Author’s response to reviews

Title: Futile Reperfusion and Predicted Therapeutic Benefits after Successful Endovascular Treatment According to Initial Stroke Severity

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Dear Reviewers and Editorial Staffs of BMC Neurology:

My coauthors and I are pleased to hereby submit the revised manuscript, “Futile Reperfusion and Predicted Therapeutic Benefits after Successful Endovascular Treatment According to Initial Stroke Severity”, for consideration as an Original Article in BMC Neurology.

We would like to thank the reviewer for their thoughtful comments in relation to our manuscript. Texts written in blue with 12-point Georgia fonts are verbatim of reviewers' comments. The
author’s responses are attached below each comment and the revised parts of the manuscript are highlighted with a yellow color.

Thank you for your consideration of our paper.

Sincerely,

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Reviewer Comments

1) This paper presents what sounds like two contradictory conclusions, which the authors report as "novel" in their discussion: increasing "benefit" but also increasing "futility" of reperfusion, with increasing NIHSS. However, this is fundamentally a problem of using two different comparison populations, and poor choice of wording. Specifically, the authors find that "futile reperfusion", defined by the proportion of patients with successful EVT (TICI 2B-3) who have a worse outcome (mRS=3-6), increases with increasing NIHSS. Multiple studies have shown worse outcomes after stroke with increasing age and increasing presenting NIHSS, with or without intervention (for example, see Figure 3 in the meta-review by the HERMES collaboration in Lancet 2016), so there's nothing new or surprising about increased "futile reperfusion" (aka worse outcomes) with increasing NIHSS at time of presentation.

In contrast, the authors define "benefit" of EVT as a relative reduction in proportion of poor outcomes (mRS=3-6) when comparing patients with successful EVT (TICI=2b-3) versus patients not selected for EVT, stratified by NIHSS. This is a different question, across different
comparison groups. Not surprisingly, they find that the higher the NIHSS, the worse the non-
EVT patients do, relative to patients with successful EVT. Again, there is nothing new or
surprising to this analysis: increasing NIHSS leads to increasing poor outcomes, which is much
more pronounced in those who aren't able to undergo EVT.

Response: We agree with Reviewer#3’s opinion and have updated the paper accordingly.
Obviously, worse outcome is observed as age and NIHSS increases, and outcome is even worse
in patients who do not receive EVT. The objective of the study was to identify the proportion of
poor outcome in patients who were treated with EVT and did receive full perfusion, and to
compare them to patients who did not EVT, using real world data. Therefore, our goal is to
illustrate to the neurologist that, despite the concern of worse outcome in increasing age and
NIHSS, successful EVT had a better “gain” compared to those not having the procedure at all.
While individual trials and pooled analyses have already shown the benefit of EVT in subgroups
with older age and higher NIHSS, we believe that this real-world demonstration is helpful for the
clinician to understand the likely benefit of EVT in real-world practice when just focused on
patients’ factors and when excluding the technical and system-level problems. We have revised
the manuscript to communicate these points more effectively, and to focus more on predictors of
futile reperfusion, as suggested in the reviewer’s next comment.

[Conclusion] [page 17, paragraph 2]

Our study suggests that both futility of EVT and therapeutic gains of EVT increase as stroke
severity increases. By confining this analysis to those patients who were successfully reperfused,
we provide clinicians with considerations regarding predicted outcomes with EVT. While
individual trials and pooled analyses have already shown the benefit of EVT in subgroups with
older age and higher NIHSS, we believe that this demonstration is helpful for the clinician to
understand the likely benefit of EVT in real-world practice.

2) Given the numerous publications, across multiple countries/sites, using randomized data to
show benefit of EVT across all ages/NIHSS, the data in this paper (retrospective, non-
randomized, without uniform patient selection via ASPECTS, CTP, DWI-mismatch, etc) is less
applicable to current practice, especially when making claims regarding "predicted therapeutic
benefits after successful EVT". The paper would be more useful to simply focus on what are
predictors of worse outcome (aka "futile reperfusion") in patients who've already been selected
for EVT, and omit discussion of "therapeutic benefit" of EVT - the latter simply confuses the
message of the paper. I recommend focus on data in Table 1 and Table 2, which suggest that on
multivariate analysis increasing age and NIHSS and decreasing premorbid antithrombotic use are
associated with worse outcomes after EVT despite TICI 2b-3. Finally, the authors state that
"negative association of pre-stroke antithrombotics with futile reperfusion as not been reported
previously", which is not absolutely correct: subgroup analysis of MR CLEAN found "futile
reperfusion" (mRS=3-6 after TICI 2b-3) in 53% of patients with antithrombotics versus 62% of patients without antithrombotics (Int J Stroke Vol 12, Issue 4, pages 368-376, 2017)

Response: As recommended, we have revised the Discussion sections of Manuscript as follows:

[Discussion] [page 15, 2nd paragraph]

“The positive associations of age and NIHSS score with futile reperfusion are concordant with the results of earlier studies [9, 10]. However, the negative association of pre-stroke antithrombotics with futile reperfusion is not consistent with a prior subgroup analysis of MR CLEAN.[19]

3) Lastly, from a semantic point of view, the use of the phrase "futile" is unfortunate here, since it implies reperfusion is of decreasing benefit with increasing age/NIHSS - which we know is not true (see prior RCT's showing benefit of EVT across all age and NIHSS subgroups). True "futility" of reperfusion across age/NIHSS strata can only be determined if the authors had compared their patients selected for EVT who achieved TICI-2b-3, versus patients selected for EVT who did not achieve TICI2b-3, across age/NIHSS strata (ideally with matched pairs or propensity scoring). So, a better way of phrasing the topic is to simply state "worse outcomes" (mRS 3-6) despite TICI 2b-3 reperfusion, and not necessarily "futility" of opening an occluded vessel - for example, achieving an mRS of 3 (e.g. ability to walk without assistance!) after successful reperfusion in someone initially presenting with NIHSS>20 and an ICA T-occlusion, would generally not be felt to be "futile".

Response: We agree with Reviewer#3’s opinion that the semantics are unfortunate. Nonetheless, there is now a substantial literature studying this concept with the label of “futile recanalization” (Stroke. 2010;41:842-843).

To ensure clarity, while allowing us to still refer to this concept using literature-based terminology, we have added the following point in the manuscript:

[Discussion] [page 17, paragraph 1]

Lastly, as described above, we were unable to obtain data regarding onset to reperfusion times or specific EVT devices used, and these factors could critically affect clinical outcomes. An important thing that should be noted for this study, the concept of “futile reperfusion” [1] is not referring to the overall futility of treatment. For example, while more patients with older age and
higher NIHSS will have poor outcomes with reperfusion (i.e., futile reperfusion), this group of patients will have overall better outcomes with EVT treatment; this well established by randomized trial results. Our findings, by showing worse outcomes in patients with futile reperfusion, as compared to those with no reperfusion attempted, reinforce the findings of randomized trials with real-world data.