PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Predicting the risk of stroke among patients with type 2 diabetes: A systematic review and meta-analysis of C-statistics
AUTHORS	Chowdhury, Mohammad; Yeasmin, Fahmida; Rabi, Doreen; Ronksley, Paul; Turin, Tanvir

VERSION 1 - REVIEW

REVIEWER	Aladeen Alloubani King Hussein Cancer Center, Jordan
REVIEW RETURNED	19-Aug-2018

GENERAL COMMENTS	Thanks for giving me the opportunity to review this manuscript. The paper is well written and covers a topic of high importance. The subject matter is timely and a current "hot topic." While the title is of interest to readers of this journal, the content of the paper falls short of delivering on the promise of the title. Notably, the paper title implies content includes the Predicting the risk of stroke among patients with diabetes. Unfortunately, the strategies in the paper are derived from a biased analysis. In the case of stroke risk factors, many factors outside the scope of the reviewed literature potentially influence this outcome. As the literature reviewed only includes articles studying diabetes, risk prediction with specific names of known risk scores and stroke, bias not identified in the manuscript is introduced. For example, bias is introduced by excluding research with an intervention, and when authors fail to consider or mention that risk factors are influenced by other non-intervention or was any other cardiovascular conditions characteristics. However, this implies that the conceptual basis for the study (an intervention is needed) is limited, but this fact is never stated in the article. The issue of study internal validity is of significant importance because it determines the degree to which the results should guide future practice, as well as the determination that the results of the study are not publishable. Internal validity is of greatest concern when implications of the study imply findings are the best solution. The manuscript should have included mention of patient and intervention factor's contributing (or potentially contributing) to patient and outcomes, acknowledgment of the limited (biased) theoretical framework used to in the literature review. Additionally, there are several claims made in the abstract and manuscript that are must be supported by evidence.

	Other comments: • I could advise (but not require) improving the abstract to identify more of the results obtained, as many healthcare workers will only read the abstract to see if reading further is indicated. • Please clarify the inclusion criteria. • I note many of your references are old, and although I use Wikipedia regularly as a first point of reference, I don't believe it should be used in journal manuscripts. You should use primary sources only (generally not older than 5 years). • Moreover, my review encourages your research group to review the feature articles in an issue or two of the BMJ Open. Such a review may provide additional insights regarding the tone and flow of an accepted paper. Good Luck!

REVIEWER	Prof Antonino Tuttolomondo, MD, PhD Internal Medicine and Stroke Ward Unit, University of Palermo, Italy
REVIEW RETURNED	15-Sep-2018

GENERAL COMMENTS	Chowdhury and coworkers conducted a systematic review of the literature on available stroke prediction models specifically developed or validated on diabetic patients and assess their predictive performance through meta-analysis. They evaluated 21,479 relevant papers and finally yielded 24 stroke prediction models, of which 19 were specifically developed for patients with diabetes and 5 were developed in general populations but validated in patients with diabetes. Authors concluded that overall, performance of the stroke prediction models was not satisfactory and that research is needed to identify new risk factors with high associated relative risk that add large predictive ability over and above currently used factors to improve the currently available prediction models. This is a very interesting and well conducted review with some original conclusions I have only minor comment to do: Discussion Authors should add a brief sentence on discussion sentence about the possible role of stroke prediction models also in the clinical context of some genetic disease that encompass stroke as possible clinical manifestation and they should add these citations on their reference section • Neurological complications of Anderson-Fabry disease. Tuttolomondo A, Pecoraro R, Simonetta I, Miceli S, Arnao V, Licata G, Pinto A. Curr Pharm Des. 2013;19(33):6014-30. Review. • Anderson-Fabry disease: a multiorgan disease. Tuttolomondo A, Pecoraro R, Simonetta I, Miceli S, Pinto A, Licata G. Curr Pharm Des. 2013;19(33):5974-96 • Tuttolomondo A, Di Sciacca R, Di Raimondo D, Pedone C, La Placa S, Pinto A, Licata G.Effects of clinical and laboratory variables and of pretreatment with cardiovascular drugs in acute ischaemic stroke: a retrospective chart review from the GIFA study.Int J Cardiol. 2011 Sep 15;151(3):318-22.

REVIEWER	Dr Pappachan M Joseph New Cross Hospital, United Kingdom
REVIEW RETURNED	17-Sep-2018

GENERAL COMMENTS	Comments to the Authors General Comments: The manuscript entitled: “Predicting the risk of stroke among patients with diabetes: A systematic review and meta-analysis of C-statistics; bmjopen-2018-025579” was read with much interest. This paper is good attempt to address this issue prediction of stroke risk factors in diabetes to the worldwide audience. However, there are some technical and language errors that should be rectified to improve the quality of the paper as pointed out below. Specific Comments: Title: Metaanalysis is better written as meta-analysis. Article summary: The first sentence about the comprehensiveness of the review should be weakened as the review is not that robust (search in only 3 databases that includes both Medline and PubMed). Abstract: This section seems appropriate. Introduction: Introduction is written well although there are occasional minor syntax errors in the section and others that need rectification. For e.g., page 7: the sentence “People with diabetes…. without diabetes” will not convey the right meaning the authors meant. Methods: Authors need to explain why the language limit was applied and why both Medline and PubMed were searched (un-necessary duplication of results). It is also worth mentioning reasons for exclusion of some of the studies (12 as per your report) mentioned in the qualitative synthesis are excluded from quantitative synthesis. Results: I am not convinced about the correctness of the way the authors excluded duplicates from the 3 databases as Medline and PubMed should have had similar citations mostly (Fig 1 PRISMA diagram). Please also explain all the abbreviations in the tables in the title/ bottom of the table (for e.g., I didn’t understand what you meant by NR). Discussion: As mentioned above, the claim about the comprehensiveness of the study should be weekend in the discussion. References: this section seems appropriate to me.

REVIEWER	Dr Alice Richardson Australian National University, Australia
REVIEW RETURNED	11-Dec-2018

GENERAL COMMENTS	This paper consists of a systematic review and meta-analysis of the literature on predicting the risk of stroke among patients with diabetes. On reading it through I was left with the impression that this is a useful contribution to knowledge for a specific kind of statistical tool that generates C-statistics (AUROCs) as its main measure of effect. The review appears to be thorough and to have been conducted according to guidelines. My main concern is around Figures S1 and S2. Both funnel plots look decidedly unsatisfactory, with most (Fig S2) or all (Fig S1)

	points outside the funnel. The authors should comment more fully on the patterns observed here, and explain why they think that these patterns are not a limitation on the meta-analyses performed. Secondly, the authors are a little too keen to dismiss a p-value of 0.057 (page 16 line 16) as non-significant. They should rewrite the decision making here to draw attention to the fact that the p-value is very close to the usual cutoff for statistical significance, and they should comment on the clinical significance (or non-significance) of the result. Overall I am recommending that the paper undergo these minor revisions and be resubmitted. Typos: Page 14 line 36: in diabetes not is diabetes

VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 1

Reviewer Name: Aladeen Alloubani

Institution and Country: King Hussein Cancer Center, Jordan

Please state any competing interests or state ‘None declared’: None declared

Comment: Thanks for giving me the opportunity to review this manuscript.

The paper is well written and covers a topic of high importance. The subject matter is timely and a current "hot topic." While the title is of interest to readers of this journal, the content of the paper falls short of delivering on the promise of the title. Notably, the paper title implies content includes the Predicting the risk of stroke among patients with diabetes. Unfortunately, the strategies in the paper are derived from a biased analysis.

In the case of stroke risk factors, many factors outside the scope of the reviewed literature potentially influence this outcome. As the literature reviewed only includes articles studying diabetes, risk prediction with specific names of known risk scores and stroke, bias not identified in the manuscript is introduced. For example, bias is introduced by excluding research with an intervention, and when authors fail to consider or mention that risk factors are influenced by other non-intervention or was any other cardiovascular conditions characteristics. However, this implies that the conceptual basis for the study (an intervention is needed) is limited, but this fact is never stated in the article.

Response: Thank you for your comments. We would like to point out that the objective of this manuscript was to identify all stroke risk prediction models developed or validated in diabetes patients through a comprehensive systematic review and then evaluate the model performance of these models through meta-analysis. We acknowledge that there are other prediction models for stroke that were developed on patients with other potential risk factors (e.g., hypertensive patients). Inclusion of all stroke prediction models developed on patients with all of these different risk factors for stroke would have made the study extremely large to accommodate in a single article. Considering this, inclusion of stroke prediction models developed on patients with different risk factors for stroke was

out of the scope of this review in our opinions. Rather, we choose to focus stroke prediction models within diabetes patients in this paper to provide the readers with a clear and focused insight.

We acknowledge that the inclusion of all stroke prediction models developed on the patients with all the potential risk factors for stroke could potentially improve the generalizability of our findings, however, it would have also increased the amount of between study heterogeneity that exists within these models making the pooled estimates more difficult to interpret.

Given that this is an important area for future work to understand the differential predictive ability of these models if we had looked at stroke prediction models developed on patients with different risk factors, we have included text within our manuscript to highlight this point. Specifically, we state:

"In this paper, we only considered studies that developed or validated stroke prediction models within diabetes patients. While prediction models for stroke have been developed for patients with other potential risk factors (e.g. hypertensive patients), we felt that an exploration of a broad range of risk factors was outside the scope of this review. Though the inclusion of all stroke prediction models (regardless of the underlying risk factor(s)) could potentially improve the generalizability of our findings, it would have also increased the amount of between study heterogeneity that exists within these models making the pooled estimates more difficult to interpret."

(Please see revised version of the manuscript, "Discussion" section, Page 19, Red Colored texts)

Comment: The issue of study internal validity is of significant importance because it determines the degree to which the results should guide future practice, as well as the determination that the results of the study are not publishable. Internal validity is of greatest concern when implications of the study imply findings are the best solution.

Response: Thank you so much for your comment. We acknowledge the importance of internal validation. However, we would like to state here that once a model is developed, its performance in general is assessed through an internal validation. The reported C-statistics in Table 1 and Table 3 are mostly derived from the internal validations of the models. For our review, where the study objective was to assess performance of stroke prediction models, we felt external validation was more important than internal validation. As we know, reliability and acceptability of a prediction model largely depends on how well it performs in a validation cohort, outside of the derivation cohort where the model was developed. Internal validation of prediction models are often not sufficient for generalizability, and external validation is necessary before implementing prediction models in clinical practice. To this end, in this study, we have focused on external validation rather than internal validation.

Comment: The manuscript should have included mention of patient and intervention factor's contributing (or potentially contributing) to patient and outcomes, acknowledgment of the limited (biased) theoretical framework used to in the literature review. Additionally, there are several claims made in the abstract and manuscript that are must be supported by evidence.

Response: We would like to clarify that our systematic review and meta-analysis was conducted at the study level. While there are significant differences in patient characteristics across the included studies, we used random effects models, and meta regression to examine between-study differences. We found no factors that explained the heterogeneity but recognize the need for future studies to explore reasons for the differences in model performance we observed.

Other comments:

Comment: I could advise (but not require) improving the abstract to identify more of the results obtained, as many healthcare workers will only read the abstract to see if reading further is indicated.

Response: Thank you so much for your comment. We now have updated the abstract and have followed PRISMA to improve its transparency.

(Please see the revised abstract, Page 3 and 4, Red Colored texts)

Comment: Please clarify the inclusion criteria.

Response: We have now clarified the inclusion criteria in the methods section. This includes type 2 diabetes.

Comment: I note many of your references are old, and although I use Wikipedia regularly as a first point of reference, I don't believe it should be used in journal manuscripts. You should use primary sources only (generally not older than 5 years).

Response: As suggested, we have updated a few of the references. However, we have always referenced the original source of these findings as do the more recent papers in this field.

(Please see revised version of the manuscript, “Reference” section, Pages 21 - 31)

Comment: Moreover, my review encourages your research group to review the feature articles in an issue or two of the BMJ Open. Such a review may provide additional insights regarding the tone and flow of an accepted paper.

Response: Thank you so much for your comment. We have gone through a few of the review articles published in BMJ Open to get a better sense of the tone and flow of an accepted paper and have revised our manuscript accordingly. As suggested by the editorial board, we have made edits throughout the manuscript to address this concern and feel the flow of this paper has improved substantially.

Reviewer: 2

Reviewer Name: Prof Antonino Tuttolomondo, MD, PhD

Institution and Country: Internal Medicine and Stroke Ward Unit, University of Palermo, Italy

Please state any competing interests or state ‘None declared’: None declared

Comment: Chowdhury and coworkers conducted a systematic review of the literature on available stroke prediction models specifically developed or validated on diabetic patients and assess their predictive performance through meta-analysis.

They evaluated 21,479 relevant papers and finally yielded 24 stroke prediction models, of

which 19 were specifically developed for patients with diabetes and 5 were developed in general

populations but validated in patients with diabetes. Authors concluded that overall, performance of the stroke prediction models was not satisfactory and that research is needed to identify new risk factors

with high associated relative risk that add large predictive ability over and above currently used factors to improve the currently available prediction models.

This is a very interesting and well conducted review with some original conclusions

Response: Thank you so much for your comment.

Comment: I have only minor comment to do:

Discussion

Authors should add a brief sentence on discussion sentence about the possible role of stroke prediction models also in the clinical context of some genetic disease that encompass stroke as possible clinical manifestation and they should add these citations on their reference section

- Neurological complications of Anderson-Fabry disease. Tuttolomondo A, Pecoraro R, Simonetta I, Miceli S, Arnao V, Licata G, Pinto A. Curr Pharm Des. 2013;19(33):6014-30. Review.

- Anderson-Fabry disease: a multiorgan disease. Tuttolomondo A, Pecoraro R, Simonetta I, Miceli S, Pinto A, Licata G. Curr Pharm Des. 2013;19(33):5974-96

- Tuttolomondo A, Di Sciacca R, Di Raimondo D, Pedone C, La Placa S, Pinto A, Licata G.Effects of clinical and laboratory variables and of pretreatment with cardiovascular drugs in acute ischaemic stroke: a retrospective chart review from the GIFA study.Int J Cardiol. 2011 Sep 15;151(3):318-22.

Response: As suggested by the reviewer, we have added the following sentences to the introduction section to describe the role of stroke prediction models and risk factors for stroke prediction models including genetic components.

“Prediction of stroke is important for a number of reasons: to detect or screen high-risk subjects in order to prevent developing stroke through early interventions, to facilitate patient-doctor communication based on more objective information, and to help patients make an informed choice regarding their treatment.”

“Risk factors for stroke include lifestyle-related factors10, 11, predisposing medical conditions10, 12, specific genetic diseases13, 14, as well as socio-demographic factors11, 12”

(Please see revised version of the manuscript, “Introduction” section, Page 8, Red Colored texts)

Reviewer: 3

Reviewer Name: Dr Pappachan M Joseph

Institution and Country: New Cross Hospital, United Kingdom

Please state any competing interests or state ‘None declared’: None declared

General Comments:

The manuscript entitled: “Predicting the risk of stroke among patients with diabetes: A systematic review and meta-analysis of C-statistics; bmjopen-2018-025579” was read with much interest. This

paper is good attempt to address this issue prediction of stroke risk factors in diabetes to the worldwide audience.

Response: Thank you so much for your comment.

Comment: However, there are some technical and language errors that should be rectified to improve the quality of the paper as pointed out below.

Specific Comments:

Title: Metaanalysis is better written as meta-analysis.

Response: Thank you for identifying this error, we have made the correction accordingly.

(Please see the revised title)

Comment: Article summary: The first sentence about the comprehensiveness of the review should be weakened as the review is not that robust (search in only 3 databases that includes both Medline and PubMed).

Response: We understand the reviewer's comment regarding the comprehensiveness of our search strategy. While we searched three of the most commonly used databases within the medical literature and employed a large set of key words to cover all relevant studies within these databases in addition to a search of reference lists of included studies, there is still the possibility of missing relevant studies. We have therefore changed the wording to balance the fact that this is still a strong search strategy (though not entirely comprehensive).

(Please see the revised manuscript, "Article Summary" section, Page 5, Red Colored texts)

Comment: Abstract: This section seems appropriate.

Response: Thank you so much for your comment.

Comment: Introduction: Introduction is written well although there are occasional minor syntax errors in the section and others that need rectification. For e.g., page 7: the sentence "People with diabetes…. without diabetes" will not convey the right meaning the authors meant.

Response: We have made these suggested corrections. Thank you for highlighting these syntax errors.

(Please see the revised manuscript, "Introduction" section, Page 7, Red Colored texts)

Comment: Methods: Authors need to explain why the language limit was applied and why both Medline and PubMed were searched (un-necessary duplication of results). It is also worth mentioning reasons for exclusion of some of the studies (12 as per your report) mentioned in the qualitative synthesis are excluded from quantitative synthesis.

Response: Thank you so much for your comment. We acknowledge that we limited inclusion to studies published in English only. This was mainly due to resource limitations. Although the English language is generally perceived to be the universal language of science but selection of research findings in a particular language can introduce systematic bias we have acknowledged this fact in our study limitation section. Specifically, we have added the following sentences.

“Although the English language is generally perceived to be the universal language of science, selection of research findings in a particular language can introduce language bias and may lead to erroneous conclusions. With this in mind, readers should be cautious when interpreting the findings of our results.”

(Please see the revised manuscript, “Discussion” section, Page 19, Red Colored texts)

We also acknowledge the fact that Medline is a subset of PubMed and can produce duplicate results. However, we still searched both of these databases on the grounds that Medline allowed us to perform a more focused search while PubMed allowed us to find more content/articles that were “in process”, “ahead of print”, older, or in non-medical journals.

With respect to the exclusion of some studies between the qualitative and quantitative synthesis, we only considered studies for quantitative synthesis if they had multiple validations (two or more) and reported the value of the C-statistic. We have clarified this point in our revised manuscript.

“Models with multiple validations (two or more) and reported C-statistics are provided in Fig. 4. Models that had only been validated once were excluded from the meta-analysis. In addition, only those studies that provided enough information to estimate the variance of the provided C-statistic for meta-analysis were considered for analysis.”

(Please see the revised manuscript, “Validation Studies of Stroke Prediction Models Developed in Populations with and without Diabetes” section, Page 15, Red Colored Texts)

Comment: Results: I am not convinced about the correctness of the way the authors excluded duplicates from the 3 databases as Medline and PubMed should have had similar citations mostly (Fig 1 PRISMA diagram). Please also explain all the abbreviations in the tables in the title/ bottom of the table (for e.g., I didn’t understand what you meant by NR).

Response: Thank you so much for your comment. We used automated de-duplication during the initial search stage. During the title-abstract screening stage any identified duplication was removed manually. We can confirm that we were able to appropriately remove duplicates in our study. It is worth mentioning, our search initially identified 26,202 papers from three databases and after removing duplicates, we found 21,797 papers for screening. In total, we removed 4,405 duplicate papers, which was not big considering the fact that we have used both Medline and PubMed. This justifies inclusion of both Medline and PubMed in our search and provide evidence that including both did produce a large amount of distinct papers to capture most of the relevant studies on our research topic.

In our revised manuscript, we explain all the abbreviations in the tables at the bottom of the tables.

(Please see the revised Tables, Red Colored Texts)

Comment: Discussion: As mentioned above, the claim about the comprehensiveness of the study should be weekend in the discussion.

Response: As discussed earlier, we have changed the wording to something we believe is more in-line with the strength of the search strategy.

Comment: References: this section seems appropriate to me.

Response: Thank you so much for your comment.

Reviewer: 4

Reviewer Name: Dr Alice Richardson

Institution and Country: Australian National University, Australia

Please state any competing interests or state ‘None declared’: None declared

Comment: This paper consists of a systematic review and meta-analysis of the literature on predicting the risk of stroke among patients with diabetes. On reading it through I was left with the impression that this is a useful contribution to knowledge for a specific kind of statistical tool that generates C-statistics (AUROCs) as its main measure of effect.

The review appears to be thorough and to have been conducted according to guidelines.

Response: Thank you so much for your comment.

Comment: My main concern is around Figures S1 and S2. Both funnel plots look decidedly unsatisfactory, with most (Fig S2) or all (Fig S1) points outside the funnel. The authors should comment more fully on the patterns observed here, and explain why they think that these patterns are not a limitation on the meta-analyses performed.

Response: Thank you for your comment. The observed pattern reflected extreme heterogeneity as observed in the text of results. However, it is important to note that in our revised analysis (after including 14 new models in the analysis) the patterns of the funnel plots (Figure S1 and Figure S2) have changed. As a result, we did not make any additional explanations or comments on the pattern of the funnel plots in our revised manuscript.

(Please see the revised figures S1 and S2)

Comment: Secondly, the authors are a little too keen to dismiss a p-value of 0.057 (page 16 line 16) as non-significant. They should rewrite the decision making here to draw attention to the fact that the p-value is very close to the usual cutoff for statistical significance, and they should comment on the clinical significance (or non-significance) of the result.

Response: Thank you so much for your comment. In response to reviewer’s comment, we now have changed the sentences as follows,

‘did show borderline significantly higher C-statistics (meta-regression p = 0.052), although, the value of the C-statistic is still low. This observed difference in the two models makes sense as models that include stroke as part of a composite outcome are expected to be different from models where stroke is the only outcome”.

(Please see the revised manuscript, “Validation Studies of Stroke Prediction Models Developed in Populations with and without Diabetes” section, Page 16, Red Colored texts)

Comment: Overall I am recommending that the paper undergo these minor revisions and be resubmitted.

Response: Thank you so much for your comment. We have made the suggested revisions and feel the manuscript has improved substantially based on the suggests from the editorial board and reviewers.

Comment: Typos:

Page 14 line 36: in diabetes not is diabetes

Response: Thank you for highlighting this error. We have made the correction accordingly.

(Please see the revised manuscript, “Validation Studies of Stroke Prediction Models Developed in Populations with and without Diabetes” section, Page 15, Red Colored texts)

VERSION 2 – REVIEW

REVIEWER	Aladeen Alloubani King Hussein Cancer Center, Jordan
REVIEW RETURNED	07-Jun-2019

GENERAL COMMENTS	Thank you for giving me the opportunity to review again your paper titled “Predicting the risk of stroke among patients with type 2 diabetes: A systematic review and meta-analysis of C-statistics” I went through your previous publication titled “Mohammad Z.I. Chowdhury, Fahmida Yeasmin, Doreen M. Rabi, Paul E. Ronksley, Tanvir C. Turin. "Prognostic tools for cardiovascular disease in patients with type 2 diabetes: A systematic review and meta-analysis of C-statistics", Journal of Diabetes and its Complications, 2018.” However, a part of your current manuscript is matching some text from your previous publication. So, please make sure that this text is paraphrased and properly referenced because this is considered as a self-plagiarism. • Page 79, Line 19 to 31” little is known about……selection of models for clinical implementation” • All of the method section. • The author used personal pronouns many times throughout the manuscript. I suggest revising the manuscript to keep the focus on research instead of the researchers. Revise as necessary throughout the document to remove self-referent pronouns. Good luck!

REVIEWER	Pappachan M Joseph Lancashire Teaching Hospitals NHS Foundation Trust,UK
REVIEW RETURNED	07-Jun-2019

GENERAL COMMENTS	The authors addressed all the comments by the reviewers and modified the paper appropriately

REVIEWER	Dr Alice Richardson Australian National University, Australia
REVIEW RETURNED	12-Jun-2019

GENERAL COMMENTS	The paper has been revised and the authors have made extensive edits to improve the manuscript (shown in red). The concerns I raised were around Figures S1 and S2, and the interpretation of a p-value of 0.057. Due to the addition of extra studies in the meta-analysis, Figures S1 and S2 look somewhat more supportive of the conclusions drawn (though the scatter of points is still somewhat surprising in both cases). As far as the interpretation of p-values is concerned, I acknowledge that a clinical explanation is now included, but a p-value of 0.052 is now interpreted as “borderline significant” (page 16 line 48)! I don’t think this shows any understanding of the recent advice from the American Statistical Association regarding the interpretation of p-values and the moving to a world beyond $p < 0.05$. However I am satisfied that the authors have addressed my concerns in some manner, and I am happy to recommend that the paper be accepted for publication.

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Aladeen Alloubani

Institution and Country: King Hussein Cancer Center, Jordan

Please state any competing interests or state ‘None declared’: There is no conflict of interest

Comment: Thank you for giving me the opportunity to review again your paper titled “Predicting the risk of stroke among patients with type 2 diabetes: A systematic review and meta-analysis of C-statistics”

I went through your previous publication titled “Mohammad Z.I. Chowdhury, Fahmida Yeasmin, Doreen M. Rabi, Paul E. Ronksley, Tanvir C. Turin. "Prognostic tools for cardiovascular disease in patients with type 2 diabetes: A systematic review and meta-analysis of C-statistics", Journal of Diabetes and its Complications, 2018.” However, a part of your current manuscript is matching some text from your previous publication. So, please make sure that this text is paraphrased and properly referenced because this is considered as a self-plagiarism.

- Page 79, Line 19 to 31” little is known about……selection of models for clinical implementation”
- All of the method section.
- The author used personal pronouns many times throughout the manuscript. I suggest revising the manuscript to keep the focus on research instead of the researchers. Revise as necessary throughout the document to remove self-referent pronouns.

Good luck!

Response: Thank you so much for your comments. In our revised manuscript, we tried to paraphrase our texts when appropriate to overcome the issue.

(Please see the revised manuscript, track changes)

Reviewer: 3

Reviewer Name: Pappachan M Joseph

Institution and Country: Lancashire Teaching Hospitals NHS Foundation Trust,UK

Please state any competing interests or state ‘None declared’: None

Comment: The authors addressed all the comments by the reviewers and modified the paper appropriately

Response: Thank you so much.

Reviewer: 4

Reviewer Name: Dr Alice Richardson

Institution and Country: Australian National University, Australia

Please state any competing interests or state ‘None declared’: None declared

Comment: The paper has been revised and the authors have made extensive edits to improve the manuscript (shown in red). The concerns I raised were around Figures S1 and S2, and the interpretation of a p-value of 0.057. Due to the addition of extra studies in the meta-analysis, Figures S1 and S2 look somewhat more supportive of the conclusions drawn (though the scatter of points is still somewhat surprising in both cases). As far as the interpretation of p-values is concerned, I acknowledge that a clinical explanation is now included, but a p-value of 0.052 is now interpreted as “borderline significant” (page 16 line 48)! I don’t think this shows any understanding of the recent advice from the American Statistical Association regarding the interpretation of p-values and the moving to a world beyond $p < 0.05$.

However I am satisfied that the authors have addressed my concerns in some manner, and I am happy to recommend that the paper be accepted for publication.

Response: Thank you so much for your comments.