

Evidence-based Practice Center Systematic Review Protocol

Project 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*

I. Background and Objectives for the Systematic Review

Coronary stents and adjunctive pharmacologic agents—including glycoprotein IIb/IIIa receptor inhibitors and thienopyridines—have improved the efficacy of percutaneous coronary intervention (PCI).^{1,2} However, dislodgement of atherothrombotic material from coronary lesions during PCI can result in distal embolization that leads to what is commonly referred to as the “no-reflow phenomenon.” This phenomenon, characterized by inadequate flow at the cardiac tissue level despite patent coronary vessels—often defined as (1) a thrombolysis in myocardial infarction (TIMI) flow grade ≤ 2 despite vessel patency and the absence of dissection, spasm or distal macroembolus, or (2) a myocardial blush grade (MBG) of 0 or 1—has been associated with larger infarcts, more significant left ventricular systolic dysfunction, and an increased risk of major adverse cardiovascular events (MACE) or death. Depending on the exact clinical definition used, the incidence of no-reflow has been found to range from 12 to 39 percent.^{1,2}

Numerous adjunctive devices have been developed in an attempt to improve clinical outcomes by removing thrombi and to protect against distal embolization during PCI.³ These devices utilize different technologies and can be broadly classified as thrombus aspiration, mechanical thrombectomy, or embolic protection devices (i.e., distal embolic balloon or filter protection devices or proximal embolic balloon or filter protection devices). Although such devices (mainly embolic protection devices) have previously been demonstrated to reduce MACE in patients undergoing PCI for degenerative saphenous vein grafts (Class 1 recommendation),^{1,2} their use during acute coronary syndromes (ACSs)—particularly, ST-segment elevation myocardial infarction (STEMI)—has been less well supported mainly because of underpowered clinical trials that evaluated intermediate markers (Class IIb C recommendation).² More recently, larger randomized controlled trials of patients with STEMI have evaluated MACE as an end point and followed patients beyond hospital discharge (typically 3 to 12 months) but have given conflicting results.⁴⁻⁷

Recent data suggest that different types of adjunctive device may be associated with different degrees of benefit,⁸ with some (AngioJet[®], Possis Medical Inc., Minneapolis, MN) even being shown to increase MACE when compared to a control.⁴ Thus, the comparative efficacy and safety of these devices is unclear and needs to be systematically evaluated.

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Objective

To perform a comparative effectiveness review examining the benefits and harms associated with using adjunctive devices to remove thrombi or protect against distal embolization in patients with ACS who are undergoing PCI of native vessels.

II. The Key Questions

Question 1

In patients with ACS who are undergoing PCI of native vessels, what are the comparative effects of adjunctive devices from different classes (e.g., thrombus aspiration, mechanical thrombectomy, distal embolic balloon, distal embolic filter protection, proximal embolic balloon, proximal embolic filter protection) on intermediate outcomes (e.g., ST-segment resolution, MBG, TIMI-3 flow, ejection fraction and distal embolization) and terminal outcomes (mortality, MACE, health-related quality-of-life)?

Question 2

In patients with ACS who are undergoing PCI of native vessels, how does the rate and type of adverse events (e.g., coronary dissection, perforation, prolonged procedure time) differ between device types when compared to PCI alone?

Question 3

In patients with ACS who are undergoing PCI of native vessels, which patient characteristics (e.g., gender, age, ethnicity, diabetes, smoker, ejection fraction, primary or rescue PCI, use of glycoprotein IIb/IIIa inhibitors, ischemia time, presence of a thrombus-containing lesion, infarct-related artery and pre-PCI TIMI flow, use of direct stenting) affect outcomes?

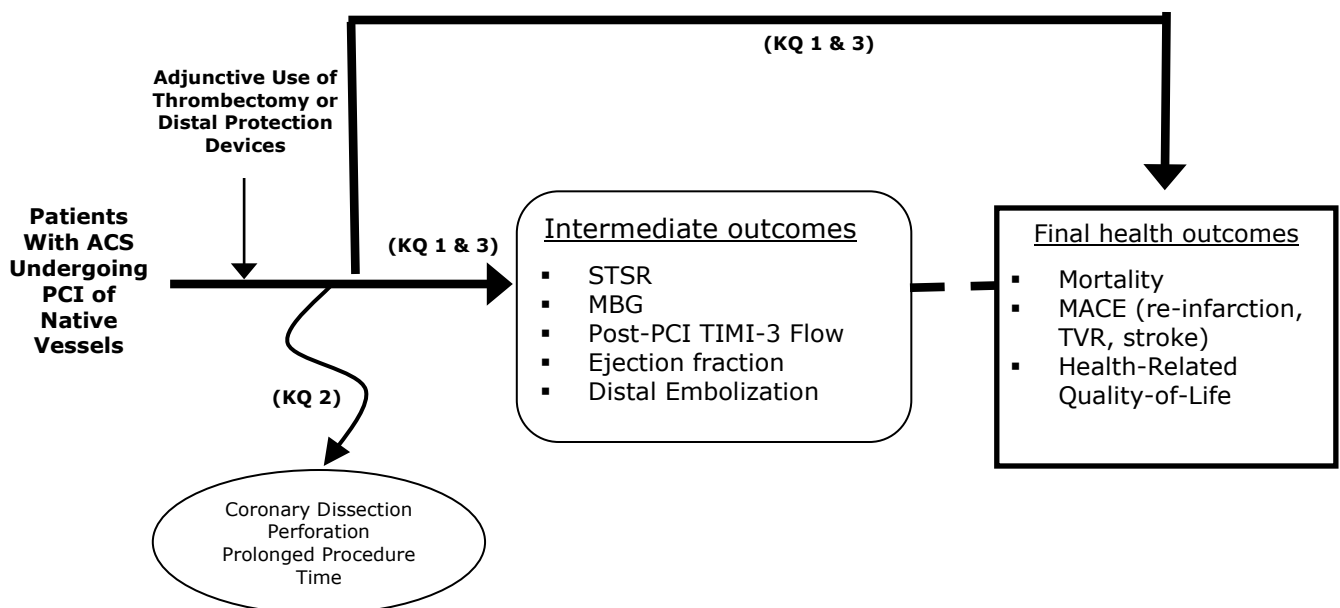
Public Comment

The Draft Key Questions were posted for public comment. Based on the comments received and input from the Technical Expert Panel, we have not altered our Key Questions.

III. Analytic Framework

To guide our assessment of studies examining the association between using adjunctive devices to remove thrombi or protect against distal embolization in patients with ACS who are undergoing PCI of native vessels and the various benefits and harms and harms of those devices, we developed an analytic framework to map specific linkages from comparisons to subpopulations of interest, mechanisms of benefit, and outcomes of interest (Fig. 1). It is a logic chain that supports the link from the intervention to the outcomes of interest.

Figure 1. Provisional Analytic Framework for Adjunctive Devices To Remove Thrombi and Protect Against Distal Embolization in Patients With ACS Who Are Undergoing PCI of Native Vessels.



IV. Methods

A. Criteria for Inclusion and Exclusion of Studies in the Review

Two independent reviewers will assess studies for inclusion in a parallel manner by using criteria defined a priori. Randomized controlled trials (RCTs) or controlled observational studies that enrolled ≥ 500 patients will be eligible for inclusion if they (1)

compared the use of adjunctive devices (i.e., thrombus aspiration, mechanical thrombectomy, distal embolic balloon, distal embolic filter protection, proximal embolic balloon, proximal embolic filter protection) to remove thrombi or protect against distal embolization versus a control (active or nonactive) before PCI, (2) included only patients with ACS, (3) enrolled only patients with a target lesion(s) in native vessels, and (4) reported data on at least one prespecified patient morbidity (ST segment resolution, MBG, TIMI-3 blood flow, ejection fraction, distal embolization, MACE), mortality, safety (coronary dissection, perforation, prolonged procedure time), or health-related quality-of-life outcome. Observational studies that enrolled <500 subjects will be excluded, since numerous RCTs already exist within this smaller sample size range, observational studies in this range contain small initial experiences not representative of current practice, and small studies will not help define the applicability of evidence in a tangible way.

B. Searching for the Evidence: Literature Search Strategies for Identifying Relevant Studies To Answer the Key Questions.

We will conduct a computerized literature search of the Cochrane Library and MEDLINE databases for both RCTs and observational studies that were published from January 1996 through March 2010. The complete search strategy is included in Appendix A. We will not apply any language restrictions. Additionally, in an attempt to locate unpublished studies and increase the sensitivity of our search, references from identified studies, systematic reviews, and meta-analyses will be reviewed. Abstracts from major cardiology meetings (American Heart Association, American College of Cardiology, European Society of Cardiology, and the Transcatheter Cardiovascular Therapeutics Conference of the Cardiovascular Research Foundation) and from the TCTMD (<http://www.tctmd.com>), the CardioSource Plus (<http://www.cardiosource.com>), and ClinicalTrials.gov (<http://www.clinicaltrials.gov>) Web sites will be searched and reviewed.

The literature search will be updated concurrently with the peer-review process. Newly identified literature will be evaluated by two independent reviewers who will use the aforementioned inclusion criteria. Relevant literature will be discussed with the Task Order Officer to determine whether to incorporate it qualitatively or quantitatively into the report. This review process will all occur before the submission of the revised report.

C. Data Abstraction and Data Management

Two reviewers will use a standardized data-abstraction tool to independently extract study data. Data abstracted from each study will include interventions, study design, inclusion and exclusion criteria, methodological quality criteria, study population, baseline patient characteristics, use of concurrent standard medical therapies, data needed to assess for applicability (as specified in section F below), and prespecified benefits and harms (as specified in the Key Questions).

D. Assessment of Methodological Quality of Individual Studies

Validity assessment will be performed using the recommendations in the [Methods Guide for Effectiveness and Comparative Effectiveness Reviews](#). Each study will be assessed for the following individual criteria: comparable study groups at baseline, detailed description of study outcomes, blinding of outcome assessors, intent-to-treat analysis, description of participant withdrawals (percent followup), and potential conflict of interest. Additionally, RTCs will be assessed for randomization technique and allocation concealment. Observational studies will be assessed for sample size, participant selection method, exposure measurement method, potential design biases, and appropriate analyses to control for confounding. Studies will then be given an overall score of good, bad, or poor (Table 1).

Table 1. Summary ratings of quality of individual studies

Quality Rating	Definition
Good (low risk of bias)	These studies have the least bias and results are considered valid. A study that adheres mostly to the commonly held concepts of high quality include the following: a formal randomized, controlled study; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; less than 20 percent dropout; and clear reporting of dropouts.
Fair	These studies are susceptible to some bias, but it is not sufficient to invalidate results. They do not meet all the criteria required for a rating of good quality because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
Poor (high risk of bias)	These studies have significant flaws that imply biases of various types that may invalidate the results. They have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

E. Data Synthesis

We will qualitatively examine data from all identified studies. For each outcome, we will conduct separate analyses of studies and compare each individual adjunctive device (e.g., thrombus aspiration, mechanical thrombectomy, distal embolic balloon, distal embolic filter protection, proximal embolic balloon, proximal embolic filter protection) with control and studies in which different adjunctive device were compared to each other. We will conduct separate analyses for studies that enrolled patients

experiencing only STEMI and studies that enrolled patients experiencing non-ST segment elevation myocardial infarction or unstable angina. We will conduct meta-analyses when two or more RCTs that are adequate for data pooling are available for any outcome. Observational studies will not be pooled with RCTs. For dichotomous outcomes, weighted averages will be reported as relative risks and risk differences with associated 95 percent confidence intervals. As heterogeneity between included studies is expected, a DerSimonian and Laird random-effects model will be used when pooling data and calculating relative risks, risk differences, and 95 percent confidence intervals.⁹ When pooling continuous outcomes, weighted mean differences along with 95 percent confidence intervals will be calculated by using a DerSimonian and Laird random-effects model.⁹

Statistical heterogeneity will be addressed by using the I^2 statistic, which assesses the degree of inconsistency not due to chance across studies and ranges from 0-100 percent with the higher percentage representing a higher likelihood of the existence of heterogeneity. Whereas categorization of I^2 values may not be appropriate in all situations, an I^2 value of >50 percent has been regarded as representative of important statistical heterogeneity. Visual inspection of funnel plots and Egger's weighted regression statistics will be used to assess for the presence of publication bias.¹⁰ Statistics will be performed by using StatsDirect statistical software, version 2.4.6 (StatsDirect Ltd., Cheshire, England). For all analyses, a p -value of <0.05 will be considered statistically significant.

To assess the effect of heterogeneity (both clinical and methodological) on the conclusions of our meta-analysis, we will conduct subgroup, meta-regression, and sensitivity analyses. These analyses will also be conducted to assess the effect of trial inclusion criteria, patient demographics (age, sex, and ethnicity), baseline patient health status (smoking history, history of diabetes, type of ACS, ejection fraction, ischemia time, pre-PCI TIMI flow, presence of thrombus-containing lesion, and patency of the infarct-related artery), selected treatment (rescue PCI, administration of glycoprotein IIb/IIIa inhibitors, and direct stenting), follow-up duration (<6 months vs. \geq 6 months and publication type (full-text vs. abstract only) on the efficacy of adjunctive devices.

F. Grading the Evidence for Each Key Question

We will use the [Grading of Recommendations Assessment, Development and Evaluation](#) system to assess the strength of evidence for each outcome of interest separately. This system uses four required domains—risk of bias, consistency, directness, and precision. Additional domains will not be assessed because they were deemed irrelevant to this review. All assessments will be made by two investigators, who will resolve disagreements through discussion. The evidence pertaining to each key question will be classified into three broad categories: high, moderate, or low grade (Table 2). Below we describe in more detail the features that will determine the strength of evidence for the different outcomes evaluated in this report.

Table 2. Definitions for grading the strength of evidence

Grade	Definition
High	There is high confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

Risk of Bias

Risk of bias is the degree to which the included studies for any given outcome or comparison has a high likelihood of adequate protection against bias. This can be assessed through the evaluation of both design and study limitations. Whether the study was designed as an RCT or an observational study will be recorded. Studies will be ranked as having no limitations, serious limitations, or very serious limitations.

Consistency

Consistency refers to the degree of similarity in the direction of the effect sizes from included studies within an evidence base. We will assess whether or not the effect sizes were on the same side of unity; whether the range of effect sizes was narrow, and the degree of statistical heterogeneity in evaluating consistency. We will rank this domain as no inconsistency, serious inconsistency, and very serious inconsistency. When only a single study is included, consistency cannot be judged.

Directness

Directness refers to whether the evidence links the compared interventions directly with health outcomes, and compares two or more interventions in head-to-head trials. Indirectness implies that more than one body of evidence is required to link interventions to the most important health outcomes. We will rank this domain as no indirectness, serious indirectness, and very serious indirectness.

Precision

Precision refers to the degree of certainty surrounding an effect estimate with respect to a given outcome. For example, when a meta-analysis is performed, we will evaluate the confidence interval around the summary effect size. A precise estimate is an estimate that would allow a clinically useful conclusion. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions

(e.g. both clinically important superiority and inferiority), a circumstance that will preclude a conclusion.

Applicability of Evidence

To be included in the comparative effectiveness review, studies must meet five of the following seven criteria: used a primary care population, used less-stringent eligibility criteria, assessed final health outcomes, had an adequate study duration with clinically relevant treatment modalities, assessed adverse events, had an adequate sample size, and used intention-to-treat analysis.¹¹ Studies meeting fewer than five criteria would be classified as efficacy trials and be deemed to have less applicability. Table 3 identifies the factors that are important for determining applicability; those factors will be extracted into evidence tables for every study we evaluate. By using all of the applicable studies to answer a key question, the applicability of the body of evidence will then be determined and reported separately and qualitatively for each outcome of interest.

Table 3. Applicability PICOTS and data to extract

Feature	Condition that limits applicability	Features to be extracted into evidence table
Population	Differences between patients in the study and the community	Eligibility criteria, demographics
Population	Events rates markedly different than in the community	Event rates in treatment and control groups
Intervention	Treatment not reflective of current practice	Type of device, device name
Comparator	Use of substandard alternative therapy	Type of comparator
Outcomes	Intermediate end points, brief followup periods, improper definitions for outcomes, composite end points	Outcomes (benefits and harms) and how they were defined
Settings	Settings where standards of care differ markedly from setting of interest	Clinical setting and geographic setting



V. References

1. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Assoc Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *J Am Coll Cardiol* 2005;47:1-121.
2. Silber S, Albertsson P, Aviles FF, et al. Guidelines for percutaneous coronary intervention. *Eur Heart J* 2005;26:804-47.
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4. Ali A, Cox D, Dib N, et al. Rheolytic thrombectomy with percutaneous coronary intervention for infarct size reduction in acute myocardial infarction: 30-day results from a multicenter randomized study. *J Am Coll Cardiol* 2006;48:244–52.
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6. Kelbaek H, Terkelsen CJ, Helqvist S, et al. Randomized comparison of distal protection versus conventional treatment in primary percutaneous coronary intervention: the Drug Elution and Distal Protection in ST-Elevation Myocardial Infarction (DEDICATION) Trial. *J Am Coll Cardiol* 2008;51:899–905.
7. Tahk SJ, Choi BJ, Choi SY, et al. Distal protection device protects microvascular integrity during primary percutaneous intervention in acute myocardial infarction: A prospective, randomized, multicenter trial. *Int J Cardiol* 2008;123:162–8.
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9. DerSimonian R, Laird N. Meta-Analysis in clinical trials. *Controlled Clin Trials*. 1986 ;7 :177-188.
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11. Gartlehner G, Hansen RA, Nissman D, et al. A simple and valid tool distinguished efficacy from effectiveness studies. *J Clin Epidemiol* 2006;59:1040-8.

VI. Definition of Terms

Term	Definition
ACS	acute coronary syndrome
EPC	Evidence-based Practice Center
MACE	major adverse cardiac event
MBG	myocardial blush grade
PCI	percutaneous coronary intervention
RCT	randomized controlled trial
STEMI	ST-segment elevation myocardial infarction
TIMI	thrombolysis in myocardial infarction

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

NOTE: The following protocol elements are standard procedures for all protocols.

VIII. Review of Key Questions

For Comparative Effectiveness reviews (CERs) the key questions were posted for public comment and finalized after review of the comments. For other systematic reviews, key questions submitted by partners are reviewed and refined as needed by the EPC and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed.

IX. Technical Expert Panel (TEP)

A TEP panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. The TEP provides information to the EPC to identify literature search strategies, review the draft report and recommend approaches to specific issues as requested by the EPC. The TEP does not do analysis of any kind nor contribute to the writing of the report.

X. Peer Review

Approximately five experts in the field will be asked to peer review the draft report and provide comments. The peer reviewer may represent stakeholder groups such as professional or advocacy organizations with knowledge of the topic. On some specific reports such as reports requested by the Office of Medical Applications of Research, National Institutes of Health there may be other rules that apply regarding participation in the peer review process. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

It is our policy not to release the names of the Peer reviewers or TEP panel members until the report is published so that they can maintain their objectivity during the review process.



APPENDIX A. Search Strategy for MEDLINE, CENTRAL, CDSR (each in OVID starting in 1996), and Web of Science (limited to meeting abstracts only)

1. myocardial infarction
2. acute myocardial infraction
3. AMI
4. MI
5. STEMI
6. ST-segment elevation
7. acute coronary syndrome
8. ACS
9. NSTEMI
10. unstable angina
11. ST-segment resolution
12. Q-wave
13. no reflow
14. distal embolization
15. percutaneous coronary intervention
16. PCI
17. OR/1-16
18. thrombectomy
19. embolic protection
20. distal protection
21. proximal protection
22. thrombus aspiration
23. aspiration catheter
24. Rescue catheter
25. Diver CE
26. Export catheter
27. Transvascular aspiration catheter
28. TVAC
29. Pronto
30. X-sizer
31. Angiojet
32. Filterwire
33. Spiderx
34. Spiderfx
35. Angioguard
36. Proxis
37. Interceptor plus
38. Rinspirator
39. Microvena Trap



40. Percusurge
41. Triactiv
42. Cardioshield
43. Thrombobuster
44. Rio catheter
45. Fetch catheter
46. QuickCat
47. Rubicon catheter
48. Parodi Anti-EmboliSation
49. OR/18-49
50. 17 AND 49
51. 50 NOT carotid
52. Limit 51 to humans