We would like to thank again for your keenness to publish our manuscript.
Please find below the answers to your comments, which we have very much appreciated and significantly helped improving our manuscript.
All changes made to the resubmitted manuscript were highlighted in yellow.
We would also like to underlie that in this revised version of the manuscript we have updated our search, which resulted in more than 400 additional references and that we were able to include two additional unpublished studies.
All comments and criticisms raised by Dr. Jose Merino were addressed and the final result is a manuscript different from others recently published, not only because we included more studies, but also because the resulting deep clinical critical discussion in our paper on how the obtained results translate into clinical practice is, we think, unique and help deciding the best therapeutic option for an individual patient with an acute stroke.
Following one strong suggestion of the Editorial Board, we have also included in the authors team José Manuel Ferro, a very experienced stroke specialist (Member of the Steering Committees of the EAFT, ESPS II, TESS II, TACIP, SCOPE, FOP/ASIA, SPIRIT, ESPRIT, and ICTUS trials; Past President of the European Neurological Society; Member of the Editorial Board of "Stroke" and of "Cerebrovascular Disease"). Professor José Manuel Ferro has significantly contributed to improve the critical clinical interpretation of the studies and of the overall results.
We hope that you find this version of the manuscript suitable for publication.
Sincerely,
Filipe Brogueira Rodrigues, on behalf of all authors.

***
09-Nov-2015

Dear Mr. Rodrigues:

Manuscript ID BMJ.2015.027448.R2 entitled "Adjunctive intra-arterial mechanical thrombectomy versus medical care alone for ischemic stroke – a systematic review and meta-analysis" which you submitted to BMJ,

Thank you for revising your paper.

Since my last letter, some important issues have surfaced and I hope you'll agree to work with us further to resolve them. Our clinical editor in the US, Jose Merino, identified a number of omissions and inconsistencies while drafting a linked editorial to accompany your paper in the BMJ. We all believe these are resolvable with further revision, and important for the correct clinical interpretation of your findings. His comments are at the end of this letter. Might you be willing to revise and respond again within a month or so?

Most of the problems lie with the clinical context of these studies, and you should consider recruiting a clinical stroke neurologist to help with the revision.

Answer: A highly experienced and renowned stroke neurologist (José Manuel Ferro) offered his consultancy to our project and was added to the list of contributing authors. Furthermore, two of the other authors (JJF and JC) are neurology and clinical pharmacology specialists.

A brief CV of José Manuel Ferro is attached.

It's unusual for us to ask for further work at this stage, but I hope you agree that it's worth it to improve your paper further, and enhance its value to both doctors and patients.

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IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

I look forward to seeing the revision. As before, please include a point by point response to Dr Merino's comments, and a marked up copy showing the changes.

With thanks and best wishes

Alison Tonks
associate editor BMJ
atonks@bmj.com,

COMMENTS. Jose Merino

I think this MA has the potential to contribute to the literature because it is well done but I think it needs more detail to be better than others recently published, and more relevant to practicing clinicians. The authors can add additional data that can help explain why the newer trials had better results and also can guide doctors and patients when making decisions about the best course of action.

Answer: Please find below the answers to your comments, which we have very much appreciated and significantly helped improving our manuscript.

All changes made to the resubmitted manuscript were highlighted in yellow.

We would also like to underlie that in this revised version of the manuscript we have updated our search, which resulted in more than 400 additional references and that we were able to include two additional unpublished studies. All comments and criticisms raised by Dr. Jose Merino were addressed and the final result is a manuscript different from others recently published, not only because we included more studies, but also because the resulting deep clinical critical discussion in our paper on how the obtained results translate into clinical practice is, we think, unique and help deciding the best therapeutic option for an individual patient with an acute stroke.

Following one strong suggestion of the Editorial Board, we have also included in the authors team José Manuel Ferro, a very experienced stroke specialist (Member of the Steering Committees of the EAFT, ESPS II, TESS II, TACIP, SCOPE, FOP/ASIA, SPIRIT, ESPRIT, and ICTUS trials; Past President of the European Neurological Society; Member of the Editorial Board of "Stroke" and of "Cerebrovascular Disease"). Professor José Manuel Ferro have significantly contributed to improve the critical clinical interpretation of the studies and of the overall results.

*Use of "medical therapy"

An important issue that may be missed because the paper refers "medical therapy" is that for most patients in the analysis, "medical therapy" means IV tPA used according to local guidelines. Table 2 in the paper shows that IV tPA was the comparator in many studies and that it could be used in others. But it may be helpful to readers to discuss the proportion of patients in these studies that actually received standard IV tPA (and perhaps the time window used). This information is very important because it helps interpret the recent recommendations in updated guidelines that recommend the use of endovascular therapy in patients treated with IV tPA within 4.5 hours and who can be treated with a stent retriever within 6 hours (see the 2015 American heart Association/American Stroke Association focused update of the 2013 guidelines… (Stroke 2015; 46:3020-3035, http://stroke.ahajournals.org/content/46/10/3020) .
• SYNTHESE (randomized IV vs IA tPA)
• IMS-III: 100% had IV tPA
• MR RESCUE: 37% had IV tPA (long time window, recruit non-IV tPA eligible)
• MR CLEAN: 100% had IV tPA
• ESCAPE: 72% had IV tPA
• EXTEND IA: 100% had IV tPA
• SWIFT-PRIME: 100% had IV tPA
• REVASCAT 73% had IV tPA

The use of IV tPA in these studies highlights a major clinical issue: the evidence supports the use of thrombectomy devices early after onset of symptoms and preferably in patients who got standard IV tPA.

Answer: We agree with the reviewer that this important clinical issue was not clear in the manuscript. In this revised version we have specifically addressed this aspect.

*Use of devices

One of the possible reasons why the 2015 trials were positive while the 2013 were negative is that the former used a stent retriever and the latter did not (or did only for a few patients, particularly those enrolled late in the trial when the stent retrievers became available). Stent retrievers can be deployed more rapidly than other thrombectomy devices and lead to higher rates of recanalization. This may explain why the later studies had higher recanalization rates and higher rates of good outcome. The authors address this issue in the discussion but I think they should describe the devices used in each study in the results section. This is crucial information and should be included on page 13.

While the authors list the differences in terms of devices, they do not discuss this issue in sufficient detail. It is incorrect to say, as they do, that MR CLEAN used the Merci retriever (see page 13). MR RESCUE did. They also mention that some studies used the solitaire device. While this was the most commonly used device (and in some studies the only device) other stent retrievers were used and it may be helpful if they refer to these in generic terms (stent retrievers) rather than by brand name.

Endovascular interventions used in each study (some is included in supplemental appendices): the authors might consider creating a table using data from the studies:
• SYNTHESIS: 66% had intra-arterial tPA and guide wire fragmentation, 20% had MERCI, penumbra or another device, 14% had stent retriever
• IMS-III: 41% had IA tPA alone and 59% had a device with or without IA tPA(Merci retriever [Concentric Medical], Penumbra System [Penumbra], or Solitaire FR revascularization device [Covidien], or endovascular delivery of t-PA by means of the MicroSonic SV infusion system [EKOS] or a standard microcatheter). Only 1.5% had a stent retriever
• MR RESCUE: All had MERCI device or Penumbra +/- IA tPA (none had a stent retriever)
• MR CLEAN: Of 233 patients randomized to mechanical intervention, 81% were treated with a stent retriever, 2% had another mechanical therapy, 1 patient had IA tPA and 16% did not have a procedure.
• ESCAPE: Of 165 patients randomized to mechanical intervention, 86% had a stent retriever.
• SWIFT PRIME: 100% had stent retriever
• EXTEND-IA: 100% had stent retriever
• REVASCAT: 100% had stent retriever

The authors should confirm that all patients treated with a stent retriever were indeed treated with the solitaire device and not with other stent retrievers such as TREVO. (page 16)

Answer: We agree with the reviewer that the type of device is most probably a crucial variable for the obtained results and that in this case it can behave like a confounder. In the previously submitted version of the manuscript, we tried to call the attention of the reader to this aspect. However, looking again to the manuscript, we do agree with the reviewer that the emphasis and level of detail previously provided is insufficient. Therefore, more detail was added to the text, mainly in the results section and by creating an additional table (Table S2).

*Imaging and selection of patients

The authors address some issues around imaging selection of patients in the discussion. But the use of imaging criteria is a major difference between the 2013 and 2015 studies, and the criteria used in each study should be described in the results. These are critical aspects of the included studies.

Differences in the use of imaging criteria may explain why the studies published in 2015 were positive: they used imaging to identify patients most likely to benefit if they had the intervention (because there was a large vessel occlusion –the target pathology- documented before the procedure began) and also most likely to do poorly if only treated with IV tPA (because large vessel clots respond less well to IV tPA.)

The main difference is that the studies in 2015 used imaging criteria to identify those who had a small ischemic core (most often using non contrast CT brain and ASPECTS scores) and large vessel occlusion (with CTA, MRA and, in some studies, DSA). The studies published in 2013 did not use imaging to select patients for treatment. A table with the difference may be helpful.

Answer: More detail was added to the text, mainly in the results section. We also added a table (Table S1) to detail the imaging used to select patients.

*Other points.

Page 6, line 9: Ischemic heart disease AND ischemic stroke combined are the leading cause of death, if we separate all cancers by location according to the reference provided by the authors. The first statement in the paper needs qualification. Please review the cited reference.

Answer: Thank you for the correction.

Page 6, line 35. Please provide a figure to quantify recanalization rates with thrombolysis.

Answer: Figure added. Thank you for your suggestion.

Page 6, line 39. The studies included in this MA look at mechanical thrombectomy. The protocol in PROSPERO mentions the criteria of Saver and Jauch (as the combination of pharmacological fibrinolysis and mechanical thrombectomy, where arterial recanalization is achieved by thrombus fragmentation and retrieval, and enhancement of fibrinolytic penetration.) But some studies are limited to intravascular thrombolysis without mechanical disruption (SYNTHESIS, some patients in IMS-III) or intra-arterial thrombolysis along with mechanical disruption (IMS-III, MR RESCUE). While many of the studies in this analysis focus on mechanical thrombectomy, it is more accurate to refer to the MA as
for stroke. You could add a paragraph describing the different methods of endovascular therapy. I suggest you look at recent reviews that discuss the different embolectomy devices (and the pharmacological methods for embolectomy).

Answer: Thank you for the suggestion. We reformulated the paragraph according to the indications. It is now clearer what the goal of our work is.

Page 7, line 2: The study was REPORTED following PRISMA-P…

Answer: Corrected.

Page 7, line 27: Consider adding: "this review includes…" or something to that effect to make the text appear less telegraphic. Again, these studies are not limited to AIMT but to endovascular interventions (devices and drugs).

Answer: Thank you for the suggestion.

Page 7, line 29: Were there other inclusion criteria? Did you have any exclusion criteria a priori?

Answer: No other inclusion criteria were used. Exclusion criteria a priori included study design (as referred in the text) and trials in which the endovascular intervention did not included any patient treated with mechanical thrombectomy. We have now mentioned it clearer in the text.

Page 9, line 19: Do you have enough information to identify sICH by SITS-MOST criteria? Not all studies in the MA used this definition. In order to recode sICH using SITS-MOST you need access to the images and patient data. You may state that you are recording sICH as defined by the author in each study. In that case, it will be helpful to include a table with the definition. Upon review of a few of the studies, I found this info in the paper most often but sometimes more details in the appended protocol.

Answer: Thank again for the suggestion. We added a new paragraph detailing the sICH criteria in the results section.

Page 10, line 17: Explain the rationale for exploring the risk of non-event. How can a clinician interpret this information? Is it helpful for decision making? Same concern for TSA. other

Answer:

A secondary analysis of the primary efficacy outcome was performed in order to explore the risk of non -event: the risk of patients achieving an unfavourable functional outcome – dependency or death – at 90 days after symptom onset (mRS>2). Interventions in the acute phase of stroke, including endovascular thrombectomy, aim to reduce complications. Therefore, we thought that it was relevant to estimate the risk of becoming dead or dependent in addition to the probability of achieving a good ("positive") outcome.

Vascular interventions (device therapy or pharmacologic treatment) in the acute phase of stroke are meant to reduce complications of the condition. Customarily the impact of such interventions was measured in term of prevention of "negative" outcomes (Wardiaw et al. Cochrane Database Syst Rev. 2014;7:CD000213.), furthermore the relative risks of 'negative outcomes' are usually more consistent than relative risks of 'positive outcomes' (Deeks JJ. Stat Med. 2002 Jun 15;21(11):1575-600.).

Furthermore, the estimated result for risk of achieving an unfavourable functional outcome is expected to be different of the inverse of the pooled estimate for risk of achieving a good functional outcome because, despite the same sample size, the weighting method for statistical analysis takes into account the differences in event rates. Consistency between results of the primary and secondary analyses for the primary outcome would further increase confidence in the results.

Having stated the above mentioned reasons as rational for conducting the non-event analysis, we recognize that it does not add (in this case) vital information. Therefore, we have deleted this analysis.

For comment on TSA, please see our answer to a following comment.

Page 12, line 30: This statement is partially correct. The time to endovascular therapy was from 5-12 hours. But for inclusion, some trials had shorter time windows. IMS-III, for example, required treatment with IV tPA within 3 hours. Other studies required IV tPA within 4.5 hours. It may be more accurate to describe the inclusion criteria including the time constraints due to IV tPA requirements and then also the requirement for endovascular access by a certain point.

Answer: Thank you for the suggestion. This point was clarified

Page 12, line 36: Clarify that this refers to IV tPA. Mention the fact that some trials evaluated IV vs IA tPA (SYNTHESIS).

Answer: Added.

Page 13, line 3: It is necessary to qualify what you mean by proximal artery strokes. Only the studies published in 2015 required imaging confirmation of the vessel occlusion. All included patients with occlusion of the distal (intracranial) carotid artery or M1 portion of the MCA. Some studies allowed vessel occlusions of the M2 branches. Some also allowed basilar occlusions (please mention which study allowed which occlusions). This information is useful for a neurologist or neuroradiologist considering these therapies.

Answer: This information was added to the results section.

Page 13, line 17: The intervention was endovascular therapy (that could be AIMT or just IA lytics) compared with standard medical therapy. For some studies, standard medical therapy meant treatment with IV tPA. For other studies this meant other measures. And for some, IV tPA or other measures. See my comments above.

Answer: This comment related to a previous one. The reviewer was also previously right in that the way text was written is misleading regarding both intervention and control arms under consideration. We have changed the text to make it clearer that intervention was endovascular therapy providing that mechanical thrombectomy was at least one of the possible interventions in the endovascular treatment arm of the study. It is also clearer in this revised version of the manuscript what was considered under the control medical therapy arm.

Page 13, line 33: See comments above regarding endovascular devices. Also, correct statement about MR CLEAN requiring MERCI.

Answer: Corrected and further information was added in an additional table.

Page 14, line 10: Allocation concealment was not possible due to nature of procedure. The authors could discuss the PROBE design.

Answer: We elaborated on the PROBE design in the discussion section.

Page 14: what do the authors mean here: "Concerning attrition bias, IMS III and MR CLEAN showed imbalances between withdrawals in the active and control arms and in MR RESCUE and REVASCAT the reduced number of participants limited considerations"?

Answer: The concept was further developed.

Page 14: While all the trials report on mRS 0-2, mRS 0-1, mortality and sICH, these were not the primary outcome in all trials. Could the authors provide information on which were the primary and secondary outcomes for each trial?

Answer: The requested information was added.

Page 15: See my comments above regarding medical care alone. Need to qualify when IV tPA is medical care alone vs. other interventions.

Answer: The concept of medical care alone was more developed in the description of study interventions.

Page 15, line 32: "captured" is not the right word, it implies that the authors do not know if the other 95% of patients died. You may say that XX patients died…

Answer: Thank you for your correction

Page 15: An important piece of information for neurologists and neuroradiologists would be the recanalization rates achieved in the endovascular therapy arms. These numbers are provided in all the reports and can show how the newer studies had greater recanalization. This may explain the differences in outcomes. You should consider including this information.

Answer: The requested information was added to the results section and a new table (Table S3) was built.

Page 16, line 13: Can the authors interpret the results of the TSA analysis for readers not familiar with it? What does this paragraph mean?

Answer: This issue was further clarified in the manuscript. We created a box to explain to reader what TSA is – if that is acceptable from the editorial point of view.

Page 16, line 34: Clarify that you mean intravenous rt-PA (some studies, particularly those from 2013 but also some of the newer ones, used IA rt-PA)

Answer: Added.

Page 16, line 25: There are more than 2 thrombectomy devices used in all trials (Merci retriever, Penumbra System Solitaire FR revascularization device, TREVO, or endovascular delivery of t-PA by means of the MicroSonic SV infusion system or a standard microcatheter). The authors should make sure that the comparison mentioned here is limited to MERCI and Solitaire or change the wording in the text and tables. MR RESCUE allowed use of different iterations of the MERCI device as well as the Penumbra device. IMS-III used a variety of devices, as mentioned above. Some of the new trombectomy trials use several devices.

Answer: Subgroup analysis for the different devices was redone and the results were changed accordingly.

Page 17, line 47: Documentation of a large vessel occlusion was NOT required for enrollment into SYNTHESIS, IMS-III OR MR RESCUE (the authors do not list MR RESCUE here). MR RESCUE required documentation of an anterior circulation stroke but nor documentation of a vascular occlusion. While MR RESCUE was evaluating the value of penumbral imaging for patient selection for thrombectomy, the appearance on imaging was not an inclusion or exclusion criterion. The authors should clarify this issue.

Answer: Thank you for the correction.

Page 17, line 52: The difference in terms of the proportion of patients with atrial fibrillation between studies is most likely due to chance. When we speak about the trials looking for patients with vascular occlusion, we do not mean a difference in terms of patients with larger artery disease (typically cervical carotid artery) but rather an occlusion of the intracranial ICA or MCA.

Answer: This aspect was changed in accordance to editorial suggestion.

Page 18, line 3: You should clarify that IMS-III by design was designed to compare standard dose IV tPA with a combination of lower dose IV tPA PLUS intra-arterial therapy (in most cases, intra-arterial tPA). The reason why the lower dose of IV tPA was used was to prevent overdosing patients who later had IA tPA. The difference was by design and designed for safety. This should be clarified.

Answer: The issue was clarified in the results section

Page 18: Line 3: The authors write, "in SYNTHESIS IV rt-PA was withheld." SYNTHESIS was a study to compare IV-tPA versus IA-tPA or other mechanical embolectomy in the standard time window. It is not that IV tPA was withheld. That was the point of the trial. The wording could be modified to reflect this fact.

Answer: Corrected.

Page 18, line 7: The authors write, "Compliance with thrombectomy in the intervention arm was low (<40%) in IMS-III and SYNTHESIS." This is an incorrect statement.

• Compliance with thrombectomy in SYNTHESIS was 90%. ("Of the 181 patients assigned to endovascular treatment, 15 did not receive the treatment (6 because of clinical improvement, 3 because of a lack of evidence of occlusion, 3 because of dissection, 1 because of an unknown bleeding diathesis, 1 because of a groin hematoma, and 1 because of the delayed availability of the interventionist). Three procedures had to be interrupted, owing to equipment breakdown (in one procedure) and intraprocedural complications (in two procedures). Endovascular treatment was thus completed in 163 patients.")
•

Answer: Thank you for your alert. We were referring to the proportion of patients that performed mechanical thrombectomy in the endovascular interventional arm and not to the proportion of patients assigned to thrombectomy that actually did it. We agree that this was unclear and we have changed the text.

Page 20: They write, "However, spontaneous neurological recovery usually ceases only after six months, so longer follow-ups could have more accurately predicted the endpoints." I am not sure that this statement is correct. Most neurologists will tell you that most gains occur in the first few months and that is why stroke trial outcomes are usually measured at 3 months. Other comorbidities may affect recovery after 3 months. But neurologic recovery continues over months and even years. It is important to highlight this issue for patients and their families.

Answer: This sentence was rephrased according to the reviewer suggestion.

* Two recently published MAs on related research questions.

http://jama.jamanetwork.com/article.aspx?articleid=2467553

and

Stroke. 2015;46:3177-3183. DOI: 10.1161/STROKEAHA.115.009847

The authors should cite these two papers and discuss what their paper adds. We acknowledge both papers were published after the review process at the BMJ began and they will not influence our final decision.

Answer: Added.

• Statements about funding

The authors claim that all studies but one were industry funded. This is NOT an accurate statement. Only two studies had predominant industry support. In italics are the sources of funding as reported:
• SWIFT PRIME "Supported by Covidien."
• ESCAPE "Supported by Covidien through an unrestricted grant to the University of Calgary. Also supported by the University of Calgary (Hotchkiss Brain Institute, the Department of Clinical Neurosciences and Calgary Stroke Program, and the Department of Radiology), Alberta Innovates–Health Solutions, the Heart and Stroke Foundation of Canada, and Alberta Health Services."
Other studies derive most of their funding from sources other than industry, and funders, authors and participants will be surprised to see some studies listed as industry-funded. MR RESCUE and IMS-III are considered as NIH-funded (to the tone of several million dollars) but some of the supplies used for the study at the sites (catheters, etc.) were donated by industry. Industry did not pay the investigators or the infrastructure of the trial. An more accurate statement would be that the studies were publicly funded but had industry support

• MR RESCUE: Supported by a grant (P50 NS044378) from NINDS. Concentric Medical provided study catheters and devices from the initiation of the study until August 2007; thereafter, costs for all study catheters and devices were

covered by study funds or third-party payers. (This means that the manufacturer only provided a minority of the catheters. The rest of funds came from NIH and from insurance and government payers as part of routine care). The text of the paper states: "The trial was funded by the National Institute of Neurological Disorders and Stroke (NINDS). An independent medical monitor and a NINDSappointed data and safety monitoring board oversaw the conduct of the trial. There were no confidentiality agreements between NINDS and the investigators. Concentric Medical provided study devices until August 2007; thereafter, costs were covered by study funds or third-party payers. Concentric Medical had no involvement in the study design or in the analysis or interpretation of the data. No other commercial support for the study was provided."
• IMS III: Supported by grants from the National Institutes of Health and the National Institute of Neurological Disorders and Stroke (UC U01NS052220, MUSC U01NS054630, and U01NS077304) and by Genentech, EKOS, Concentric Medical, Cordis Neurovascular, and Boehringer Ingelheim. The industry players provided the drug and devices only.
• SYNTHESIS: Supported by a grant from the Italian Medicines Agency (AIFA) (FARM6LN3KS). The trial received t-PA from Boehringer Ingelheim Italia, which was paid by the AIFA for use in the experimental group and by the individual participating hospitals for use in the control group. The catheters and devices used in the study were those present in the participating interventional radiologists' apparatus and were refunded by Niguarda Ca' Granda Hospital (Milan) with the AIFA funding. This study only got the tPA from the manufacturer but all other trial expenses, including the catheters, were paid by a State organism. (NB The authors claim this was the only study free of industry ties. This is not an accurate statement either because some of the supplies in the study (tPA) came from industry).

These studies had support from governmental bodies and industry. Could state mixed funding. You will note that the industry support for these trials is different from that received from the studies listed above.

• EXTEND IA: Supported by grants from the Australian National Health and Medical Research Council of Australia (1043242 and 1035688), Royal Australasian College of Physicians, Royal Melbourne Hospital Foundation, the National Heart Foundation of Australia, and the National Stroke Foundation of Australia; and by infra- structure funding from the state government of Victoria. The Solitaire FR device and trial infrastructure were provided under an unrestricted grant from Covidien.
• REVASCAT: Supported by Fundació Ictus Malaltia Vascular through an unrestricted grant from Covidien, by a grant from the Spanish Ministry of Health cofinanced by Fondo Europeo de Desarrollo Regional (Instituto de Salud Carlos III, Red Temática de Investigación Cooperativa Invictus, RD 12/0014/008), and a grant from the Generalitat de Catalunya (SGR 464/2014).

Answer: We understand the point raised by the reviewer, although in pure terms study independency can only be ascertained when there is no industry support at all. However, we have clarified the type of support provided by the industry for each of the trials and we have amended the risk of bias table accordingly.

*Registration

MR RESCUE was indeed retrospectively registered. It is worth noting that the study started in 2004, before the 2005 ICMJE policy was implemented. The BMJ would not have requested registration for publication. Registration was done in 2006 (after journals began requesting it) and many years before the study data were collected or analyzed.

Answer: Added.

* Trials stopping early

As the authors state, five trials were stopped early. Four were stopped for efficacy and one for futility. The authors mention the information but it may help readers understand why so many trials were stopped early if they include some details about the percentage of patients included in the final sample as well as the reasons and justification for stopping the studies.

After MR CLEAN was published in 2015, investigators of the other five trials did interim analyses and decided to stop early because, in most cases, pre-specified criteria for stopping the studies were met (it is important that in one trial the DSMB felt equipoise had been lost but the stopping criteria were not met). Here are the relevant data (the authors can decide how much detail to include –This information is in the 2015 guidelines referenced below but the authors should look at the papers to confirm the information)
• ESCAPE: The interim analysis was done earlier than planned and it showed that the pre-specified O'Brien-Fleming a stopping boundary had been crossed and thus the trial was stopped.
• SWIFT PRIME: After the MR CLEAN results and the decision to stop ESCAPE were announced, an interim efficacy analysis was done earlier than planned and demonstrated that the pre-specified criteria for stopping the trial at the first interim analysis had been met and the trial was thus stopped.
• EXTEND-IA: "An unplanned interim efficacy analysis was implemented on the basis of a Haybittle-Peto stopping rule.
• REVASCAT: "When results of other similar trials became known, the DSMB recommended the recruitment be stopped because the emerging results showed that equipoise was lost, although the interim results did not reach the pre-specified stopping boundaries.
One trial was stopped early for futility.
• IMS-III was stopped for futility after 656 of the planned 900 patients had been enrolled. There was no difference between the treatment arms.

Answer: Thank you. Information added.

*Please add detail to your abstract. This is an important summary and should contain all the core details that doctors need for correct interpretation of your findings.

Answer: This aspect is now further developed on the manuscript.

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Essential Items to include with your revision (see http://www.bmj.com/about-bmj/resources-authors/article-types/research):

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2. Name of the ethics committee or IRB, ID# of the approval, and a statement that participants gave informed consent before taking part. If ethics committee approval was not required, please state so clearly and explain the reasons why (see http://resources.bmj.com/bmj/authors/editorial-policies/guidelines.)

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g. Footnotes and statements

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