Author’s response to reviews

Title: A Systematic Review and Meta-Analysis of Interventions to Increase Stroke Thrombolysis

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Author’s response to reviews:

Dear Editor,

Thank you for the opportunity to resubmit this manuscript. We would appreciate your opinion about whether we should remove Figure 2 given our new Table 1. Thank you very much.

Mollie McDermott

Dear Reviewers,

Thank you for your comments and recommendations which have significantly improved our manuscript. Herein we have addressed each comment individually. We have provided copies of the manuscript with and without changes tracked. Each page number included below refers to the manuscript without tracked changes (clean copy).
Janika Kõrv (Reviewer 1): The authors have answered to all questions. There are no more comments.

RESPONSE: Thank you again for your feedback.

Joshua Willey (Reviewer 2): The authors have addressed all of my comments.

RESPONSE: Thank you again for your feedback.

Dominique Anne-Michele Cadilhac, PhD, MPH, BN, RN (Reviewer 3): The aim of this paper is to provide a summary of the literature using a systematic approach on the evidence for implementation interventions that might be effective to increase use of thrombolysis in patients with acute stroke. This is an important issue given there is wide variation in practice in different parts of the world and equitable access to this treatment even with the same country can be problematic.

I have read the paper and have a number of concerns and this might be addressed by the authors. The main issue I have is that the authors have undertaken meta-analyses of very diverse interventions. Therefore, the statistics for heterogeneity are very large (e.g. I² >75%) and this means that it is inappropriate to generate pooled effect size estimates. In other words, there are large inconsistencies and variation in the studies and they may not be similar enough clinically to be sensible to meta-analyses.

RESPONSE: Thank you for this comment. We have made two changes in response to this critique. First, we have updated the methods section to clarify that we have followed the Cochrane handbook for systematic reviews of interventions and considered the random effects analysis as the primary analysis (page 6). Second, we have added to our limitations on page 11: “In addition, the statistics for heterogeneity among studies is high given our analysis of varied interventions. Interpretation of the pooled effect sizes should be cautious due to the heterogeneity among the studies. We have followed the Cochrane handbook for systematic reviews of interventions by reporting our random effects analysis as our primary analysis as it better accounts for heterogeneity.”

Aim: refers to efficacy but this is terminology for RCTs yet their review includes a range of study types. The authors need to change this to ‘effectiveness’ in particular because many of the studies are undertaken in real-world settings.

RESPONSE: We have replaced the word efficacy with effectiveness where we had previously used the term incorrectly.
Also, in the aim it is stated that the intervention approaches and settings will be describe but this wasn't covered in detail. I think the authors need to expand Table 1. included studies and provide details of each included paper in a new row and provide information such as Study location, Design, Participants, Sample size, Intervention, Control, Outcome, Adverse events, Limitations.

RESPONSE: We have created a new table (Table 1, page 25) to present this information more clearly. This table includes study location, design, intervention detail, number of participants in control group, number of participants in intervention group, treatment rate in the intervention group, and treatment rate in the control group.

It would also be better if Fig 1 followed the PRISMA format as per Moher D, Int J Surg 2108(5): 336-341

RESPONSE: Thank you for this recommendation. We have reformatted figure 1 to more closely follow the PRISMA format (page 19).

In stroke pre/post design are problematic because 'stroke onset time' (necessary to determine if people are eligible for tPA) is often recorded better in the post phase and missing data in the pre phase can create distortions.

RESPONSE: This is an interesting criticism that we had not fully considered. We now explicitly cite this limitation without our limitations section on page 11: “Thirteen of the 25 studies in our review were pre-post design. Pre-post studies can be biased as data may be differently collected (e.g. more systematically) after an intervention than before an intervention.”

I think this paper could be redesigned to provide more detail of what interventions have been used, etc. The authors need to be clear how their paper adds to the literature and complements any other reviews that may have been undertaken on this topic.

RESPONSE: We have added to the second paragraph of the conclusion (page 9) what we consider the most unique contribution of this paper to the literature: “Our review uniquely contributes to the literature by exploring the entire spectrum of interventions that have been explored to increase thrombolysis use. As such, our analysis attempts to inform the question for a region or hospital about how best to increase tPA treatment rates.”
It should be noted as a limitation in the Discussion that often organizational interventions to improve access to thrombolysis may not be published in journal articles. For example, government policies to increase access and pre-post assessments of impact of such policies.

RESPONSE: We now state within our limitations on page 11: “Furthermore, many governmental, regional, and organizational interventions to improve access to thrombolysis are not published as studies or trials. Our meta-analysis fails to capture these interventions.”

If their literature review was completed in 2015, then any new advances could be mentioned in the Discussion. e.g the advent of Mobile Stroke Units. See authors Grotta J et al and the PRESTO group papers.

RESPONSE: This is a very good point. We have added the mobile stroke unit literature to our discussion section (page 10-11), even though those studies were completed after our literature review: “In addition to the interventions identified in our review, since completion of the review, additional studies have suggested that mobile stroke units may also be effective in increasing tPA treatment rates in selected regions.” We have added several references, including those cited by the reviewer. In the limitations section (page 11), we have added: “In addition, because our literature review was completed in 2015, our analysis includes limited studies about the effectiveness of mobile stroke units in increasing thrombolysis rates.”

Again, thank you very much for your kind attention and comments.

Sincerely,

Mollie McDermott