Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Comparative Effectiveness of Adjunctive Devices to Remove Thrombi or Protect Against Distal Embolization in Patients with Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention of Native Vessels*

Draft review available for public comment from February 1, 2011 to March 1, 2011.

Research Review Citation: Sobieraj DM, White CM, DM, Kluger J, Tongbram V, Colby J, Chen WT, Makanji SS, Lee S, Ashaye A, Quercia R, Mather J, Giovenale S, Coleman CI. Comparative effectiveness of adjunctive devices to remove thrombi or protect against distal embolization in patients with acute coronary syndrome undergoing percutaneous coronary intervention of native vessels. Comparative Effectiveness Review No. 42 (Prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center under Contract No. 290-2007-10067-I.) AHRQ Publication No. 11(12)-EHC089-EF, Rockville, MD: Agency for Healthcare Research and Quality. May 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the EHC Program Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	General	No comments.	
Peer Reviewer #2	General	Superb summary and interpretation of the current literature. I would recommend explicitly discussing saphenous vein graft intervention where embolic protection devices are recommended (even though the evidence is not extensive). I realize the scope of this document is to cover native coronary vessels, but it may be worthwhile to point out that the data for embolic protection devices in SVGs are limited also.	Specific reference to the use of embolic protection devices in saphenous vein grafts has been added into the introduction to point out that the data is limited overall as well as in this population.
Peer Reviewer #3	General	As a general rule, I think, while reporting results for a given outcome, evidence should be synthesized (qualitatively or quantitatively) from the most applicable and highest quality of study designs at one's disposal. When higher and equally, if not more, applicable RCT evidence is available, observational studies are better removed from strength of evidence tables and results write-up	Although observational data was included in the report (as per methods), when randomized trial data were available it was used to make conclusions while the observational data was provided as supplemental information.
Peer Reviewer #3	General	Not included in key questions, but rather answered KQs	As suggested, language changed.
Peer Reviewer #3	General	Not trials versus controls.	Corrected
Peer Reviewer #3	General	trail	Corrected
Peer Reviewer #3	General	iii 42-44	Section was checked for typos and corrections were made when necessary.
Peer Reviewer #3	General	iii 57	Section was checked for typos and corrections were made when necessary.
Peer Reviewer #3	General	iv 10, 23, 48, 51-52	Section was checked for typos and corrections were made when necessary.
Peer Reviewer #3	General	vi 18	Section was checked for typos and corrections were made when necessary.
Peer Reviewer #3	General	11 18	Section was checked for typos and corrections were made when necessary.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	General	16 15	Section was checked for typos and corrections were made when necessary.
Peer Reviewer #3	General	131, 41	Section was checked for typos and corrections were made when necessary.
Peer Reviewer #3	Executive Summary	Although it's clear that such is not intended, KQ 3 reads like the intervention of interest is PCI rather than adjunctive devices	The key questions were jointly constructed and decided upon with the Technical Expert Panel and Task order Officer and worded as such in the report.
Peer Reviewer #3	Executive Summary	before PCI" replace with "before balloon angioplasty and stenting"	The language was reworded to clarify and reduce confusion as suggested.
Peer Reviewer #3	Executive Summary	Applicability assessment missing	Applicability assessment was added as suggested
Peer Reviewer #3	Executive Summary	Intervention – proximal embolic protection devices missing	Intervention terminology was modified to reflect inclusion of proximal devices as suggested.
Peer Reviewer #3	Executive Summary	These are direct comparative results of two different adjunctive devices. Are the following two paragraphs comparing devices to PCI alone (control needs defining)	The introductory sentences of the referenced paragraphs were clarified so that it is now clear the data pertains to controlled trials (versus standard PCI) and not direct comparative trials, as suggested.
Peer Reviewer #3	Executive Summary	How consistent was the definition of this composite outcome of MACE across studies to have been eligible for pooling?	The definition of MACE was collected from each included trial and study that reported this outcome and can be found in Appendix F. We felt the definitions were consistent enough to permit pooling of data. We have also added details regarding the definitions and consistency across definitions to the main report prior to presenting the results of MACE analyses.
Peer Reviewer #3	Executive Summary	For a positive outcome, please consider replacing "increased risk" with something like "favors device"	All instances of "increased risk" were clarified by adding "(favors devices)", as suggested.
Peer Reviewer #3	Executive Summary	Combined protection device improved MBG	Since the literature update, there have been some changes to results regarding the significance and direction of effect ad MBG was one. The sentence now reflects the results after the update.

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Peer Reviewer #3	Executive Summary	Increase in EF is not reported on page XI, ES-1	Ejection fraction was evaluated qualitatively, and in this example there was no majority in the significance and direction. The conclusion was changed to insufficient to reflect the insufficient amount of evidence to make conclusion.
Peer Reviewer #3	Executive Summary	On page XI, why was reflow graded as high?	The majority of trials (6 of 8) were considered "good" quality and this was the approach we used when evaluating the first SOE criterion "risk of bias", along with RCT versus observational data. The two trials which were of lesser quality were scored as such because they were abstracts and therefore we did not have enough information to adequately assess the quality characteristics. These two studies provided a small amount of events to the overall analysis as well.
Peer Reviewer #3	Executive Summary	Not all of these outcomes are reported in Table ES-1	The tables in the executive summary list only those outcomes/analyses that had a SOE of low, moderate or high. Those graded as "insufficient" are not listed in the executive summary table, due to the sheer mass of outcomes. We were asked to condense the executive summary tables during the first editorial review. There is a symbol which describes that "outcomes graded as 'insufficient" are not reported in this Executive Summary table" and refer the reader to the full report.
Peer Reviewer #3	Executive Summary	Why some data were qualitatively synthesized?	Within KQ 2, procedure time was qualitatively synthesized. This was due to heterogeneity in the reporting of this endpoint (i.e., median with IQRs and means with SDs, different definitions of "procedure time).
Peer Reviewer #3	Executive Summary	It would be helpful, at least in the Exec. Summary, to remind the reader what that KQ is about. For example,"KQ3 (analysis of covariates)	Although we agree this would help to remind the reader what the KQ was, we did not repeat the KQ since they are listed earlier in the Executive Summary and because we are considerably over the word limit including the two tables.

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Peer Reviewer #3	Executive Summary	It seems this is a qualitative synthesis of available studies. Was meta-analysis of subgroup data, estimates of association, or meta-regression not possible? If so, consider reporting this	Although we had intentions of quantitative analysis, there was a limited amount of data reported for each variable as well as heterogeneity within the definition of outcomes, variable of interest and time period. Therefore, we felt that qualitative synthesis was more appropriate for this key question.
Peer Reviewer #3	Executive Summary	Would it be better to summarize the write-up by presenting tabular data? E.g. specific outcomes in rows, covariates in columns and available evidence (pooled or otherwise) in cells such that it is also possible to tell (e.g. from superscripts) where the evidence originated in – RCT, meta-analysis or observational studies	In the main report we do present the data in tabular and text form. However, due to the limited space within the executive summary, we did not present the tables in addition to the text.
Peer Reviewer #3	Executive Summary	Consider specifying either the specify coronary artery or stating "those with anterior infarcts versus other infarcts"	Although we would like to comply with this suggestion and provide more specific detail, the data source does not further specify what "other infarcts" are. We have used the exact terminology as the data source.
Peer Reviewer #3	Executive Summary	Most of the evidence for KQ1 and KQ2 came from RCTs….were these mostly in men? If so, such was not reported in the results above. If the evidence is from refs 61-62-64, then that's hardly representative of all the studies in the review, no?	In reviewing the applicability of studies as well as for the body of evidence, for the majority of outcomes/comparisons there was a higher percent of males enrolled in the trials, and therefore females may be under-represented in the literature for this topic. This was clarified in the discussion to more accurately describe the relative applicability between the two genders.
Peer Reviewer #3	Executive Summary	Like grading of the SOE, assessment of applicability might better fit in the results section.	We prefer to discuss a summary of the SOE and applicability of the body of evidence in the discussion. As the reader can refer to the individual SOE and applicability tables to find details regarding specific comparisons/outcomes, we provide a summary of the SOE and applicability findings of the entire report.

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Peer Reviewer #3	Executive Summary	I think it's better to open the discussion highlighting why this review is novel (what new does it investigate and find that was not investigated before). Then present the main conclusion for the direct comparison. Follow this by a concise para of device-PCI comparison. It is also important to say something about the range of duration of most studies – mostly short-term less 1 year or less. Applicability can be briefly presented along with. I think it is also important to note that safety is UNCLEAR given sparse data and lack of power. Non-significant estimates didn't mean no effect, juts that effect could not be measured given the power. The way I see things, Evidence is insufficient for most outcomes. However, there is some evidence, at best of moderate strength (because mostly its surrogate outcomes), that adjunctive devices offer some benefit. Insufficient evidence compared between devices, and safety remains unclear. These conclusions of mine could change if we focus exclusively on good quality evidence for grading that showed some benefit to on health outcomes (see my thoughts on grading SOE). MACE being a composite outcome, is difficult to value as much as discrete health outcomes.	We have organized the report according to the specific population (STEMI vs. other ACS) for several reasons. First, the population of interest is largely the STEMI population. This was strongly expressed by the Technical Experts and the organization of material by ACS is a common method within the literature on this topic. Secondly, the large majority of data were within the STEMI population and very little if any data were within the NSTEMI/US or mixed populations.
Peer Reviewer #3	Executive Summary	Consider not discussing trends and non-significant findings	All comments regarding trends and nonsignificant findings have been removed, as suggested.
Peer Reviewer #3	Executive Summary	Even longer term?	As suggested, the appropriate duration to study final health outcomes can be subjective and vary between individual patients, therefore we have removed the specified 180-365d but the suggestion to study these outcomes for longer periods of followup remains.
Peer Reviewer #3	Abstract	Instead of direct comparative and controls, consider adjunctive device (plus PCI) versus PCI alone; and adjunctive device (plus PCI) versus PCI plus another adjunctive device	As suggested, we clarified that the "control" group refers to standard PCI.
Peer Reviewer #3	Abstract	Appears to disagree a bit with line 43-44	The results for this outcome have changed with the updated literature search and are consistent with current results.
Peer Reviewer #3	Abstract	Was association weak, or studies mostly under powered?	This sentence was clarified, as suggested, to reflect a lack of power.

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Peer Reviewer #3	Abstract	If the overall body of evidence (RCTs and observational) originated mostly in men (see page XVI, line 18), then this needs mention here in abstract	Same response as above: In reviewing the applicability of studies as well as for the body of evidence, for the majority of outcomes/comparisons there was a higher percent of males enrolled in the trials, and therefore females may be under-represented in the literature for this topic. This was clarified in the discussion of applicability to more accurately describe the relative applicability between the two genders.
Peer Reviewer #3	Abstract	I tend to see things a bit differently: benefits do not outweigh harms in STEMI population. Safety, because of potential type II error, is mostly unclear.	As stated above, we modified the conclusion. For most devices, there are few RCTs evaluating final health outcomes over a long period of followup and furthermore the data outside of STEMI is scarce. Due to type II error, the safety of these devices is unclear.
Peer Reviewer #3	Methods	Did a SIP request go out to the manufacturers of devices?	Yes, and a sentence was added to the Search section of methods to reflect this.
Peer Reviewer #3	Methods	2 reviewers assessed it?	Yes, quality was assessed by 2 reviewers. This was clarified in the corresponding quality section of the methods.
Peer Reviewer #3	Methods	What was the reference community and its event rate?	The events rate in the control and intervention groups can be derived from the evidence tables in the Appendix. Along with the rates, the reader can refer to the baseline characteristics tables also found the appendix to judge the population and setting from the trial in order to evaluate the applicability of the data to their own population and setting.
Peer Reviewer #3	Methods	It is recommended that publication bias should be assessed when there are 10 or more studies in a meta-analysis	Since there is no clear evidence on the minimum number of studies to allow the assessment of publication bias, we reported the evidence whenever there were enough studies to report it. While some may be skeptical of publication bias with smaller numbers of studies, the number of studies included in the analyses are clearly delineated. If we limited it to 10 or more, others would be denied the information that may be important to them.

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Peer Reviewer #3	Results	Total in PRISMA diagram corresponding to "identification" is 1058 and not 1056. Also since there were duplicates, they are not unique citations	With the addition of new literature from the updated literature search, the numbers of the PRISMA diagram have been updated to match current results.
Peer Reviewer #3	Results	There are no Risk of Bias charts	Our evaluation of each included trial and study is presented in the quality and characteristics tables found in Appendix D. The quality criteria were used to determine if the study was "good", "fair" or "poor" and then subsequently used to grade the strength of evidence.
Peer Reviewer #3	Results	Why were so many systematic reviews and meta-analyses included but only one was used in synthesis of evidence?	We were interested in the methodology and results of similar meta-analyses previously conducted on this topic and therefore did not exclude them from our literature base. Additionally, the design and results of each review/analysis were reviewed to make comparisons with our findings. As a result, we found that although several meta-analyses have been conducted recently, the majority are limited to patients with STEMI and do not evaluate adjunctive devices in other ACS, few included the analysis of adverse events which are further limited to procedure time and coronary perforation, and the most recent analyses did not evaluate embolic protection devices. Therefore, our CER would add to the literature and reflect contemporary practice. This is specified on page 38 in the "study design and characteristics" section.
Peer Reviewer #3	Results	This sensitivity analysis on good trials, instead, should have been graded instead of all RCTs for Cath. Aspiration in STEMI population	When a large preponderance of the evidence was from "good" quality trials we did not inherently downgrade the strength of evidence due to few poorer quality trials.
Peer Reviewer #3	Results	This evidence from good quality trials on longest followup should have been graded for SOE instead	When a large preponderance of the evidence was from "good" quality trials we did not inherently downgrade the strength of evidence due to few poorer quality trials.

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Peer Reviewer #3	Results	A summary table can obviate this write-up and may be more useful. Unless I have missed, number of “direct comparative” trials is not reported Consider an overall overview, not one presented separately for quantitative and qualitative syntheses.	We felt it was important to give the reader an overview of the trials which were summarize quantitatively separately from those discussed qualitatively to aid in the understanding of the population and study design. We also separately evaluated STEMI and NSTEMI/UA and therefore felt it was important to describe these two populations independently. The direct comparative trials are included (and referenced) in the last paragraph on page 34.
Peer Reviewer #3	Results	Fig 3 should preferably be moved here – ditto for others	The figures were all embedded in the text as suggested to make a more reader friendly presentation.
Peer Reviwer #3	Results	Was this abbreviation for percutaneous thrombectomy introduced before? Would this trial also feature under thrombectomy category?	The page was reviewed entirely and there are no un-identified abbreviations used. All device categories are stated as throughout the document. There are references to specific device names that were used in specific trials, which was commonly done in the event there was only one trial evaluating the specific outcome/comparison.
Peer Reviewer #3	Results	This title is better as it informs of the subpopulation of interest unlike previous figures	As suggested, the title of figures have been modified to reflect the subpopulation of interest
Peer Reviewer #3	Results	It will be helpful to see n/N of intervention and control for each study in the forest plot?	We strongly disagree that this would provide much value. The figures show relative weighting, have the effect size with 95% CIs and is clear to view. Adding additional information to the report figures will not improve its readability or its interpretation in a substantive way we strongly believe.
Peer Reviewer #3	Results	If the event rate is quite low, some statisticians might object to the use of random effects model – see AHRQs guidance for rare events	This topic was discussed at length after initial associate editor review and agreed upon to move forward with the methodology as is.
Peer Reviewer #3	Results	Consider replacing Table 45 with Appendix G	Table 45 was a summary table which was recommended for addition into the report by initial AHRQ/ associate editor review to replace the strength of evidence tables, which we were asked to move into the Appendix.

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Peer Reviewer #3	Discussion	This section lacks comparison with extant literature and a discussion of discordant findings such as line 4-6, page VII	You need to remember that we have discussion sections at the end of each key questions and an overall discussion at the end of the document for the entire report. We did not want to be duplicative in the report discussion. So we believe that we have all the discussion required with all the discussions (for each key question and the overall discussion) viewed as a whole.

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Peer Reviewer #3	Grading the Strength of Evidence	▪ Only important outcomes are to be graded – outcomes that matter. These are usually clinical/health outcomes rather than surrogate ones, unless surrogate outcomes have incontrovertibly strong association with clinical outcomes in epidemiologic literature. Reflow, MBG, TIMI, I am confident, do not meet these criteria. But perhaps, investigators would still want to grade them so I agree to disagree. However, their surrogacy should be acknowledged as important indirectness. ▪ The domain names do not conform to the paper by Owens et al. for the EPCs ▪ Limitations, or rather risk of bias, should be rated as low, medium or high for the bunch of studies rated as good/fair/poor. (current usage is that of GRADE working group) ▪ Only one body of evidence should be rated per outcome, not both – RCT or observational ▪ Rating of consistency and directness should also follow that in the right column in Table 1 of Owen's paper ▪ Even when all contributing studies are rated as good and overall limitation/ROB for the body of evidence is rated as low risk of bias; there is no inconsistency; imprecision – I would still grade outcomes such as TIMI, MBG, no-reflow not as high but moderate because of important indirectness. ▪ When, for an outcome, a subset of higher quality studies are met-analyzed in a sensitivity analysis, then one must use that best evidence for grading – quality over quantity (Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions!) ▪ When estimates are not significant, and CIs are wide enough to go beyond the margins of clinically relevant efficacy and harm, no effect should not be concluded. True effect could lie anywhere along the CI. What we can conclude about the grade is that evidence is insufficient (insufficient in power) even when there are several studies in a meta-analysis (Owen`s paper in Journal of clinEpi.). Just as an example, and there are others, in Table 191 (page G-10), for TIMI-3, evidence was rated as very imprecise….yet the grade was assigned `Low` instead of insufficient. ▪ Direct comparative evidence should also be graded…even when insufficient. ▪ Side branch occlusion was not an a priori outcome…was never part of the analytic framework. Can only be graded by being transparent about this post hoc decision and after thoughtful consideration that it represents a clinically meaningful outcome.	As suggested, for outcomes which had nonsignificant findings with confidence intervals beyond meaningful efficacy and harm, strength of evidence was modified to insufficient. As suggested, strength of evidence tables were added to reflect direct comparative evidence. As suggested, since side branch occlusion was not listed in the analytic framework, strength of evidence was not graded. In the methods section, we specify that the GRADE system was used for the grading of the strength of evidence, therefore the terminology used in the strength of evidence tables is consistent with the GRADE system. The key informants and technical experts strongly believe that intermediate outcomes such ass MBG and TIMI3 are clinically important and meaningful outcomes and therefore these outcomes were not downgraded as "indirect" since they themselves have value in the clinical setting. Additionally, there are no conclusions made in the report suggesting that a decrease in MBG or TIMI3 flow decreases final health outcomes.