Author's response to reviews

Title: Safety and efficacy of thrombectomy in patients undergoing primary percutaneous coronary intervention for Acute ST elevation MI: A Meta-Analysis of Randomized Controlled Trials

Authors:

Umesh U Tamhane (umesh@med.umich.edu)
Stanley J Chetcuti (chetcuti@med.umich.edu)
Irfan Hameed (irfanham@med.umich.edu)
Michael Grossman (pagross@med.umich.edu)
Mauro Moscucci (moscucci@med.umich.edu)
Hitinder S Gurm (hgurm@umich.edu)

Version: 4 Date: 20 January 2010

Author's response to reviews: see over
Professor Melissa Norton, MD  
Editor-in-Chief,  
BMC Cardiovascular Disorders

Re – Revised manuscript submission - Safety and efficacy of thrombectomy in patients undergoing primary percutaneous coronary intervention for Acute ST elevation MI: A Meta-Analysis of Randomized Controlled Trials.

Dear Professor Norton,

We would like to submit the attached revised manuscript “Safety and efficacy of thrombectomy in patients undergoing primary percutaneous coronary intervention for Acute ST elevation MI: A Meta-Analysis of Randomized Controlled Trials.” for consideration for publication in the “BMC Cardiovascular Disorders Journal”.

We would like to thank the reviewers for their insightful comments and feel that the additional modifications suggested have further enhanced the manuscript. We have made the following changes in response to the issues highlighted by the reviewers.

Reviewer 1: Franz Weidinger

Reviewer's report:

This meta-analysis evaluates results of studies comparing thrombectomy-assisted versus conventional primary PCI in acute ST-elevation myocardial infarction.
Due to the wealth of data that is continuing to emerge in this rapidly moving field of interventional cardiology, this paper is an important update of previous reports on one of the most problematic situations in primary PCI, the thrombotic culprit lesion and subsequent no-reflow. As so often with novel device-based interventional techniques, the clinician is left with uncertainty about risks and benefits of its use in the daily practice, and meta-analyses are the only way to overcome, albeit with all their inherent limitations, the scarcity of large adequately powered randomized trials.

Results of 17 randomized trials qualifying for this meta-analysis showed that for surrogate endpoints of myocardial reperfusion, such as ST-segment resolution, or angiographic measures (TIMI flow, myocardial blush grade), thrombectomy showed a significant benefit compared with conventional primary PCI. Hard clinical endpoints, such as 30-day mortality, target vessel revascularization (TVR) or reinfarction, however, were similar in the 2 treatment groups. Stroke was more often seen with thrombectomy than without, and there was a trend toward increased mortality with mechanical thrombectomy devices.

Comments:

1) The distinction between mechanical, manual and vacuum types of thrombectomy devices seems somewhat exaggerated. Both Rescue and Extract devices use vacuum as aspiration mechanism of thrombus removal. Therefore, it would seem more logical to limit the subcategories to “Aspiration” and “Mechanical”. The main difference to previous meta analyses is the exclusion of distal protection devices, which have shown no benefit but rather harm in the
primary PCI setting.

The difference between vacuum and manual aspiration devices relates to the control that the operator has over the process of aspiration. While the mechanism of the vacuum and manual aspiration devices is similar, the results of the two classes of devices have been dissimilar and prior work has consistently classified the devices as a distinct class. We have accordingly chosen to maintain the distinction.

2) Statistical analyses are a major part of this paper, but too complex for a clinician to judge its validity and strength supporting the main conclusions.

NA

3) The apparent increase in stroke should be addressed and discussed in more detail, as it may be seen as an important caveat against the too liberal use of these “easy” devices.

We thank the reviewer for highlighting stroke as an important complication post thrombectomy. We believe that stroke may in part occur due to embolization of aspirated thrombus and may be partly avoided by meticulous technique. We have expanded this section in the discussion.

Reviewer 2: Heinz Drexel

Reviewer's report:

- Major Compulsory Revisions

1.) The investigated issue is an important focus of current research. It is therefore unacceptable to perform literature research up to February 2008 in a paper
submitted in March 2009. Important original work and review material concerning
the study question addressed by the authors has been published in the last year
and must be included (for examples see literature list below).

2.) In particular, recent data from large meta-analyses evaluating similar study
questions need to be discussed. The authors must clarify in as far their work
adds new information to existing meta-analyses (see literature list below).

We thank the reviewer for taking the time and effort to provide us with the updated
literature. We performed an updated search although that did not identify any new studies
that met our original inclusion criteria. Some of the abstracts have now been published
and these studies were reviewed to ensure that the data included is unchanged and the
bibliography has been updated. We have incorporated the results of the recently
published, individual patient data based analysis from the ATTEMPT study.

3.) Even with the approach of a meta-analysis the number of endpoints e.g. for
mortality, stroke, or MI is low in the submitted manuscript. The presented
meta-analysis therefore does not appear to be powered to detect significant
differences with respect to these endpoints. This needs to be discussed.

We agree with the reviewer that the incidence of events such as myocardial infarction and
stroke after primary PCI is so low that subtle differences can be missed even in a meta-
analysis. We have discussed this in our limitation section.

- Minor Essential Revisions

1.) Abstract p 2, lines 1-2: The sentence is grammatically incomplete. Please
reword.
The sentence has been corrected.

4.) The absolute number of endpoints should be provided already in the abstract. The absolute numbers have been provided in the brackets before the Odds ratio.

2.) Stroke and mortality data should be mentioned in the conclusion section of the abstract.

These data has been added.

3.) The authors state that “attempt was made to retrieve the data from the original source in unpublished studies” (page 5, second paragraph). They must state how often these attempts were successful.

Our attempts to obtain data from unpublished studies were universally unsuccessful. We have included this in the methods sections.

- Literature

We would like to thank Dr Drexel for suggesting the pertinent references. Some of the studies listed were not included in our original paper since they were published after our original submission. Other papers (Grines et al ) combine observational and randomized data and hence are not included in the revised manuscript. We have incorporated the 1: De Vita M, Burzotta F, Biondi-Zoccai GG, Lefevre T, Dudek D, Antoniucci D, Orrego PS, De Luca L, Kaltoft A, Sardella G, Zijlstra F, Isshiki T, Crea F. Individual patient-data meta-analysis comparing clinical outcome in patients with ST-elevation myocardial infarction treated with percutaneous coronary intervention with or without prior thrombectomy. ATTEMPT study: A pooled

PubMed PMID: 19436647; PubMed Central PMCID: PMC2672436.

Clinical impact of thrombectomy in acute ST-elevation myocardial infarction: an individual patient-data pooled analysis of 11 trials.


PMID: 19726437

This interesting analysis has been included in the discussion section.


Review.

PubMed PMID: 19273732.

Review article with no meta analytical data recommending aspiration thrombectomy as the primary adjunctive mechanical strategy of choice for the majority of patients undergoing primary PCI based on the TAPAS trial.


PubMed PMID: 19249433.
This small study (n = 44) evaluated the effect of thrombectomy on infarct size. Clinical endpoints were not available. Since significant number of trials in our meta analysis did not include this endpoint, we could not include this endpoint in our meta analysis.


The Angiojet thrombectomy group included RCT’s and non-RCT’s. The RCTs have been included in our meta-analysis while we have chosen to not include observational data.


The authors showed improved myocardial perfusion by thrombectomy at tissue level assessed by quantitative myocardial contrast echocardiography which were not recorded in the trials of our meta analysis. This study did not have clinical endpoints and could not be included.

Our results corroborate with the results of this study as they have shown an increase in the incidence of stroke with manual and mechanical aspiration devices. We have cited this study in our discussion section


The results of this study are similar to our study in terms of improvement in myocardial perfusion. The authors show a significant improvement in the mortality with the use of manual aspiration devices. While the directionality of the results is similar, our results did not achieve statistical significance. This may relate to differences in statistical tests use. This paper has been incorporated in the discussion.


This study was a non randomized study which showed the benefit of aspiration thrombectomy using export catheter in STEMI patients in terms of reperfusion and late
mortality. Our analysis includes only RCT’s and hence this study cannot be included in our analysis.

10: Chao CL, Hung CS, Lin YH, Lin MS, Lin LC, Ho YL, Liu CP, Chiang CH, Kao HL.


This prospective randomized study shows that primary PCI with IT may improve epicardial flow and myocardial reperfusion in patients with STEMI but it did not have any data on 30 day outcomes and hence was not included in our analysis.

Reviewer 3: Marek Brabec

This is an interesting paper summarizing a lot of empirical work which has a substantial practical/clinical potential. Statistical methodology of the paper seems to be at a reasonable level. It uses modern and well-known meta-analytical approaches. The authors properly acknowledge limitations of the general methods used as well as of the particular setup employed in this paper.

Nevertheless, it might be useful to add a short discussion of implications related to the fact that the power of the presented study can be quite low for certain
endpoints – even if it is meta-analytical. That is just a fact that can be hardly criticized per se – not much can be done about it until further accumulation of randomized clinical trials results. Nevertheless, it would be useful to emphasize that, in such a situation, it is not wise to interpret results that are statistically not significant as proofs of homogeneity, no differences among groups, etc.

Insignificant results should be taken as preliminary outcomes, and they should be reviewed in future, when more evidence will become available (and/or when the analyses will be performed in more homogeneous groups).

Discussion of the fact that analyses did not show much difference between thrombectomy+PCI versus PCI alone but did show some differences within the first group, with respect to the detailed device classification should follow similar lines. More technically speaking, it might be interesting to consider also different amount of variability (e.g. in random effects) for different groups/subgroups (e.g. for different device classes).

We thank the reviewer for his excellent comments.

There might be some points that would deserve clarification. For instance, on page 5, the text says: “Data was independently abstracted by two reviewers (UT, IH) and disagreements were resolved by consensus.” It is not clear, how often such the disagreement occurred. At least a rough figure would help to judge uncertainty underlying this phase of data processing.

The disagreement did not occur very often. However we did not prospectively record the number of times it occurred and hence are unable to provide these numbers.
Similarly, on page 7, the sentence “When the outcome did not occur in either group, we were unable to calculate effect sizes due to the empty cells and data were excluded from that particular trial.” does not provide any sense of how frequently the authors used this strategy. If it was not rare, than at least some sensitivity analysis should be done (e.g. replacing empty cells by some low number and comparing the results and comparing them to those obtained already). If the empty cells occurred really often, then the omission strategy might not be very good at all (those trials that have only one type of response in either arm might be very informative and their omission might be very much wasteful, if not biasing). An alternative would have to be quite a bit more sophisticated and technically demanding, however.

Our original methods section provides an erroneous sense of our analysis. We only excluded studies when an event did not occur in both arms. We did not exclude any study where events occurred in one arm and not in other. We whole heartedly agree with the reviewer that this can be a major problem for rare events. This is evident in the case of stroke where the total number of events is low in both arms and in 5 of the studies, the event occurred in one arm only (Thrombectomy). Exclusion of these trials could have introduced bias in favor of thrombectomy. We used continuity correction to correct for this by adding 0.1 to both the numerator and the denominator to allow correction of odds. Only a small number of trials were excluded due to the fact that no event occurred in either arm. Thus for mortality only 1 trial was excluded, for angiographic endpoints
(TIMI3 flow, ST resolution, MBG3) no trials were excluded while one trial was excluded for re infarction, two for TVR and four trials were excluded for stroke.

There are some places in the text, where an acronym use precedes its definition (several examples can be seen on page 2, right in the Abstract) – that is inconvenient and inconsistent – to say the least.

We apologize for this inconvenience, this error has been corrected.

Typography might be improved – e.g. Background, Methods, Results paragraphs on page 2 should be emphasized (using bold, indentation, etc.).

The typography has been improved.

All the authors have contributed to and approved the final manuscript and this manuscript has not been published or submitted elsewhere. No conflict of interest exists.

Once again, we would like to thank the editors and Prof. Weidinger, Prof. Drexel and Prof. Brabec for their helpful suggestions. We hope you find this manuscript of interest and look forward to your thoughts. Please do not hesitate to contact us if we can provide further information.

For the authors,

Hitinder S Gurm, MBBS
Division of Cardiovascular Medicine,
University of Michigan,
2A394, 1500 E. Medical Center Drive,
Ann Arbor, MI 48109-5853
734- 232-4276
Fax 734-764-4142
hgurm@med.umich.edu