Editor

BMC Cardiovascular Disorders

Dear Editor,

We take up the recommendation of the Editors of BMC Medicine and submit this revised manuscript for your consideration.

For reasons already outlined in our original submission, we believe this work is relevant and important.

Of the two Reviewers of the previous version whose comments have been made available, HC Wijeysundera fully endorsed the revised work while HE Jones had additional comments that we address below. Importantly, HC Wijeysundera is the first author of an earlier meta-analysis on the very subject of our manuscript and that we critiqued in our manuscript.

The notable differences between the last version and the present one of this work is first, the addition of a new Figure (5) and second, reference to another, but also inadequate in our estimation, meta-analysis on this topic that was published like the one by Desch et al in late 2010. Reference to these meta-analyses makes our work complete and up-to-date and also buttresses its relevance since like the first meta-analysis by Wijeysundera et al, these meta-analyses are subject to our critique of having lumped together RCTs of too disparate designs and having disregarded the important biases that we highlight in our systematic review. The third notable modification is addition of a new short first paragraph in Discussion that summarizes our findings making for easier readability.

All these changes plus all the others since the previous version that are
essentially stylistic ones that enhance the quality of this work are underlined.

We thank you for considering our work and hope that after this long journey (first submitted to BMC in November 2010), we may have the pleasure of your favorable response.

Sincerely,

Peter Bogaty, MD (on behalf of the other two authors, KB Filion and J Brophy)

RESPONSE TO REVIEWER’S COMMENTS

We thank HE Jones for comments, which we believe have strengthened the manuscript. Below, we address the comments one-by-one. All changes in the present manuscript from the previous version are underlined.

1) I am very pleased to see that the authors have included forest plots in the revised version of this manuscript. The authors note a concern that, while it would not be practical to include forest plots of composite endpoints (because these are too disparate and numerous), these actually tend to be the primary outcomes in the included trials and are the most familiar to the intended audience. Given the authors’ concern, it would be beneficial to explain briefly in the text (bottom of page 7) why it was not practical to include these additional forest plots. In addition, perhaps it is possible to include forest plots for some subset of these composite outcomes after all?

Response

Only two composite endpoints (death/reinfarction and death/reinfarction/stroke) were reported by at least 3 RCTs at 30 days, and no outcomes were reported by at least 3 RCTs at 6 or 12 months. The revised manuscript now contains a forest plot of these two outcomes (new Figure 5). In addition, we now explain on the bottom of page 7 why it is not practical to include forest plots of the other composite outcomes.

2) The x-axis for each forest plot currently only covers quite a limited range, with the effect that many confidence intervals go beyond the edge of the plot, and for at least one study (WEST, recurrent ischemia) even the point estimate is outside of this range! Please widen the range of the x-axes, so that both the upper and lower limits of the vast majority of confidence intervals are visible.

Response

In response to the Reviewer’s comment, we have widened the range of the x-axes. The lower limit has been decreased from 0.25 to 0.1 and upper limit as
been increased from 4 to 10. All point estimates are now included in the presented range.

3) When re-reading this manuscript, I realised that not all of the included trials are actually RCTs: the authors state on page 15 that patients were not randomised in NORDISTEMI. They do not mention whether patients were randomised in GRACIA-1 or LEIPZIG. Please make explicit whether or not this was the case for these two trials. In addition, wherever “randomised clinical trials” or “RCTs” are currently referred to (including the current title), this should be replaced with “controlled trials” or “controlled clinical trials”, to reflect that not all control groups were based on randomisation.

Response

The present systematic review is, and was previously and unambiguously indicated to be, restricted to randomized clinical trials. This is stated in the last paragraph of the Introduction and throughout the Methods. We have also clarified this issue in our descriptions of GRACIA-1, LEIPZIG, and NORDISTEMI.

4) The authors now mention a recent meta-analysis by Desch et al, published in Heart, in which meta-analyses were performed on the same 9 trials that are discussed in this manuscript. Although I have not read the Desch et al paper, I believe that this draft manuscript may still be valuable in that it highlights the various potential biases and other problems with the evidence base in some detail, which I presume was not the case in Desch et al. Please make explicit whether this is the case. In light of this recently published meta-analysis of the same data, I suggest changing the title to make it immediately clear what is new here (incorporating something like “the evidence is inconclusive” or “limitations and potential biases”?).

Response

After careful consideration, we have left the title of our manuscript as “Routine Invasive Management After Fibrinolysis in Patients With ST-Elevation Myocardial Infarction: A Systematic Review of Randomized Clinical Trials”. The current subtitle of the manuscript is in accordance with the principles outlined in the PRISMA statement. Furthermore, a systematic discussion of the strengths and limitations of the included trials is an inherent component of a systematic review and thus is implied by the current title.

In this revised manuscript, we are more complete and up to date by referring to another recent meta-analysis (also published in 2010) of which we have become aware since the previous submission and that addresses this same topic (Borgia F et al, Eur Heart J 2010;31:2156-69). This meta-analysis, like the one by Desch et al, and like the one we originally referred to in our initial submission (Wijeysundera HC et al, Am Heart J 2008, who also happened to be one of the reviewers of the present work and has given our manuscript his approval, see
comments of Reviewer #1), all endorse the conclusion we question, that the evidence base supports the superiority of an early invasive strategy versus a selective ischemia-guided strategy after fibrinolysis for ST-elevation myocardial infarction. All 3 meta-analyses have the same limitations that we critique in our work; they crunch together the numbers of heterogeneous studies and fail to address the biases inherent in the constitutive RCTs we review. This is why we believe our work is so very relevant as HE Jones suggests. We believe we address sufficiently the limitations of this meta-analytical approach in the manuscript in Methods (page 7, Data Synthesis):

“The disparate protocols and heterogeneous comparative groups of the included trials precluded a formal meta-analysis. The limited available data also prevented the exploration of sources of heterogeneity via meta-analytic tools such as meta-regression. We have therefore opted to systematically review each individual trial. “

and in Discussion, pages 17-18:

“However, given the diverse and non-standardized study interventions, routine invasive versus a fluctuating standard care approach (with invasive rates varying from 7% to 67%) or simply an early versus deferred universal invasive strategy (in which there was no contrast in intervention rates only in timing), we believe a quantitative meta-analysis is inappropriate. We have therefore chosen instead to qualitatively review the RCTs individually.”

And further on page 18:

“Importantly, meta-analysis with a summary effect size and corresponding 95% CI represents only the random error and not the systematic errors associated with these potential biases.”

5) A very minor point, but please make explicit that the RR of 0.65 given for PRAGUE on page 8 relates to the composite endpoint of death, reinfarction or stroke.

Response

We have revised this sentence, which now reads, “The relative risk for the occurrence of the composite endpoint of death, reinfarction, and stroke in favor of the latter group was 0.65 (95% CI: 0.36-1.16, p=0.14)” on page 8 of the revised manuscript.

6) I do not fully understand what the authors mean by their sentence (page 18) “Importantly, meta-analysis with a summary effect size and corresponding 95% CI represents only the random error and not the systematic errors associated with these potential biases, underscoring the pitfalls of a quantitative meta-analysis”. I suspect that they mean that a standard summary meta-analytic
measure only takes into account random error, and is unable to take into account systematic errors (biases). Please rephrase to make this clearer.

Response

In response to HE Jones' comment, we have revised this sentence to improve its clarity (page 18 of the revised manuscript) as follows:

“Importantly, meta-analysis with a summary effect size and corresponding 95% CI represents only the random error and not the systematic errors associated with these potential biases.”