistically significant.

**Response:**

Thanks again. The abbreviations of "HR" and "CI" have been added in the revised manuscript (**Page 8, Line 23**). Besides, 0.26 and 0.74 are the *P* values for the

heterogeneity statistics ( $I^2$ ), which indicate no evidence of heterogeneity across trials in our meta-analyses. In the revised manuscript, the  $P$  values for HRs have been added in the Abstract and the Results, and we hope the description is clear and understandable (**Page 3, Lines 17 to 19; Page 10, Lines 4 to 6, and Lines 18-19**).

**Comment 7:**

Page 10, consider to define 'STEMI' before abbreviating it. Results Suggest to correct the numbering of the Tables. The second 'Table 1' should be 'Table 2'

**Response:**

The abbreviation of "STEMI" has been added in the revised manuscript (**Page 11, Lines 7 to 8**). We are sorry for that there are two different "Table 1" in this manuscript, because we uploaded a separate word file including a wrong Table 1 to the manuscript system. In this revised manuscript, we have deleted the wrong Table 1 from our manuscript.

**Response to Reviewer #2:**

**Comment:**

The present manuscript by Liana L, et al. a Systemic Review and Meta-analysis on the dual antiplatelet treatment of diabetes people with ischemic cardiovascular disease is very interesting from a clinical practice point of view. I recommend its publication in the WDJ.

**Response:**

Thank you so much for your favorable comments.

**Response to Reviewer #3:**

**Comment 1:**

This work is not presently organized as a scientific manuscript. The background for this study is provided in the Discussion, paragraph 3. This information should be moved to the Introduction. The authors can then provide a hypothesis for this study. In the present Introduction, the authors begin with the phrase “Recent studies”, but reference 7 is from 2012.

**Response:**

Thank you so much for your comments. According to your suggestion, we have moved the third paragraph in the Discussion to the Introduction (**Page 6, Lines 12 to 22**). We also proposed a hypothesis for this meta-analysis in the Introduction (**Page 7, Lines 4 to 8**). Additionally, “Recent studies” has been changed to “Previous studies”.

**Comment 2:**

In the Introduction, the authors need to be clear how their study will provide information that adds to the present literature (e.g. References 10, 11, and 12).

**Response:**

Thanks. We have added a sentence Introduction (**Page 7, Lines 4 to 5**) in the Introduction to indicate that this meta-analysis will provide additional knowledge to the current literature.

**Comment 3:**

If a studied effect does not reach statistical significance, then it cannot be used to form a conclusion. If the authors believe that the study size is too small, then they should state that. The phrase “was lessened in diabetics” is incorrect and should not be used. In the Results, under “Effect of clopidogrel by diabetes status”, the authors state “significantly lowered the risk”, but they provide a p-value of 0.26. In the next sentence of this section, the authors provide a statement based on a p-value of 0.74.

**Response:**

Thank you so much for these helpful comments. According to your suggestion, we have revised our conclusion as “The benefit effect of clopidogrel added to aspirin in patients with DM was lower than that in patients without DM, although the modifying effect of DM did not reach significance”, and the “was lessened in diabetics” has been changed to “was lower than”. Besides, 0.26 and 0.74 are the *P* values for the heterogeneity statistics ( $I^2$ ), which indicate no evidence of heterogeneity across trials in our meta-analyses. In the revised manuscript, the *P* values for HRs have been added in the Abstract and the Results, and we hope the description is clear and understandable (**Page 3, Lines 17 to 19; Page 10, Lines 4 to 6, and Lines 18-19**).

**Comment 4:**

In Discussion, the authors state that the results of Reference 7 are “not consistent with our findings”. Results presented from Reference 7 are with regards to 1-year all-cause death and cardiovascular death. The present authors however in Table 1 have included studies of patients with “high-risk TIA” (Chance 2013 and Point 2018), “multiple risk factors” (Charism 2006), and “those would undergo elective PCI (? what does this mean?)” (Credo 2002). It is unclear how these studies contribute to an understanding of 1-year cardiovascular death when compared to Reference 7 (in which subjects were enrolled for that study after a myocardial infarction). These are clearly different study groups.

**Response:**

Thanks for your comments. Firstly, “those would undergo elective PCI” means patients with symptomatic coronary artery disease who have been referred for a planned percutaneous coronary intervention. Secondly, we agree with you that in participants included in this Reference-study and those included in our meta-analysis are different, therefore, we have revised the relevant paragraph in the Discussion (Page 12, Lines 1 to 10).

**Comment 5:**

In Discussion, under limitations. It is unclear whether the six studies included in this present analysis contained patients with poorly controlled diabetes. Were Hemoglobin A1C levels provided for the diabetic subjects in these six studies? Is it

not likely that clopidogrel may not be as effective in individuals with poorly controlled diabetes?

**Response:**

Thank you for your professional comments. We have read these studies carefully, unfortunately, the data on HbA<sub>1C</sub> levels and the percentages of poorly controlled diabetes were not provided in these studies.

**Comment 6:**

In the Introduction the authors use the sentence “effect of clopidogrel is weakened with the presence of diabetes is still limited and unsummarized”. I have no idea what this means. I would suggest obtaining an English consultation.

**Response:**

We apologize for the unclear descriptions in the original manuscript. We have carefully revised the relevant paragraphs. This sentence has been modified to “However, the long-term effects of clopidogrel in patients with and without DM have not been systematically reviewed. Therefore, we hypothesized that the presence of DM modifies the long-term efficacy of clopidogrel for a reduction in cardiovascular risk, and we performed a systematic review and meta-analysis to test this hypothesis.” (**Page 7, Lines 4 to 8**). In addition, we used the editorial service of a professional English-language editing company (Edanz Group Ltd., <http://www.edanzediting.com>) to improve the language of our manuscript. We hope

you agree that the language is now acceptable. The following figure is the editing certification provided by a native English-speaking science editor.



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Date Completed  
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### **Comment 7:**

When the authors use the word "weaken", I believe that they mean "reduce".

### **Response:**

Thanks. We have avoided using the word "weaken" in our revised manuscript, and adopted "reduce" or "reduced" to replace it.

### **Comment 8:**

There are two separate "Table 1". The second Table 1 should be included in the Results section and is not needed as a separate Table.

### **Response:**

We are sorry for that there are two different “Table 1” in this manuscript, because we uploaded a separate word file including a wrong Table 1 to the manuscript system by mistake. In this revised manuscript, we have deleted the wrong Table 1 from our manuscript.

**Comment 9:**

Table 2 is not needed. Exclusion criteria can be summarized in Methods.

**Response:**

Thanks for your comments. However, the reasons for excluding studies should be summarized in the Results according to Cochrane Guidelines.

**Comment 10:**

First Table 1 and Table 3 are repetitive.

**Response:**

We are sorry for that there are two different “Table 1” in this manuscript, because we uploaded a separate word file including a wrong Table 1 (the repetitive table) to the manuscript system. In this revised manuscript, we have deleted the wrong Table 1 from our manuscript.