Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: *Antiplatelet and Anticoagulant Treatments for Unstable Angina/Non-ST Elevation Myocardial Infarction*

Draft review available for public comment from November 1 to November 29, 2012.

Research Review Citation: Melloni C, Jones WS, Washam JB, Hasselblad V, Mayer SB, Halim S, Subherwal S, Alexander K, Kong DF, Heidenfelder BL, Irvine RJ, Wing L, Dolor RJ. Antiplatelet and Anticoagulant Treatments for Unstable Angina/Non–ST Elevation Myocardial Infarction. Comparative Effectiveness Review No. 129. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-2007-10066-I.) AHRQ Publication No. 13(14)-EHC125-EF. Rockville, MD: Agency for Healthcare Research and Quality; updated January 2014. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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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
TEP Member 2	Structured Abstract	Good, except seems to waffle about relative value of RCTs over observational studies (especially where extreme selection bias is likely—i.e., for PPIs). Page 49. I-17-22 gives a better summary of this.	The wording has been changed in the Abstract.
Gans-Brangs, Kathleen (AstraZeneca)	Structured Abstract	Page iv Results section, para 2, sentence 3 Event rates are incorrect for ticagrelor and clarification is needed on type of death evaluated; Values for prasugrel were switched. Revise to: At 30 days, prasugrel reduced rates of cardiovascular death/myocardial infarction/stroke (5.7% prasugrel, 7.4% clopidogrel) and ticagrelor reduced the same composite endpoint (4.8% ticagrelor, 5.4% clopidogrel) compared with clopidogrel (moderate SOE). Source: Wallentin 2009- PLATO, pg 1052, Table 3	We have corrected this in the Abstract.
Gans-Brangs, Kathleen (AstraZeneca)	Structured Abstract	Page iv Results section, para 2, sent 4 The event rates for the combined UA + NSTEMI population were not reported in the PLATO publication. Data for the UA or NSTEMI population individually was reported in PLATO. It appears that the event rates for the primary composite endpoint in the combined UA + NSTEMI population were calculated using K-M estimates of the individual UA and NSTEMI data reported in PLATO; therefore, the methodology of these calculations should be disclosed in this report.	We have added further detail regarding the combination of UA and NSTEMI data to the Results section. Namely "Combined UA/NSTEMI subgroup data for the primary composite endpoint were available for the TRITON-TIMI 38 study; these percentages were manually calculated for the PLATO study from the individually reported UA and NSTEMI subgroup data."
Peer Reviewer 6	Executive Summary	ES-3 line 45 "rapid and potent" is used again; it was stated in a previous sentence. This may be a typo.	We do use this phrase and one similar to it in the same paragraph; however, we are using it in the first instance to compare prasugrel with clopidogrel, and in the second instance to compare ticagrelor with clopidogrel. In both instances, this description is accurate.
TEP Member 1	Executive Summary	ES-16. A minor word order change would make the key point more clearly, as per track changes which follow: "A 600 mg loading dose of Clopidogrel at 30 days was associated with lower rates of nonfatal MI and lower incidence of stent thrombosis at 30 days compared with a 300 mg loading dose."	The change has been made.
TEP Member 1	Executive Summary	ES-25. The listed order and wording of the two key points on low dose vs high dose aspirin appear to strongly favor high dose aspirin. However, the analysis on pp. 114-15 and summary on pp. 177-178 are far more circumspect and would suggest that the use of low dose aspirin has supporting data. Would therefore recommend re-wording the final key point statements to more strongly highlight the low or insufficient strength of evidence for much of the information in this section, since most providers will turn directly to those summary sentences for guidance.	We now combine these two key points in to one key point highlighting where there is low strength of evidence and stating that the evidence for all other outcomes was insufficient

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TEP Member 4	Executive Summary	Objective: the objective is really never stated. There is a description of the problem.	The objective is described in the Scope section of the Executive Summary.
TEP Member 4	Executive Summary	ES-3 Table A, should the aspirin doses be defined. As written high and low, one could assume that low for early invasive in 80 mg, where most would argue it is 162 mg and for outpatient low may be 81 mg. This may be useful to put in a footnote.	Thank you for the comment, a footnote has been added to the table.
TEP Member 4	Executive Summary	ES-3. Line 49. Statement comparing Ticagrelor and Clopidogrel should have a reference.	The reference has been added.
TEP Member4	Executive Summary	ES-5. Is the initial ASA dose 160-325 or 162-325 mg?	The initial dose is 162–325 mg, as found in the UA/NSTEMI guidelines (Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: Executive summary - A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 2002 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction). Circulation. 2007;116(7):803-877).
TEP Member 4	Executive Summary	ES-8, line 35. A comma is needed between the clinicians and patients	The comma has been added.
TEP Member 4	Executive Summary	ES-11, line 42: I would define PICOTS as it appears this is the first time it is used.	We have added the definition of PICOTS at first use.
TEP Member 4	Executive Summary	ES-14, line 55. Need a period not a comma	Thank you for finding this typo. We have since deleted this key point as it duplicated part of the previous key point.
TEP Member 4	Executive Summary	ES-34, line 41. The above sentences state that there was insufficient evidence regarding triple therapy and then quote the AHA guidelines level I and IIb recommendation. I think I would state more clearly if the results of this systematic review support these recommendations.	The relationship between the triple therapy results and the guidelines is more fully discussed in the "Findings in Relation to What is Already Known" section of the main report.
TEP Member 4	Executive Summary	ES-35, limitations: Other limitations include improved diagnostic tests that have altered the definition and classification of MI and varying definitions of UA included in all of these studies.	As you suggested, we have included these additional limitations.
TEP Member 4	Executive Summary	ES-35, line 37. I think the knowing the optimal time prior of upstream administration is a research gap. Should drugs be administered right before PCI, 6 hours prior, 12 hours prior if possible?	We have added this as a limitation and highlighted this in research gaps section.

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TEP Member 4	Executive Summary	The objective section describes uncertainty around dosing and timing and yet only with the glycoprotein inhibitors is timing addressed. It may be helpful to state the results around the timing issue	Given the complexity of the report, we primarily listed key points around findings with high, moderate or low evidence. Expanding the key points to include the results of all timing issues makes this section lengthy.
TEP Member 4	Executive Summary	I did not repeat the comments noted in the Executive Summary on the full document. However, some of these issues are present in that section also.	We have addressed these issues in the main report as well as the Executive Summary.
Bradfield, Lisa (American College of Cardiology)	Executive Summary	Really helpful for the current ongoing UA/NSTEMI guideline revision.	Thank you.
Chapell, Richard	Executive Summary	For the reasons discussed under "Introduction", please include GPIs as a treatment option when an initial conservative approach is implemented.	GPI has been added to the Introduction of both the main report and the Executive Summary in Table A/Table 1 and Figure A/Figure 1.
Gans-Brangs, Kathleen (AstraZeneca)	Executive Summary	ES-3 Section: Aspirin and Antiplatelet Agents, para 1, sentence 8 Ticagrelor is reversibly-binding. There is currently no known treatment or antidote to reverse the antiplatelet effects of ticagrelor in the acute treatment setting. Revise to: Ticagrelor is a reversibly-binding reversible P2Y12 receptor antagonist that, when compared with clopidogrel, provides a more rapid and more potent inhibition of platelets. Source: BRILINTA Prescribing Information	The sentence has been revised as suggested.
Gans-Brangs, Kathleen (AstraZeneca)	Executive Summary	ES-17 3rd bullet. Change low SOE to Moderate SOE as the composite endpoint after 1 year is shown as moderate SOE in Table D. Revise to: After 1 year, both ticagrelor and prasugrel were associated with lower composite ischemic endpoints and individual endpoints (all-cause mortality, cardiovascular mortality, nonfatal MI, stent thrombosis) when compared with clopidogrel (low moderate SOE).	We have reviewed and modified the SOE ratings to be consistent with the bulleted text.
Gans-Brangs, Kathleen (AstraZeneca)	Executive Summary	ES-17 3rd bullet under heading: Key Points for Clopidogrel vs. Ticagrelor vs. Prasugrel: Original text: "After 1 year, both ticagrelor and prasugrel were associated with lower composite ischemic endpoints and individual endpoints (all-cause mortality, cardiovascular mortality, nonfatal MI, stent thrombosis) when compared with clopidogrel (low SOE)." This bullet states that both ticagrelor and prasugrel were associated with lower individual endpoints including all-cause mortality, cardiovascular mortality. However, based on the TRITON-TIMI study, prasugrel was not associated with statistically significant lower individual endpoints of all-cause mortality, cardiovascular mortality.	We have now separated out our findings and key points in to clopidogrel vs. ticagrelor and clopidogrel vs. prasugrel and feel that this helps clarify the different strength of evidence and supporting data.

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Gans-Brangs, Kathleen (AstraZeneca)	Executive Summary	Table D,Row 3, Page ES-17. Composite of CV mortality, nonfatal MI, or nonfatal stroke at 30 days – One of the ticagrelor studies (DISPERSE-2) reported values for ticagrelor that were not lower than clopidogrel (4.3%, ticagrelor vs 3.8%, clopidogrel). The DISPERSE-2 study was not designed to evaluate the efficacy of ticagrelor; there were not sufficient numbers of clinical events to reliably determine the efficacy of ticagrelor versus clopidogrel. Please either remove reference to DISPERSE-2 or provide appropriate context regarding limitations of that study. Revise to: SOE=Moderate (2 3 studies, 32,232 33,216 patients) Ticagrelor (4.3% and 4.8%) and prasugrel (5.7%) were both associated with lower composite endpoints than clopidogrel (3.8%, 5.4% and 7.4%). Source: Cannon 2007-DISPERSE-2, pg 1848, Table 3	We have revised the text and strength of evidence table to show the data and strength of evidence separately for clopidogrel vs. ticagrelor and clopidogrel vs. prasugrel.
Gans-Brangs, Kathleen (AstraZeneca)	Executive Summary	Table D, Row 4, Page ES17. Composite of cardiovascular mortality, nonfatal MI, or nonfatal stroke after 1 year- The event rates for the combined UA + NSTEMI population were not reported in the PLATO publication. Data for the UA or NSTEMI population individually was reported in PLATO. It appears that the event rates for the primary composite endpoint in the combined UA + NSTEMI population were calculated using K-M estimates of the individual UA and NSTEMI data reported in PLATO; therefore, the methodology of these calculations should be disclosed in this report. Additionally, the clopidogrel event rate for TRITON-TIMI study (12.1%) was omitted.	We have added further detail regarding the combination of UA and NSTEMI data to the report. We have added the missing TRITON-TIMI event rate.
Gans-Brangs, Kathleen (AstraZeneca)	Executive Summary	Page ES28, last bullet. A discrepancy in describing the association of DAPT with and without PPI and CV outcomes and the association between low dose ASA with and without PPI and CV outcomes is noted. On DAPT with and without PPI, the following wording is provided (page 182): “Findings based on observational studies may be confounded by selection bias, where sicker patients with more comorbidites are treated with a PPI and therefore have more adverse clinical outcomes”. Although not mentioned in the summary of observational study results for aspirin monotherapy with and without PPI (page 149) similar limitation applies as also recognized by the authors of the published studies (Charlot et al 2010, Charlot et al 2011). Revise to: In observational studies assessing use of PPIs with aspirin monotherapy, there was a higher rate of composite ischemic events, all-cause mortality, and nonfatal MI at 1 year in the group receiving any type of PPI (moderate SOE). As for dual antiplatelet therapy, possible confounding cannot be excluded.	As suggested the sentence on possible confounding has been added to the PPI + aspirin section.

Commentator & Affiliation	Section	Comment	Response
Gans-Brangs, Kathleen (AstraZeneca)	Executive Summary	Page ES32, Para 2, Sent 5 Sentence incorrectly states that ticagrelor did not reduce ischemic endpoints at 30 days compared with clopidogrel. Revise to: Ticagrelor is associated with a significant reduction in ischemic endpoints at 1 year (not at 30 days) when compared with clopidogrel, but unlike prasugrel, the incidence of major bleeding was not significantly higher in ticagrelor-treated patients. Source: Wallentin 2009- PLATO, pg 1052, Table 3.	We have removed the "(not at 30 days)" text from this sentence.
Peer Reviewer 1	Introduction	Adequate rationale and background.	Thank you.
Peer Reviewer 2	Introduction	The introduction is well written and frames the field adequately.	Thank you.
Peer Reviewer 3	Introduction	The introduction is appropriately detailed and gives an overview of the treatment strategies for UA/NSTEMI.	Thank you.
Peer Reviewer 4	Introduction	Intravenous GP IIb/IIIa inhibitors constitute one of the treatment options available for patients who are going to be treated using a conservative management strategy. This application is discussed in the analyses. However it is perplexing not to find it presented in either the first table or the flow diagrams that display available treatment options.	We have added GPI to Table 1 and Figure 1 of the Introduction.
Peer Reviewer 4	Introduction	Similarly, proton pump inhibitors can and frequently are used during hospitalization, but haven't been subjected to RCTs in that setting. While this obviously limits the analysis that can be done, the option should be mentioned.	The original question was on the effectiveness and safety of long-term use of PPIs, so only postdischarge use of PPIs has been addressed in this report.
Peer Reviewer 5	Introduction	well written, concise	Thank you.
Peer Reviewer 6	Introduction	Comments on the background, key question, and treatment algorithm diagrams are above. I found the descriptions of the classes of drugs very helpful. Table 1 (p.2) is also a nice synthesis. What was missing for me, that may have been helpful to have, was the basis for the classification used in Table 1. Is this based on FDA indications, guidelines, consensus, or recent evidence (where guidelines may not yet be updated). Additionally, a reference to the key study(ies), especially for the new anticoagulants and anti-platelets would be helpful. Since the studies are in the references and tables, it would be nice to include a reference list to them to allow the reader to access the primary data if so desired.	All references used to support the listing of medications in Table 1 and Figure 1 are cited in the text of the introduction, therefore we are not annotating the tables and figures to add specific references. A reference list of the cited articles is available at the end of the Executive Summary and full report.
TEP Member 1	Introduction	Excellent. No Comments.	Thank you.
TEP Member 2	Introduction	Background: Concise, accurate.	Thank you.
TEP Member 2	Introduction	Treatment strategies: Good. (data is a plural word). What is missing is that the majority of patients presenting to ED with chest pain have non-cardiac or low-probability for ACS and are at low risk and should receive a conservative approach (vs p14, line 38). It is critical to put this into context for applicability.	All patients included in the analysis had a diagnosis of unstable angina and/or myocardial infarction. We also corrected the use of data in the sentence ("these recent data").

Commentator & Affiliation	Section	Comment	Response
TEP Member 3	Introduction	No major comments.	Noted.
TEP Member 4	Introduction	The introduction clearly highlights some the key issues of the systematic review.	Thank you.
TEP Member 4	Introduction	Page 3, line 44: Should the Figure describing the treatment strategy be referenced?	We created Figure 1 for this report, so there is no need to reference it.
TEP Member 5	Introduction	Introduction is clear, especially for readers familiar with the classes of drugs. Those unfamiliar might want a bit more information on mechanism. A table that provides a brief mechanism of action and also includes proton pump inhibitors (which are not described at all) would be helpful.	Thank you for the comment. This is already a very large report, and delving further into the background for these drugs is out of scope. It is our hope that readers who need more detail on mechanisms of action would be able to find references on their own.
Bradfield, Lisa (American College of Cardiology)	Introduction	Really helpful for the current ongoing UA/NSTEMI guideline revision.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Chapell, Richard	Introduction	The discussion of treatment approaches to UA/NSTEMI (pp 3 to 5, Figures 1 and 2), does not include GPIs as a treatment option when an initial conservative approach is implemented. In clinical practice, they are commonly utilized, as reflected in Table 2 of the ACCF/AHA 2012 guidelines. ACCF/AHA recommends use of eptifibatide or tirofiban in addition to anticoagulant and antiplatelet therapy with a level of evidence of B. Regardless of whether AHRQ chooses to consider the evidence for the use of GPIs at this point in therapy as part of the Key Questions, any discussion of treatment options is incomplete without their inclusion in this therapeutic approach. We request that GPIs be added to the appropriate places in Figures A, 1 and 2. We further request that the EPC add GPIs to the options they consider for Key Question 2. If GPIs are not addressed in Key Question 2, we request that the EPC add text acknowledging them as a treatment option and detailing the reasons for their omission from the review. Reference: Jneid H, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines (2012 Focused Update). J Am Coll Cardiol. 2012;60(7):645–681. Throughout the document, the risks of Major and Minor bleeding events are evaluated. However, these terms are never defined. We are aware that such definitions are difficult because they often vary from study to study, but this fact is not acknowledged in the draft review until page 190. Treatment decisions for patients with UA/NSTEMI center on the trade-offs between risk of ischemic events and risk of bleeding events. Without a thorough understanding of these risks, no evidence-based decisions can be made. For this reason, we request that the Introduction be expanded to include a discussion of the various established methods for classifying bleeding events, possibly including a descriptive table.	We have added GPI to Table 1 and Figure 1 and Table A and Figure A. The comparison of GPI with UFH versus UFH alone was included in the Key Question 2 section. We decided not to add a table of definitions for classifying the various methods for bleeding events. If we did this, then we would have to define the various methods for classifying all the other clinical endpoints (e.g., myocardial infarction, stent thrombosis, stroke, etc.). This report is lengthy and, given space limitations, we cannot expand the Introduction to include a clinical synopsis of the various endpoint definitions. For the most part, the endpoint definitions were very similar across studies, thus any subtle differences in methods for classifying the endpoints is minimal.
Gans-Brangs, Kathleen (AstraZeneca)	Introduction	Page 3, para 1, Sent 8. Ticagrelor is reversibly-binding. There is currently no known treatment or antidote to reverse the antiplatelet effects of ticagrelor in the acute treatment setting. Revise to: Ticagrelor is a reversibly-binding reversible P2Y12 receptor antagonist that, when compared with clopidogrel, provides a more rapid and more potent inhibition of platelets. Source: BRILINTA Prescribing Information	The suggested change has been made.
Peer Reviewer 1	Methods	Methodology is sound.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 2	Methods	The search criteria is largely resonable. While the outcomes measures used to define the strength of evidence (SOE) are defined in general terms, they are applied unevenly throughout the document.	We acknowledge your comment but believe that we have been consistent with our categorization of the four domains required for determining the SOE.
Peer Reviewer 2	Methods	Too many endpoints are reported for each comparison, many of which are of questionable relevance. Present fewer endpoints of more relevance.	The Key Informants and Technical Expert Panel (stakeholders) felt that these outcomes should be examined for each comparison, so we are unable to reduce the number of endpoints; however, the key points do focus on the most important findings.
Peer Reviewer 2	Methods	N's should be added for the event numbers for eacht rial in the forest plots.	We have added Ns to the plots.
Peer Reviewer 2	Methods	The authors should consistently report separately efficacy and safety. Reporting net benefits for bivalirudin but not for other drugs, while a function of the trial designs, suggests higher support for this agent, whereas there really is no efficacy advantage but only a safety one.	In the KQ 1 section, we report multiple endpoints including ischemic endpoints and bleeding endpoints separately. Very few studies, except for the bivalirudin study, reported net clinical benefit. We are describing the results as stated by the authors and are not implying our support for which method (separate efficacy and safety vs. net benefit) should be used.
Peer Reviewer 2	Methods	p93. The indirect approach (Hasselblad and Kong) used to compare fondaparinux vs UFH is problematic and this is the only place in the document such indirect comparisons are used. There are many other areas where such methods could be employed and are not. Why here? I suggest removing these given the flaws in the strategy.	We reviewed your suggestion and decided to keep the indirect comparison for fondaparinux vs. UFH given the small number of studies with a head-to-head comparison of those drugs.
Peer Reviewer 3	Methods	The inclusion and exclusion criteria are appropriate and justified. The search strategies are explicitly stated and logical. The methods for inclusion are clearly described.	Thank you.
Peer Reviewer 4	Methods	Studies were rated for a variety of criteria as specified in published guidelines. However the Mehtods shoudl state clearly what is done with studies that are rated as poor. In some cases they are cited in the text. If a study was rated as "poor" in quality, was it included in the analyses, and if so, don't the authors believe it would dilute the quality of the higher quality trials when the data are mixed?	All studies were included in analyses when appropriate, regardless of study quality since most comparisons had a small number of studies available for meta-analysis. We performed sensitivity analyses for the GPI analyses in KQ 2 because of the heterogeneity of the results, which were likely due to total study size and use of dual antiplatelet therapy. There is potential colinearity between poor study quality and a small sample size; therefore we decided not to run any sensitivity analyses based on study quality. For outcomes where a meta-analysis was not performed, the study quality was considered for determining the risk of bias domain for the SOE.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Methods	Comment should be made on the definitions used for stent thrombosis.	We collected any data that study authors defined as definite “stent thrombosis” and defer to the authors to ensure that those events categorized as stent thrombosis were done so correctly.
Peer Reviewer 4	Methods	Bare metal stents are distinguished from Drug eluting stents. However it is generally believed on the basis of multiple recent trials, that the frequency of stent thrombosis is lower in newer generations of drug eluting stents compared with the first generation stents used in most of the studies used inthe analysis. The temporal differences in the trials undoubtesly led to differential use of the newer stents and may have influenced the frequency of stent thrombosis. These differences may be particullarly pertinent with regard to the analyses of duration of DAPT after stent placement. The analysis of DAPT duration includes 4 RCTs, however three of them include stent designs (including drug and polymer) that are rarely used in current practice and only one trial that includes currently used DES. This point deserves comment, and it might make more sense to eliminate this particular section since there is a paucity of currently applicable data.	We have added text that use of bare metal or drug-eluting stents may have influenced the results of stent thrombosis in the dual antiplatelet therapy studies.
Peer Reviewer 4	Methods	The section on timing of GP IIb/IIIa antagonists used in an “upstream” versus a “deferred” strategy leaves out the obvious comparison of no GP IIb/IIIa antagonist either upstream or during PCI. Choosing between this trategy and either one of the two that include GP IIb/IIIa antagonists is usually a more crucial decision than is the timing of administering a GO IIb/IIIa antagonist. The no GP IIb/IIIa option is selected by many clinicians and deserves discussion, even if it cannot be included.	The reviewer is correct that no upstream GPI versus no deferred GPI (i.e., do not administer a GPI but rather just administer an anticoagulant) is a possible strategy which may be encountered in clinical practice. We, however, found very few comparative studies that reported a no-GPI strategy, either upstream or during PCI, and these studies were all observational and likely confounded by selection bias. They are not included in our report.
Peer Reviewer 4	Methods	The term “deferred GPI” shuld be used cautiously and requires further exposition since in the very large study by Giugliano et al (EARLY ACS), a minority of patients randomized to receive delayed provisional eptifibatide actually received eptifibatide during PCI.	We have clarified that “deferred GPI” use is defined as delayed use, provisional GPI use, or GPI use that is deferred until the time of PCI. While subtle differences in the definition may lead to heterogeneity, this approach was agreed upon by the study team based on feedback from our discussion with the Technical Expert Panel.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Methods	On P72 mention is made of “GPI vs oral antiplatelet” therapy. Isn’t the more correct wording “GPI with oral antiplatelet therapy vs oral antiplatelet therapy alone”?	The Key Questions were formulated and revised based on discussion with the Technical Expert Panel. There are many combinations (GPI without pretreatment with oral antiplatelet, GPI with pretreatment, oral antiplatelet alone, GPI with deferred oral antiplatelet, etc.) that could be considered for Key Question 1a, and so we prefer to keep the general wording as currently stated and refer the readers to the detailed comparisons as outlined with the Key Question 1 section.
Peer Reviewer 4	Methods	The title “Clopidogrel vs Prasugrel vs Ticagrelor” is misleading since it suggests that the section will review comparisons of all three drugs. The same is true of the enoxaparin vs fondaparinux vs unfractionated heparin section.	We have revised this header in KQs 1 and 2 to state “clopidogrel vs. ticagrelor **or** prasugrel.” The revision also applies to the KQ 2 comparison of unfractionated heparin vs. enoxaparin **or** fondaparinux. However, in KQ 1, all three drugs were compared.
Peer Reviewer 4	Methods	The section on 300 mg vs 600 mg of clopidogrel loading dose uses the PCI subgroup from the CURRENT trial. This is a matter of some controversy since the report is a post-randomization subgroup. Although it’s commonly cited, there’s no way arouond this basic design limitation. Whether to use it in an analysis as rigorous as the current study is questionable. Use of clearly and rigidly defined methods and statistical rigor seem are the major advantage of a report such as the current one. The use of post randomization subgroups such as the former analysis, and the non-randomized comparisons from RCTs of ‘pretreatment’ with clopidogrel and of aspirin dosing detract from this rigor. This reviewer’s niew is that they should not be included.	We acknowledge that within this section we use the postrandomization subgroup since it was the only evidence available to answer this question – this postrandomization was incorporated in to the quality of the study.
Peer Reviewer 4	Methods	The wording of the analysis of bivalirudin vs heparin based strategies should be adjusted so that it’s clear that GP IIb/IIIa use was not part of the planned bivalirudin strategies.	We have reviewed the key points and table headers for the bivalirudin vs. heparin-based strategies and confirmed that they state “with planned GPI use” or “without planned GPI use” where appropriate.
Peer Reviewer 5	Methods	definitions, search strategies, and outcome measures all explicitly presented; excellent approach to all analyses	Thank you.
Peer Reviewer 6	Methods	The inclusion/exclusion criteria are justifiable. In the table 2 (p.19-12), in the population description, is it true that comorbid or multi-morbid disease were required of patients enrolled in studies included in the review? If so, this slightly changes the target population to one with unstable angina/NSTEMI and more than one disease co-morbidity. For consistency, this may need to be clarified.	We have clarified this in Table 2. Comorbid or multimorbid disease was not a required criterion.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 6	Methods	The search strategies were well stated and the process logicalsimilar to others previously used for such reviews. This topic covers a lot of breadth. Accordingly, the search was extensive then appropriately narrowed. Outcomes measures are best listed in table in the introduction and on the analytic framework diagram (p.7-8). However, the definitions or diagnostic criteria for the outcomes measures are not clearly defined in the methods. Rather the specific description of the outcomes measures occurs in the results when the key points are specified for each analysis that was conducted. The statistical methods appear sound.	Thank you.
TEP Member 1	Methods	Methodology thorough. No comments.	Thank you.
TEP Member 2	Methods	Overall, high quality methods.	Thank you.
TEP Member 2	Methods	p19: Key questions: Good, pertinent. Good framework.	Thank you.
TEP Member 2	Methods	p20: Input, literature search: Good	Thank you.
TEP Member 2	Methods	pp21-22: Inclusion/exclusion, study selection, data extraction, data synthesis: All reasonable. Please refer to appendices where applicable.	Thank you.
TEP Member 2	Methods	p23: SOE: Good. Applicability: Use of PICTOS is appropriate. Results: Resonably set forth.	Thank you.
TEP Member 2	Methods	pp24-25: Lit search appears comprehensive.	Thank you.
TEP Member 3	Methods	Explicit and transparent methodology that is readily reproducible.	Thank you.
TEP Member 4	Methods	The methodology of the results are clear and appropriate. Criteria are well defined and explained.	Thank you.
TEP Member 5	Methods	Criteria seem reasonable and strategies explicit and logical. I couldn't find an indication that outcome definitions were assessed for rigidity or consistency (MI in particular).	We did not assess for consistency in endpoint definitions across the studies, assuming that the differences were minimal. We acknowledge in our limitations section that definitions of outcomes as standard of care vary over time.
TEP Member 5	Methods	The analytic framework states that "intermediate outcomes considered include rehospitalization, length of hospital stay and resource utilization (e.g., emergency department visits). These outcomes don't all appear in the results and it is unlikely that strong data exist for evaluating them. This section should be midified to exclude mention of outcomes that were not evaluated.	We reported the intermediate outcomes when available.
Bradfield, Lisa (American College of Cardiology)	Methods	The detail is very helpful for staff and guideline writing committee members.	Thank you.
Peer Reviewer 1	Results	Extensive details presented but well organized and summarized in tabular format.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 2	Results	I think that some of the long narrative discussion could be replaced with tables describing study results, particularly in those areas (the majority) where the SOE is “insufficient.”	The full report has to describe the study results that justify the insufficient evidence.
Peer Reviewer 2	Results	Equal discussion is provided for tiny RCTs and observational trial as for the pivotal large RCTs that should drive the conclusions.	We discuss both RCTs and observational results equally in the text, but the SOE ratings include a rating of risk of bias, where RCTs tend to have low risk of bias and observational studies have moderate to high risk of bias.
Peer Reviewer 2	Results	Fig p 25 and throughout this section and the document. The Giugliano reference should be from 2009, not 2005.	We have corrected this reference.
Peer Reviewer 2	Results	Fig 12, page 38. The 600 mg dose should be on left and HR should be <1.	The meta-analysis was set up by our statistician with the 300 mg dose on the left and the 600 mg dose on the right. Either way, the OR >1 favors the 600 mg dose (fewer MI events).
Peer Reviewer 2	Results	p43 The section comparing prasugrel, ticagrelor, and clopidogrel is problematic. First, the authors should note that the MI benefit in TRITON is largely driven by procedural MI. Second, the PLATO discussion should use non-CABG bleeding as the bleeding definition of interest, as the inclusion of CABG bleeds creates the misleading impression that ticagrelor does not increase bleeding. Third, mortality data cannot be combined for prasugrel and ticagrelor. This is done in the tables (I,e table 7) but the bullets, as written, are OK.	In the report, we primarily used the TIMI definition of major and minor bleeding when available, but we also accepted study-defined major/minor bleeding, which was very similar. We understand that there are some nuances to the way the bleeding events were reported across studies, but to define the nuances for each trial is not the purpose of this report. We have separated the results and strength of evidence for prasugrel and ticagrelor in that section of the report and in Table 7.
Peer Reviewer 2	Results	Subgroup findings from this section on p 46 do not even discuss subgroups at prohibitive bleeding risk with prasugrel. Instead, unimportant composite ischemia outcomes are presented by subgroup. In contrast, bleeding data by subgroup are reported for ticagrelor.	We describe the subgroup findings for efficacy and safety endpoints when reported in the publications. Any omissions are due to non-reporting by the study authors.
Peer Reviewer 2	Results	p 71, table 9, row 18. Why is SOE insufficient with consistent direct, precise results for death/MI/revasc	The strength of evidence (SOE) can be rated insufficient if there is imprecision or if the study did not meet criteria for an optimal information size (OIS) or meet the minimally important difference (MID).
Peer Reviewer 2	Results	P 72. The enoxaparin vs UFH vs fondaparinux section is hard to follow. The A to Z data are included in the fondaparinux section but should be in the section above comparing UFH with enoxaparin.	We have relabeled the headers to make the sections more clear.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 2	Results	Conclusions overweight observational data. The RCT data do consistently show increased bleeding with enoxaparin.	We have revised the SOE tables to separate out these studies based on their comparisons and now show the increased risk of bleeding with enoxaparin
Peer Reviewer 2	Results	p 77. The section on "Timing of clopidogrel" is weak as it doesn't address timing directly and there are no randomized data. This section should be renamed "impact of clopidogrel loading on efficacy and safety of bivalirudin vs UFH and upstream vs deferred GPI." This section essentially just repeats prior analyses in subgroups defined by timing of clopidogrel loading. As such the focus should be comparisons of efficacy and safety in the subgroups with early and deferred clopidogrel loading. This would require a modest re-organization of this section.	We understand that there is a lack of direct comparisons of timing of administration. Given the existing literature, we think that both strategies have equal pros and cons. We have retitled this section "Upstream or Deferred Clopidogrel for Patients Undergoing Percutaneous Coronary Intervention for UA/NSTEMI in Studies With a Defined Anticoagulant or Intravenous Antiplatelet Strategy" to reflect that the upstream or deferred use of clopidogrel was given under a defined anticoagulant (bivalirudin or UFH) strategy or a defined IV antiplatelet strategy (upstream vs. deferred GPI).
Peer Reviewer 2	Results	p 80. How can the SOE be sufficient (but low) for the composite of death/MI/ischemia driven revasc for comparison of upstream vs deferred GPI based on just 638 patients. The CI is wide and this decision is inconsistent with other areas in the document. This meta-analysis should be shown.	Although the evidence was rated as imprecise, the two studies were consistent, direct, and good/fair quality. We believe the SOE rating of low favoring upstream GPI was appropriate
Peer Reviewer 2	Results	p83. Why do the authors exclude ACUITY from the clopidogrel no pre-treatment vs pretreatment analysis? This is the main analysis that suggested an interaction of therapy based on pretreatment with clopidogrel. I recognize that the other studies did not include GPI, but this is the most informative study on the topic. This should also be reflected in the conclusions on p 85	We did not exclude ACUITY from this analysis; however, the results report only composite endpoints (included in our report) for UA/NSTEMI patients who underwent pretreatment or deferred treatment.
Peer Reviewer 2	Results	p89. The focus of this analysis is on conservatively managed patients. Some of these studies (i.e. A to Z) published manuscripts focusing specifically on the conservatively managed subgroup which would seem to be the preferred population to include in this meta-analysis.	In general, we reference only the main results paper for each study throughout the report. A table listing primary and companion articles is in Appendix C.
Peer Reviewer 2	Results	I disagree with the SOE "insufficient" for mortality between UFH enoxaparin. The OR is almost exactly one with a narrow confidence interval and minimal heterogeneity.	We agree that this SOE should be rated as low and have made the suggested change.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 2	Results	p 95. Recommend deleting observational data as they add little to a field with so many large RCTs. If they remain the observational analyses should focus on gaps in RCT data rather than duplication.	We agree that when possible the findings should be based on the strongest evidence – that is the evidence provided by RCTs. We, however, consider it important to report the findings of observational studies along with the findings of the RCTs especially when these studies are able to focus on gaps in the RCT evidence such as in KQ3. Per our protocol, our eligibility criteria included both types of study designs. For some treatment comparisons, there are ample numbers of RCTs; for other comparisons, there are only observational studies.
Peer Reviewer 2	Results	p99. The section on GPI in conservatively managed patients is perhaps the biggest problem area in the document. The major problem is that the authors do not focus on trials or subgroups with conservative management and define as conservative patients who went for cath 18-72 hours. In fact, this largely represents early invasive management as conventionally defined. This issue is important because the Boersma meta-analysis suggests that the large majority of the MI benefit with GPI is driven by reduction of procedural enzyme elevation. These events should not be included in a comparative effectiveness evaluation of conservative management but likely drive the findings here with regard to nonfatal MI. This analysis has real validity issues and should be either redone or removed.	We understand the reviewer's concern, but do not feel we should ignore the MI results. According to current definitions of early invasive therapy, the delay to cardiac catheterization in the GPI studies of this section do meet the initial conservative management strategy. We had previously reviewed the Boersma meta-analysis; however, that review also included GPIs that are not FDA-approved for use in the United States and therefore was not included in our analysis.
Peer Reviewer 2	Results	p 109. The definition of short vs long duration clopidogrel is not provided	The definition of short- vs. long-term duration of clopidogrel varied by study and we deferred to the author's definition when categorizing the durations. We clarify this in our main report.
Peer Reviewer 2	Results	p 109. Omeprazole lowers mortality? This should not be a top line conclusion of this section.	We have reworded this sentence to state that mortality is not increased with concomitant use of omeprazole.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 2	Results	p 112. The low vs high dose aspirin data have many problems. All the data provided are observational. Why aren't 30 day RCT results from Oasis 7 included? The observational data are incomplete as subanalysis from CURE, PLATO are not included here. How can small observational data be "sufficient" SOE to state that high dose asa prevents nonfatal MI? For this reviewer, the data are not sufficient to make such a claim that is not supported by RCT data or other observational data.	The recommended studies (CURE and PLATO) have been added to the low- vs. high-dose aspirin comparison section. As stated in the text, "The SOE for nonfatal MI at 6 months was rated low based on one large observational study that reported a statistically significant reduction…" Oasis 7 was included in our report for our KQ1 comparison. In our Methods section we define a low SOE rating as "low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate," therefore more evidence is needed to support this finding.
Peer Reviewer 2	Results	p 116. Why is COMMIT included given its short treatment duration (the focus of this section is on post D/C management) and the large component of STEMI?	Due to the high percentage (86.5%) of patients with STEMI, we have decided the COMMIT study should be excluded from this report.
Peer Reviewer 2	Results	p 118. The mortality conclusion with clopidogrel is not true for post d/c management. CURE is the only relevant trial here. COMMIT should not be included and the registry data are hopelessly biased.	Due to the high percentage (86.5%) of patients with STEMI, we have decided the COMMIT study should be excluded from this report.
Peer Reviewer 2	Results	p 118. How can the bleeding evidence for DAPT be judged insufficient. CURE alone provides at least a low SOE for increased bleeding. Not at all clear where the CURE data were pulled from for these analyses.	The SOE evidence has been updated to demonstrate low SOE for a benefit of DAPT in reduction of major bleeding.
Peer Reviewer 2	Results	p 132. The rating of "sufficient" SOE (low) for mortality benefit from PPI is not justified. There are not sufficient data for such a conclusion.	The strength of evidence favoring the no PPI group was rated low for all-cause mortality at 6 years based on one large good-quality observational study. The reviewer is correct that the data, however, are not sufficient to come to a conclusion for the shorter time period of 30 days. The largest study (good quality) showed a significant reduction in death rates with omeprazole; therefore, we felt there was low level of evidence for this outcome. As stated in the Methods section, a low SOE is defined as low confidence that the evidence reflects the true effect. Thus, further research is likely to change the confidence in the estimate of effect and is may change the estimate.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 2	Results	p 135. Why do the meta-analysis at all of the observational studies with the PPI class as a whole? These data contradict RCT data, are hopelessly confounded and subject to selection bias, and overweight observational data. The result is a SOE for hazard that is moderate which ends up being one of the firmest conclusions of the exercise, yet even the authors acknowledge it cannot be true! The authors are overweighting the importance and validity of observational data.	We acknowledge your concern about the contradictions between the data in the "PPI class as a whole" observational studies and the RCTs that used omeprazole only. We have combined the omeprazole studies (RCT and observational) with the non-specific PPI observational studies in this section. We also changed the analysis to use the adjusted or propensity-scored HRs in the meta-analysis to reduce confounding. The SOE ratings are now based on the combination of studies, specifically looking at whether the results of the RCTs and observational studies are consistent and the findings from the meta-analysis of the adjusted results. We downgraded the SOE rating due to the preponderance of observational studies, too.
Peer Reviewer 2	Results	p 155. The triple therapy section is incomplete. Why don't the authors include the robust RCT data for apixiban, rivaroxaban and dabigatran here in ACS patients? Similarly, RCT data for warfarin for STEMI exist that would certainly be better than the observational data included here.	We did not include RCT data for apixaban, rivaroxaban and dabigatran because the question clearly stated "In patients with an indication for long-term anticoagulant therapy …" These drugs were tested in patients with ACS as an "add on" to standard therapy for the treatment of ACS—not because the patients had an indication to for long-term anticoagulant.
Peer Reviewer 2	Results	p 157. How can the authors conclude that evidence is sufficient to say double therapy is associated with lower MI than triple therapy (low level of evidence) when this is based on observational data only, with 4 studies, 1425 patients, and wide CI?	We refer the reader to the explanation in the text and the detailed SOE table where this outcome was rated as consistent, direct, and imprecise. This meets criteria for low SOE. In our Methods section, we define low SOE as "low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate."
Peer Reviewer 3	Results	For KQ3, the review does not comment on the evidence basis for the INR target for those on Aspirin and P2Y12 inhibitor therapy. The 2012 ACCF/AHA guidelines mention a lower INR target (2.0-2.5) as a Class IIb recommendation for those on dual antiplatelet therapy.	The INR target was not recorded for each study. Most of these were observational studies where the INR target depended on the clinical condition (e.g., 2-3 for atrial fibrillation, and 2.5-3.5 for prosthetic valves).
Peer Reviewer 3	Results	For KQ3, it would be worthwhile to explore the issue of lower aspirin dosing with ticagrelor and the strength of evidence behind the recommendation. Current ACCF/AHA guidelines recommend a maintenance dose of 81 mg/day with ticagrelor, based on the PLATO trial.	We have added data from the recent PLATO study publication on aspirin dose.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Results	In the detailed section on GPIs, analysis is done according to TIMI Risk Score. It mus be remembered that subjects were selected for these trials on the basis of high risk features. This process would make applicability to low risk patients less meaningful.	We recorded the results for all patients enrolled in the study, not the results based on TIMI risk score. The Results section of the KQ 2 GPI analysis includes text stating that "Subjects in older studies (pre-2000) were enrolled on the basis of high risk MI features, while newer studies followed the standard definition for conservative strategy and are likely lower risk patients." Interestingly, the results of older studies are likely to have a summary estimate that was closer to the null hypothesis, and newer studies were more likely to favor GPI. We believe that favorable outcomes in the newer studies are due to routine use of dual antiplatelet therapy.
Peer Reviewer 4	Results	Mention is made of studies that did not specify either an invasive or conservative strategy are mentioned, but text of the analysis does not make explicit whether or not they are included. In fact, categorizing such studies would seem to be an analytic rather than a clinical challenge, since the initial catheterization strategy for a given patient with an ACS is not always determined before the pharmacologic therapy is selected.	We have added text about this limitation to the Limitations of the Evidence Base section in the Discussion.
Peer Reviewer 5	Results	beautifully detailed; textbook descriptions of studies and data; scholarly delineation of limitations of available data	Thank you.
Peer Reviewer 6	Results	The results are organized by the key questions with key points for each bulleted as a summary ahead of the detailed presentation of individual results. The key messages are very well delivered and important as a summary due to the density and extensive nature of this report. The figures and tables are clear. Specifically, the forest plots are nice visual representations of the meta-analyses.	Thank you.
Peer Reviewer 6	Results	The search appears very comprehensive and no studies were obviously excluded to this reviewer. The mention about the future inclusion of TRILOGY ACS was noted and thought to be important.	Thank you.
TEP Member 1	Results	p. 24. "None of the studies reported the racial and ethnic demographics of study participants." This lack should be included in the section on research gaps.	We have added this as a research gap.
TEP Member 2	Results	Overall, well done. Comprehensive, well-organized, well-presented. The fully annotated version documents well the evidence base reviewed and details (with figures, tables) the results upon which the conclusions are based (I was not able to review this version in great detail because of the length.)	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP Member 2	Results	p15, Table A: Delete prasugrel frin cibservative strategy (Trilogy ACS).	We have kept prasugrel in the table since it was studied for this indication. Also, please note that this table is not a guideline, but rather a list of the medications that have been evaluated for UA/NSTEMI.
TEP Member 2	Results	p17, I-9: 162 (not 160); I-17: note that fondaparinux must be used with UFH or another fila inhibitor with an invasive approach; I-24: delete prasugrel from conservative strategy in-hospital and (I-38) for outpatient Rx.	We understand that fondaparinux use in the invasive approach also involves the use of UFH or another antiplatelet inhibitor. We have kept prasugrel in the table since it was studied for this indication. Also note that this table is not a guideline, but rather a list of the medications that have been evaluated for UA/NSTEMI.
TEP Member 2	Results	p26, I-47-48: Express concern regarding confounding with clopidogrel early use (i.e., discern dual vs. triple antiplatelet Rx upstream); I-54-55: duplicates I-49-51.	We acknowledge the potential for confounding from dual and triple antiplatelet therapy use in those sections.
TEP Member 2	Results	p28: Table C: Why not do a metaanalysis of studies for composite endpoint?	The composite endpoint definitions varied across the studies, and we required at least three studies with common composite endpoint definitions in order to perform a meta-analysis.
TEP Member 2	Results	p29: I-40-43: presentation of comparative data confusing (e.g., “lower than” 3.8% for clopidogrel (?). I-53-55: Why lump ticagrelor (ACM significant) and prasugrel (ACM NS)? Why not in general separate out these 2 new antiplatelet agents, which are in different biochemical calsses (thienopyridine vs non-)?	We have corrected the text in Table 7 to make it congruent with the text in the Results section.
TEP Member 2	Results	p30; I-9-11. See above.	We have modified the table and text to reflect differences in stent thrombosis.
TEP Member 2	Results	pp30-31: Tables in general are nicely laid out throughout. Why not do a metaanalysis for composite endpoint?	We decided against performing an indirect meta-analysis for this composite endpoint because of differences in study design.
TEP Member 2	Results	pp32-33: Should point out an increased risk of catheter/guidewire thrombosis with fonda alone; it should be given with heparin/etc during PCI if used; for this reason, it has not been preferred in US practice (should also note that it is not FDA approved for ACS use).	We thank the reviewer for the comment. This is useful information that was not a focus of the current CER. The studies that were included in the analysis did not report catheter/guidewire thrombosis as an outcome.
TEP Member 2	Results	p33, I-51-52: Why not low rather than insufficient (HR 0.56 with UCL 1.05)?	All-cause mortality at 30 days in patients pretreated with clopidogrel randomized to upstream compared with deferred glycoprotein inhibitor use was rated insufficient due to inconsistency and imprecision.

Commentator & Affiliation	Section	Comment	Response
TEP Member 2	Results	p34, I-10-12: Same question as above (criteria for low vs insufficient SOE need clarification, and metaanalysis vs not).	Any outcome that had inconsistent results across studies or a wide confidence interval (i.e., imprecision) was rated as insufficient. This is explained in the Methods section.
TEP Member 2	Results	p36, I-7-11: Ingeneral, the GLs have viewed GPI as ineffective or marginally effective for conservative management; there must be a discrepancy between trials included here and those accepted by GLs as pertinent.	The guidelines that have viewed GPI as ineffective were primarily based on the large RCTs and on studies that used aspirin (not dual antiplatelet therapy). Newer studies using the current definition of initial conservative management and dual antiplatelet therapy have shown a benefit.
TEP Member 2	Results	p37, I-40-41: The background Rx for ASA dose should be clarified: this must be with, without clopidogrel. Does it include prasugrel? For ticagrelor, it should be emphasized that high-dose ASA increases risk and that low dose ASA is FDA recommended!	As suggested, we have added these data.
TEP Member 2	Results	p38. Clarify/stratify results by PCI vs Med Rx.	We are not able to stratify results by PCI versus medical therapy for the low versus high ASA dose comparison since the endpoint results were not reported separately for these subgroups. However, we do describe the results by subgroup for diabetes, multivessel disease, type of stent, geographic location, and dual antiplatelet therapy in the text of the main report (not in the detailed SOE table identified in your comment).
TEP Member 2	Results	p39. Clarify/stratify results by BMS vs DES (and generation of DES), or indicate limitations of conclusions.	Two studies reported the subgroup findings for the type of stent (Ho, 2007 and Valgimigli, 2012), and these findings are described in the main report (not in the summary SOE table that you have listed in your comment).
TEP Member 2	Results	p40, I-10-12. What were comparator durations?	The treatment durations varied by study. Details are outlined in the short-term vs. long-term dual antiplatelet therapy section for the stent thrombosis endpoint (not in the detailed SOE table identified in your comment).
TEP Member 2	Results	p40, I-35-43. Seems to waffle about relative value of RCTs over undoubtedly counfounded observational studies.	This section has been revised to explain how our SOE ratings were based on RCTs where possible and then the observational data was used to explore gaps in the RCT evidence and to evaluate the consistency of findings.
TEP Member 3	Results	Results appropriate for assembled evidence.	Thank you.
TEP Member 4	Results	The results are well explained and clear. There are some consistency issues between the key questions in terms of how things are phrased and presented.	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP Member 4	Results	KQ1: the term statistically nonsignificant is used often in Key Question 1. I think the mention of nonsignificance implies a statistical analysis and this may be redundant. In addition when there is no statistical difference there is usually a confidence interval around the results found. Using terms such as "favors" implies one is better than another. I would suggest that the differences just be described and avoid value terms when possible. The use of "compared to, lower, or higher" seems more appropriate. The presentation of differences seems to be presented differently in Key Question 2 and may reflect writing styles of the authors of each section.	Earlier reviewers of the draft document had asked for us to clarify the term "nonsignificant," so we added the term "statistically nonsignificant" reduction or increase.
TEP Member 4	Results	KQ2: Page 102, para 2, line 52. Is this a new paragraph? It appears that it may be and there is no indentation.	The sentence has been indented to indicate that it is a new paragraph.
TEP Member 4	Results	KQ3: Page 121, para 1, line 4. The one study is not described as RCT or observational as is done in all the other sections.	The study design has been added to this sentence.
TEP Member 4	Results	KQ3: The way the studies are referenced in this section when described in the first sentence of each analysis paragraph is similar to KQ1 but not consistent with KQ2.	We have reviewed the descriptions to make them consistent.
TEP Member 4	Results	KQ3, Dual Antiplatelet Versus Triple Therapy section. This section does not describe the type of study as done else where in the text.	This section has been changed to mirror previous sections.
TEP Member 5	Results	Detail is appropriate and tables and figures are well organized. With so many embedded questions and so little high quality data, it is difficult to derive key messages.	Thank you.
TEP Member 5	Results	Bolding results with SOE=high or medium would help.	Noted.
TEP Member 5	Results	It would also help to have a table that displays consistency or inconsistency across the three key questions for the major key messages.	The Executive Summary's key points and tables outline the key messages and strength of evidence for each key question. Given the number of comparisons within each key question, it would be difficult to have one overall table for all three Key Questions.
Bradfield, Lisa (American College of Cardiology)	Results	The key points section is very much appreciated and help guide committee in making decisions.	Thank you.
Chapell, Richard	Results	In addition to the discussion of bleeding events in the Introduction, wherever bleeding events are discussed in the Results section of the review, we request that the text state which system of nomenclature is utilized by each of the studies under discussion. If a novel nomenclature is used, or the terms "Major" and "Minor" are left undefined, this should be stated as well.	We have added text to state that the primary definition of bleeding (major or minor) reported by the authors was used for this report. A majority reported TIMI bleeding definitions.

Commentator & Affiliation	Section	Comment	Response
Gans-Brangs, Kathleen (AstraZeneca)	Results	Results, Page 20, Key Points Bullet 6 Original text: "After 1 year, both ticagrelor and prasugrel were associated with lower composite ischemic endpoints and individual endpoints (all-cause mortality, cardiovascular mortality, nonfatal MI, stent thrombosis) when compared with clopidogrel (low SOE)." This bullet states that both ticagrelor and prasugrel were associated with lower individual endpoints including all-cause mortality, cardiovascular mortality. However, based on the TRITON-TIMI study, prasugrel was not associated with statistically significant lower individual endpoints of all-cause mortality, cardiovascular mortality.	We have corrected this in the key points of the KQ 1 section.
Gans-Brangs, Kathleen (AstraZeneca)	Results	Page 44, Para 1, Sent 3. This sentence states that there are mixed results with ticagrelor without providing the appropriate context. One of the 2 studies cited (DISPERSE-2) was not designed to evaluate the efficacy of ticagrelor. The authors state that there were not sufficient numbers of clinical events to reliably determine the efficacy of ticagrelor versus clopidogrel. Remove reference to DISPERSE-2 or provide appropriate context regarding limitations of that study. Revise to: There were mixed results in the two studies comparing ticagrelor (4.3%; 4.8%) and clopidogrel (3.8%; 5.4%). However, one of these studies (DISPERSE 2) did not have sufficient numbers of clinical events to reliably determine the efficacy of ticagrelor versus clopidogrel. Source: Cannon 2007-DISPERSE-2, pg 1850, para 2, sent 1.	We have clarified which values are due to ticagrelor or prasugrel in comparison with clopidogrel in the SOE tables.
Gans-Brangs, Kathleen (AstraZeneca)	Results	Page 44, Para 1, Sent 4: The event rates for the combined UA + NSTEMI population were not reported in the PLATO publication. Data for the UA or NSTEMI population individually was reported in PLATO. It appears that the event rates for the primary composite endpoint in the combined UA + NSTEMI population were calculated using K-M estimates of the individual UA and NSTEMI data reported in PLATO; therefore, the methodology of these calculations should be disclosed in this report.	We have added further detail regarding the combination of UA and NSTEMI data to the report.
Gans-Brangs, Kathleen (AstraZeneca)	Results	Page 46, Para 1, Sent 1: Clarify patient population as follows: The incidence of TIMI major bleeding after 1 year was similar in all patients (not limited to UA/NSTEMI patients) treated with ticagrelor[...]	We agree that this is not clearly stated so we have added "not limited to UA/NSTEMI patients."
Gans-Brangs, Kathleen (AstraZeneca)	Results	Page 46, Para 3, Sent 1: Clarify patient population as follows: Two studies (good quality) of 32,232 patients (not limited to UA/NSTEMI patients) reported variations in treatment effectiveness by subgroup.	Results of the prasugrel and ticagrelor studies have been separated. We have also added "not limited to UA/NSTEMI patients."

Commentator & Affiliation	Section	Comment	Response
Gans-Brangs, Kathleen (AstraZeneca)	Results	Page 47, Para 6: Chronic Kidney Disease section. Replace Wallentin 2009 with the following reference: James S, Budaj A, Aylward P, et al. Ticagrelor versus clopidogrel in acute coronary syndromes in relation to renal function: results from the PLATelet inhibition and patient Outcomes (PLATO) trial. Circulation. 2010;122:1056-1067.	In general, we reference only the main results paper for each study throughout the report. A table listing primary and companion articles is in Appendix C.
Gans-Brangs, Kathleen (AstraZeneca)	Results	Pate 49, Para 1, Sent 1: Incorrect value for clopidogrel: ..when compared with clopidogrel (11.0%11.1%)... Source: Wallentin L, Becker RC, Budaj A, et al for the PLATO Investigators. Supplementary appendix. N Engl J Med. 2009;361(11):1045-1057. Available at: www.nejm.org/doi/suppl/10.1056/NEJMoa0904327/suppl_file/nejm_wallentin_1045sa1.pdf.	We have clarified which values are due to ticagrelor or prasugrel in comparison with clopidogrel in the SOE tables.
Gans-Brangs, Kathleen (AstraZeneca)	Results	Page 49, Para 5, Sent 1: There are only 2 studies that reported a lower incidence of the composite endpoint at 30 days in patients treated with prasugrel or ticagrelor. Cannon 2007 (DISPERSE-2) does not support the stated sentence. Revise to: In our analysis of studies comparing clopidogrel, ticagrelor, and prasugrel, two three studies reported a lower incidence of the composite outcome of cardiovascular mortality, nonfatal MI and nonfatal stroke at 30 days in patients treated with prasugrel or ticagrelor Source: Cannon 2007-DISPERSE-2, pg 1848, Table 3	We have clarified which values are due to ticagrelor or prasugrel in comparison with clopidogrel in the SOE tables.
Gans-Brangs, Kathleen (AstraZeneca)	Results	Table 7, Row 3, Page 50: Composite of CV mortality, nonfatal MI, or nonfatal stroke at 30 days – One of the ticagrelor studies (DISPERSE-2) reported values for ticagrelor that were not lower than clopidogrel (4.3%, ticagrelor vs 3.8%, clopidogrel). The DISPERSE-2 study was not designed to evaluate the efficacy of ticagrelor; there were not sufficient numbers of clinical events to reliably determine the efficacy of ticagrelor versus clopidogrel. Remove reference to DISPERSE-2 or provide appropriate context regarding limitations of that study. Revise to: Number of studies (patients) = 2 3 studies, 32,232 33,216 patients Risk of Bias: Study design/quality = 2 3 RCTs/good quality, 1 fair Consistency = Consistent Inconsistent SOE and Magnitude of effect = Ticagrelor (4.3% and 4.8%) and prasugrel (5.7%) were both associated with lower composite endpoints than clopidogrel (3.8%, 5.4% and 7.4%). Source: Cannon 2007-DISPERSE-2, pg 1848, Table 3	We have clarified which values are due to ticagrelor or prasugrel in comparison with clopidogrel in the SOE tables.

Commentator & Affiliation	Section	Comment	Response
Gans-Brangs, Kathleen (AstraZeneca)	Results	Table 7, Row 7, Page 50: Composite of cardiovascular mortality, nonfatal MI, or nonfatal stroke after 1 year- The event rates for the combined UA + NSTEMI population were not reported in the PLATO publication. Data for the UA or NSTEMI population individually was reported in PLATO. It appears that the event rates for the primary composite endpoint in the combined UA + NSTEMI population were calculated using K-M estimates of the individual UA and NSTEMI data reported in PLATO; therefore, the methodology of these calculations should be disclosed in this report. Additionally, the clopidogrel event rate for TRITON-TIMI study (12.1%) was omitted.	We have added further detail regarding the combination of UA and NSTEMI data to the report. We have added the missing TRITON-TIMI event rate.
Peer Reviewer 1	Summary/ Discussion	The limitation of this review is inherent to the literature studied. During the time course reviewed definitions have changes such as for MI and bleeding, procedural techniques have changed, the populations includced in each study differ in risk profile. The authors have presented the data, identified the weaknesses and research gaps.	Thank you.
Peer Reviewer 2	Summary/ Discussion	The authors do an excellent job highlighting the limitations of the data and the areas of need for future research. However, they do not provide enough context for some of the surprising findings, most of which are not likely to be true. I highlighted a number of these in my comments on the results above.	Thank you.
Peer Reviewer 3	Summary/ Discussion	The implications of the major findings are clearly stated and the limitations are described adequately.	Thank you.
Peer Reviewer 3	Summary/ Discussion	For KQ1, The interactions between vascular access and antiplatelet/anticoagulant therapy regimens could be explored further, especially in light of recent studies evaluating outcomes with radial access vs. femoral access in ACS settings. What are the implications of particular antiplatelet and anticoagulant regimens in the setting of radial access with respect to bleeding/ischemic complications? Practitioners might be more liberal with aggressive antiplatelet/anticoagulant strategies if radial access is utilized. Alternatively, they might be more conservative if the patient is a high risk for bleeding complications to begin with. This is a research gap that needs to be addressed in future studies.	We appreciate the reviewer's comments and agree that access site is an important variable. Unfortunately, we do not have individual patient-level data available for analysis. We agree that this is a research gap.
Peer Reviewer 3	Summary/ Discussion	Another research gap that should be mentioned under KQ1 is the role of genotype guided antiplatelet therapy or platelet function testing and whether this improves short and long term clinical outcomes in patients with NSTEMI/USA.	Thank you for this comment. This question is being addressed by another EPC group (Tufts).

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Summary/ Discussion	Multiple references are made to 'statistically non-significant differences.' Given the sample sizes analyzed, are the authors sufficiently confident to refer to findings characterized this way as "not different"? This distinction is critically important if the authors and the AHRQ believe that these findings are likely to have important decision-making implications.	We believe this terminology is correct because many of the outcomes that were "statistically nonsignificant" were not adequately powered to support a conclusion of "no difference."
Peer Reviewer 4	Summary/ Discussion	The authors conclude that in two areas, more RCTs are needed. While this response is relatively standard when the data analyzed are imperfect, there are pragmatic questions that need to modify such statements. In two areas the statement is made that more RCT data are needed. Chronic therapy with PPIs and clopidogrel is one. As it turns out, the most pronounced drug-drug interactions in this class were reported for omeprazole, which is the one drug that was subjected to a large (though incomplete) RCT. It doesn't seem practical to perform such trials for each of the PPIs. Similalry, such a statement is made for prasugrel and ticagrelor. Although the two obviously can't be compared without a head to head trial, how much do the authors believe would be gained from such a comparison?	We agree that most reviews call for more RCT evidence, and investigators must weigh the pragmatic issues to determine if an RCT is feasible. Some comparisons may be better addressed through quasi-experimental studies or high-quality observational studies. We feel, however, that in these specific cases mentioned that RCTs may still be appropriate. Specifically, other PPIs should undergo rigorous RCTs similar to omeprazole as we can not be certain these other PPIs would have the same efficacy or effectiveness as omeprazole. Similarly, there are no head-to-head comparisons of ticagrelor and prasugrel. Although they have both been shown to have benefits compared with clopidogrel, their comparative safety and effectiveness needs to be assessed.
Peer Reviewer 4	Summary/ Discussion	The research gap for KQ #1 isn't stated clearly. What do the authors mean by 'direct comparisons of intravenous and oral combination treatment strategies'? For example, are they referring to a combination of eptifibatide and prasugrel versus prasugrel alone, or of fondaparinux and ticagrelor versus fondaparinux alone? There are multiple combinations here; it's clear that we won't see all of them studied. Which combinations or types of combinations do the authors think are most important?	Given the multitude of possible intravenous and oral antiplatelet strategies, we agree that perhaps not all types of combinations can be studied. We did not want to specify which combinations should be studied further since the choice in real-world settings is often determined by the clinical presentation, initial treatment strategy, and patient risk factors for bleeding.' In the Discussion, we present one example of looking at the use of newer antiplatelet agents (prasugrel or ticagrelor) in combination with existing anticoagulants (unfractionated heparin, bivalirudin, or low molecular weight heparin), and/or with intravenous antiplatelet agents (upstream or downstream GPI).
Peer Reviewer 5	Summary/ Discussion	conclusions and guidance clear and helful both to clinicians and researchers	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 6	Summary/ Discussion	The implications and major findings are clearly stated. This concise wrap up of the report is a helpful tool to distill the important messages. The limitations are well stated, including the lack of data to answer some of the questions of interest. The limitation that was most difficult for me was the change in target population from UA/NSTEMI to include ACS patients. One wonders if the entire review should have been framed as such – ACS population excluding the exclusively STEMI group.	We agree that a majority of the studies were UA/NSTEMI only, or included a high proportion of UA/NSTEMI patients. We removed any pure STEMI studies; therefore, we cannot claim that our findings apply to the entire ACS population.
TEP Member 2	Summary/ Discussion	See my notes above.	Noted.
TEP Member 2	Summary/ Discussion	p33-38: How were patients categorized in terms of strategy if they underwent PCI at 18-72h? I would include as invasively treated or confounded rather than as conservatively treated (wrt GPI analyses)/	We categorized strategies as early or late based on how the study authors described them rather than based on objective time periods. For the KQ 2 GPI analysis, any study that prohibited cardiac catheterization or PCI within a defined time period was considered a conservative strategy.
TEP Member 2	Summary/ Discussion	p43. Should add ATLAS-ACS.	We did not have a Key Question regarding the use of oral anticoagulation (without an indication for long-term anticoagulation), and so we excluded ATLAS-ACS and APPRAISE 2.
TEP Member 2	Summary/ Discussion	p46, I-28-33: Good summary, but on I-33-35 “Indeed…” seems a non-sequitor.	Thank you; we have removed “Indeed” in the sentence.
TEP Member 2	Summary/ Discussion	P46-47: Applicability: Limitations stated are appropriate and important.	Thank you.
TEP Member 2	Summary/ Discussion	p47: Research gaps: Good section; useful; could even be expanded.	Thank you.
TEP Member 2	Summary/ Discussion	p49, I-17-22. Good summary.	Thank you.
TEP Member 2	Summary/ Discussion	Appendices: Comprehensive research resource; I could not take time to review in detail.	Thank you.
TEP Member 3	Summary/ Discussion	Clear research agenda is provided.	Thank you.
TEP Member 4	Summary/ Discussion	The future research section is clear, however leaves out some key issues. I think a summary of needed research should be presented in tthe terms of a table.	We will consider such a table if the opportunity for a subsequent publication arises that summarizes the future research needs for this topic.
TEP Member 4	Summary/ Discussion	Findings in relation to what is already known. This is a really interesting and valuable section and I feel that having it only presented as a text minimizes the potential impact this could have on practice. I think a table or figure summarizing current recommendations and potential areas for change based on this review would be useful.	We will consider such a table or figure for a subsequent publication that summarizes the major findings.

Commentator & Affiliation	Section	Comment	Response
TEP Member 5	Summary/ Discussion	All sections are nicely written. The investigators make it clear that the data to address most of the comparisons are not definitive.	Thank you.
Bradfield, Lisa (American College of Cardiology)	Summary/ Discussion	The detail is very helpful for staff and guideline writing committee members.	Thank you.
Gans-Brangs, Kathleen (AstraZeneca)	Summary/ Discussion	Page 168, Para 1, Sent 1: There are only 2 studies that reported a lower incidence of the composite endpoint at 30 days in patients treated with prasugrel or ticagrelor. Cannon 2007 (DISPERSE-2) does not support the stated sentence. Revise to: In our analysis of studies comparing clopidogrel, ticagrelor, and prasugrel, two three studies reported a lower incidence of the composite outcome of cardiovascular mortality, nonfatal MI and nonfatal stroke at 30 days in patients treated with prasugrel or ticagrelor Source: Cannon 2007-DISPERSE-2, pg 1848, Table 3.	We have modified this sentence.
Gans-Brangs, Kathleen (AstraZeneca)	Summary/ Discussion	Table 27, Row 3, Page 169Composite of CV mortality, nonfatal MI, or nonfatal stroke at 30 days – One of the ticagrelor studies (DISPERSE-2) reported values for ticagrelor that were not lower than clopidogrel (4.3%, ticagrelor vs 3.8%, clopidogrel). The DISPERSE-2 study was not designed to evaluate the efficacy of ticagrelor; there were not sufficient numbers of clinical events to reliably determine the efficacy of ticagrelor versus clopidogrel. Remove reference to DISPERSE-2 or provide appropriate context regarding limitations of that study. Revise to: SOE=Moderate (2 3 studies, 32,232 33,216 patients) Ticagrelor (4.3% and 4.8%) and prasugrel (5.7%) were both associated with lower composite endpoints than clopidogrel (3.8%, 5.4% and 7.4%). Source: Cannon 2007-DISPERSE-2, pg 1848, Table 3	We describe the endpoint results of studies that met our criteria and acknowledge that some endpoints may not have reached adequate numbers (power) to form a conclusion.
Gans-Brangs, Kathleen (AstraZeneca)	Summary/ Discussion	Table 27, Row 4, Page 169: Composite of cardiovascular mortality, nonfatal MI, or nonfatal stroke after 1 year- The event rates for the combined UA + NSTEMI population were not reported in the PLATO publication. Data for the UA or NSTEMI population individually was reported in PLATO. It appears that the event rates for the primary composite endpoint in the combined UA + NSTEMI population were calculated using K-M estimates of the individual UA and NSTEMI data reported in PLATO; therefore, the methodology of these calculations should be disclosed in this report.	We have added further detail regarding the combination of UA and NSTEMI data to the report.

Commentator & Affiliation	Section	Comment	Response
Gans-Brangs, Kathleen (AstraZeneca)	Summary/ Discussion	Additionally, the clopidogrel event rate for TRITON-TIMI study (12.1%) was omitted. Page 188-9 Last sentence on page 188 states that the cost-effectiveness of ticagrelor is not known. There are published data regarding the cost effectiveness of ticagrelor vs. generic clopidogrel. The references are follows: • Nikolic N, Janzon M, Hauch O, Wallentin L, Henriksson M. Cost-effectiveness of treating acute coronary syndrome patients with ticagrelor for 12 months: results from the PLATO study. Supplementary material. Eur Heart J. 2012. Online available at: http://eurheartj.oxfordjournals.org/content/early/2012/06/19/eurheartj.ehs149/suppl/DC1. • Crespin DJ, Federspiel JJ, Biddle AK. Ticagrelor versus genotype-driven antiplatelet therapy for secondary prevention after acute coronary syndrome: a cost-effectiveness analysis. Value Health. 2011;14:483-491.	We have amended the report to reflect this. We have changed the sentence to state that cost-effectiveness of ticagrelor versus generic clopidogrel is not known in the United States.
Gans-Brangs, Kathleen (AstraZeneca)	References	The attached information is supplied in response to an open public comment period. These materials may include information that is not found in the currently approved prescribing information for BRILINTA™ (ticagrelor) Tablets. The enclosed information is intended to provide pertinent data as part of the public comment opportunity and should in no way be construed as a recommendation for the use of these products in any manner other than as approved by the Food and Drug Administration and as described in the prescribing information for BRILINTA™ (ticagrelor) Tablets Prescribing information for BRILINTA™ (ticagrelor) Tablets may be obtained from www.astrazeneca-us.com or by calling the Information Center at AstraZeneca at 1-800-236-9933. The FDA approved BRILINTA™ (ticagrelor) Tablets to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). References: The following is a list of publications recently published in full that were not included in the original clinical evidence submission to AHRQ that was provided in response to the unsolicited request for information. (continued in next cell)	Thank you.

Commentator & Affiliation	Section	Comment	Response
Gans-Brangs, Kathleen (AstraZeneca)	References	(continued from previous cell) • Cornel JH, Becker RC, Goodman SG, et al. Prior smoking status, clinical outcomes, and the comparison of ticagrelor with clopidogrel in acute coronary syndromes-insights from the PLATelet inhibition and patient Outcomes (PLATO) trial [in press]. Am Heart J. 2012. http://dx.doi.org/10.1016/j.ahj.2012.06.005. • Husted S, James S, Becker RC, et al. Ticagrelor versus clopidogrel in elderly patients with acute coronary syndromes: a substudy from the prospective randomized PLATelet inhibition and patient Outcomes (PLATO) trial. Circ Cardiovasc Qual Outcomes. 2012;5:680-688 • James SK, Storey RF, Khurmi NS, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes and a history of stroke or transient ischemic attack. Circulation. 2012;125(23):2914-2921 • Crespin DJ, Federspiel JJ, Biddle AK. Ticagrelor versus genotype-driven antiplatelet therapy for secondary prevention after acute coronary syndrome: a cost-effectiveness analysis. Value Health. 2011;14:483-491 • Nikolic E, Janzon M, Hauch O, et al. Cost-effectiveness of treating acute coronary syndrome patients with ticagrelor for 12 months: results from the PLATO study [published online ahead of print June 19 2012]. Eur Heart J. 2012. http://dx.doi.org/10.1093/eurheartj/ehs149.	Thank you.
Bradfield, Lisa (American College of Cardiology)	Tables	The clear and concise data presentation is very helpful for staff and guideline writing committee members.	Thank you.
Gans-Brangs, Kathleen (AstraZeneca)	Tables	Table F-1 Page F-10Mean age in PLATO was 62 years. Wallentin 2009 (PLATO), study details need to be revised to:Mean age: 62 63 years Source: Wallentin 2009, pg 1048, table 1	We have revised this to 62 years.
Gans-Brangs, Kathleen (AstraZeneca)	Tables	Table F-1, Page F-48: Korovesis, 2005, Cointerventions- Delete ticagrelor and replace with ticlopidine Source: Korovesis 2005, pg 47, col 1, para 2, sent 3	We have corrected this typo.
Gans-Brangs, Kathleen (AstraZeneca)	Tables	Table G-3, Page G-9: The table does not include the primary endpoint of the PLATO trial: please add the primary composite endpoint at 1 year: Outcome = Primary Composite at 12 months Ticagrelor: 864/9333 Source: Wallentin 2009- PLATO, pg 1052, Table 3 Clopidogrel: 1014/9291	We have added the primary composite at 12 months.

Commentator & Affiliation	Section	Comment	Response
Gans-Brangs, Kathleen (AstraZeneca)	Tables	Table F-1 Page F-10Mean age in PLATO was 62 years. Wallentin 2009 (PLATO), study details need to be revised to: Mean age: 62 63 years Source: Wallentin 2009, pg 1048, table 1	We have revised this to 62 years.
Gans-Brangs, Kathleen (AstraZeneca)	Tables	Table G-3 Page G-9: It appears that the proportions shown for some of the endpoints in Table G were calculated based on K-M estimates rather than crude rates. The methodology of these calculations should be disclosed in this report. Minor bleeding alone was not reported in the PLATO trial publication. Two adverse drug reactions values are presented and the type of adverse reaction is not shown. It appears that these numbers relate to dyspnea and bradycardia. Revise as shown below: Outcome Results Reported by Authors Minor Bleeding at 12 months Ticagrelor 360/9235 Clopidogrel 322/9186 Adverse drug reactions Dyspnea at 12 months Ticagrelor 1274/9235 Clopidogrel 717/9186 Adverse drug reactions Bradycardia at 12 months Ticagrelor 406/9235 Clopidogrel 367/9186 Source: Wallentin 2009- PLATO, pg 1054, Table 4	We have revised this appendix.
Gans-Brangs, Kathleen (AstraZeneca)	Tables	Table G-3 Page G-11: Efficacy outcomes were not a primary endpoint in the DISPERSE-2 trial. The primary endpoint was bleeding at 30 days. Bleeding at 3 months was not a primary endpoint. The numbers shown for composite efficacy endpoint at 30 days and 3 months are for CV death/MI/stroke, as seen in Cannon 2007, Table 3. Revise as follows: Primary Composite Efficacy at 30 days: Total CV mortality Nonfatal MI Nonfatal stroke Recurrent ischemia Primary Composite Efficacy at 3 mo: Total CV mortality Nonfatal MI Nonfatal stroke Primary Safety Composite at 30 days: Major bleeding Minor bleeding Primary Additional Safety Composite at 3 mo: Major bleeding Minor bleeding Source: Cannon 2007-DISPERSE-2, pg 1848, Table 3	We have revised this appendix.

Commentator & Affiliation	Section	Comment	Response
Gans-Brangs, Kathleen (AstraZeneca)	Tables	Table H-1, Page H-58: Several endpoints are shown incorrectly as 30 days. Change to 1 year. Age < 65 yrs: Major bleeding at 30 days 1 year Age ? 65 years: Major bleeding at 30 days 1 year Age < 75 years: Major bleeding at 30 days 1 year Age ? 75 years: Major bleeding at 30 days 1 year Male: Major bleeding at 30 days 1 year Female: Major bleeding at 30 days 1 year Diabetes: Composite outcome (vascular death, nonfatal MI, or stroke at 30 days 1 year) Major bleeding at 30 days 1 year Total mortality at 30 days 1 year Nonfatal MI at 30 days 1 year Stent Thrombosis at 30 days 1 year Chronic Kidney Disease: Composite outcome (vascular death, nonfatal MI, or stroke at 30 days 1 year) Major bleeding at 30 days 1 year Total mortality at 30 days 1 year BMI <30kg/m2: Composite outcome (vascular death, nonfatal MI, or stroke at 30 days 1 year) Major bleeding at 30 days 1 year BMI ? 30kg/m2: Composite outcome (vascular death, nonfatal MI, or stroke at 30 days 1 year) Major bleeding at 30 days 1 year Weight < 60kg: Composite outcome (vascular death, nonfatal MI, or stroke at 30 days 1 year) Major bleeding at 30 days 1 year Weight ? 60kg: Composite outcome (vascular death, nonfatal MI, or stroke at 30 days 1 year) Major bleeding at 30 days 1 year White: Composite outcome (vascular death, nonfatal MI, or stroke at 30 days 1 year) Major bleeding at 30 days 1 year Black/AA: Composite outcome (vascular death, nonfatal MI, or stroke at 30 days 1 year) Major bleeding at 30 days 1 year Asian: Composite outcome (vascular death, nonfatal MI, or stroke at 30 days 1 year)Major bleeding at 30 days 1 year NSTEMI: Composite outcome (vascular death, nonfatal MI, or stroke at 30 days 1 year) Major bleeding at 30 days 1 year Unstable Angina: Composite outcome (vascular death, nonfatal MI, or stroke at 30 days 1 year) Major bleeding at 30 days 1 year Initially specified for a non-invasive strategy: Composite outcome (vascular death, nonfatal MI, or stroke at 31-360 days 1 year) Major bleeding at 31-360 days 1 year Nonfatal MI at 31-360 days 1 year CV mortality at 31-360 days 1 year Total mortality at 31-360 days 1 year Stroke at 31-360 days 1 year GPI use: Composite outcome (vascular death, nonfatal MI, or stroke at 30 days 1 year) Major bleeding at 30 days 1 year Source: Wallentin 2009- PLATO	We have revised these outcomes to 1 year.

Commentator & Affiliation	Section	Comment	Response
Gans-Brangs, Kathleen (AstraZeneca)	Tables	Table H-1, Page H-59: Diabetes subgroup- Reference stated does not support all of the data presented. Replace Wallentin 2009 with the following reference: James S, Angiolillo DJ, Cornel JH, et al. Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J. 2010;31(24):3006–3016.	We cite only the main paper for each study. Appendix C contains a table indicating which articles are primary/cited articles and which are companion articles.
Gans-Brangs, Kathleen (AstraZeneca)	Tables	Table H-1, Page H-60: CKD subgroup- Reference stated does not support all of the data presented. Replace Wallentin 2009 with the following reference: James S, Budaj A, Aylward P, et al. Ticagrelor versus clopidogrel in acute coronary syndromes in relation to renal function: results from the PLATelet inhibition and patient Outcomes (PLATO) trial. Circulation. 2010;122:1056-1067.	We cite only the main paper for each study. Appendix C contains a table indicating which articles are primary/cited articles and which are companion articles.
Gans-Brangs, Kathleen (AstraZeneca)	Tables	Table H-1, Page H-62: Noninvasive management patients- Reference stated does not support all of the data presented. Replace Wallentin 2009 with the following reference: James SK, Roe MT, Cannon CP, et al for the PLATO study group. Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for a noninvasive management: substudy from prospective randomized PLATelet inhibition and patient Outcomes (PLATO) trial. BMJ. 2011;342:d3527 doi: 10.1136/bmj.d3527.	We cite only the main paper for each study. Appendix C contains a table indicating which articles are primary/cited articles and which are companion articles.
Bradfield, Lisa (American College of Cardiology)	Figures	Helpful resource	Thank you.
Chapell, Richard	Figures	As discussed under “Introduction, please add GPIs as a treatment option when an initial conservative approach is implemented to figures A, 1 and 2.	We have added GPIs to these figures.
Bradfield, Lisa (American College of Cardiology)	Appendixes	Helpful resource	Thank you.
Peer Reviewer 1	General	Meaningful as a comprehensive review to determine research gaps but does not add to available practice guidelines for practitioners. Target audience and key questions are appropriate and stated.	Noted.
Peer Reviewer 1	General: Quality of the report	Good	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	General: Clarity/usability	The document is an excellent reference of available studies.	Thank you.
Peer Reviewer 2	General	The authors are to be congratulated for taking on this herculean task. The key questions themselves are clinically relevant and important. The document itself is overwhelming in scope and detail, and as would be expected for something of this size is quite uneven. The goal is to go beyond the guidelines to gain insight into comparative effectiveness of different antiplatelet and anticoagulant combinations. However, there are so few decent quality data sets that address these key issues that the result is that the conclusions largely parrot those of the guidelines. In the areas where they do not (support for GPI in conservatively managed patients, lower mortality for omemprezole, etc) the conclusions of this document are likely to be incorrect. An important issue with interpretation of the data is overweighting of observational data. “Precise” estimates from observational data get stronger strength of evidence (SOE) than consistent RCT data in many areas.	The SOE ratings for the PPI observational studies were downgraded mostly from high to low strength of evidence given the study design and the inconsistent findings with the omeprazole RCTs. The GPI studies in KQ2 were all RCTs. The Discussion has been revised to add text about our findings in contrast to the guidelines. The sensitivity analysis leads us to suspect that newer studies using DAPT are influencing the results.
Peer Reviewer 2	General	A second major issue throughout is lack of consideration of endpoint definitions in the comparative effectiveness calculation. For example, the MI definition for many of the trials is driven by procedural enzyme elevation, which is of dubious and controversial clinical relevance. In contrast, major bleeding is a tremendously important clinical event. Indeed, it could be argued that a “minor” bleed is more important than an asymptomatic procedural MI from a comparative effectiveness perspective. No insight is provided at all in these areas.	We understand that there can be heterogeneity with endpoint definitions and how these endpoints are reported within the published literature. Given the complexity of the report, we were not able to focus on the nuances in the endpoint definitions but instead used the study authors’ definitions. We however acknowledge this as a limitation of our report and now include a brief discussion of this within our report and a call for further standardization of outcome definitions and reporting.
Peer Reviewer 2	General	With regard to SOE, the authors too easily give “sufficient” SOE for studies with small meta-analysis with “positive” results and p,0.05 but too reluctant to give an interpretable SOE for full meta-analysis results even when sample size is large and CI is narrow. Specific examples are provided below	See responses below to your specific examples. The justification for the SOE ratings is in the full report text and in the detailed SOE tables for each comparison.
Peer Reviewer 2	General	Finally, and most importantly, the document is so long and complex that it is just hard to get through. If the authors tried to do less, focusing on fewer points with better data, it would be stronger.	Noted. A separate Executive Summary document will be available for those with limited time to review the full report.
Peer Reviewer 2	General: Quality of the report	Fair	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 2	General: Clarity/usability	The bulleted conclusions are concise and to the point and the figures are clean and simple. In contrast, the body of the document is difficult to follow. There are too many endpoints at too many timepoints described, with different endpoints used for each key question and subquestion. The different sections read as if they were spliced together rather than having a cohesive style.	We acknowledge the many endpoints and time points that were reported in this document. Our CER protocol outlined these endpoints and followup time points a priori.
Peer Reviewer 3	General	This is a comprehensive comparative effectiveness review of the effectiveness and safety of various antiplatelet and antithrombotic regimens for USA/NSTEMI in an early invasive approach, an initial conservative approach and post discharge. Key questions (KQ) were constructed with input from the Technical Expert Panel. The overall findings are concordant with ACCF/AHA guidelines, including the 2012 Focused update on management of patients with USA/NSTEMI. The key questions are appropriate and explicitly stated. The target audience is not explicitly defined in the manuscript, but is assumed to be intended for clinicians, consumers, and policy makers.	Thank you.
Peer Reviewer 3	General: Quality of the report	Superior	Thank you.
Peer Reviewer 3	General: Clarity/usability	In addressing the response to key questions, it would be helpful to organize the responses by the Key question/sub-question. For example, KQ1a, KQ1b, etc. For example, it is not obvious where KQ1a is explicitly being addressed (PO vs. IV antiplatelet agent). This particular question is partially addressed in the Section on "Research Gaps" where it is mentioned that there are a lack of studies directly comparing IV to PO antiplatelet agents.	We have added identifiers in the headings for the subquestions of each Key Question throughout the report.
Peer Reviewer 4	General	It isn't clear who the target audience is. On the one hand, it would seem to be practicing clinicians caring for patients with ACS, however the key questions seem rather rigidly defined and don't necessarily reflect the full panoply of options available to the clinician, probably because of limits concerning the availability of evidence.	The Key Questions were defined by the nominator and stakeholder panels. The report is not meant to be all-inclusive of UA/NSTEMI treatment. Due to limited resources, we can only assess a few questions within an evidence review.
Peer Reviewer 4	General	The key questions are stated clearly.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	General	It's not clear to me why 'triple therapy' should be included in this review. It's clearly very important in a select group of subjects, but the consideration only arises in whom there is a clear indication for oral anticoagulants (those with atrial fibrillation or mechanical prosthetic heart valves) and isn't reallya consideration in most patients with acute coronary syndromes. While the review in this very specialized group is quite good, it seems out of place in this particular analysis and seems to this reviewer to be a distraction.	The nominator of this topic asked for the effectiveness of dual antiplatelet therapy compared with triple therapy for patients with a longstanding indication for anticoagulation.
Peer Reviewer 4	General: Quality of the report	Good	Thank you.
Peer Reviewer 4	General: Clarity/usability	The report is extremely well structured and the findings are presented clearly. One of the problems of course is that the literature is rather voluminous and heterogenous in this field. As a result, there are a large number of major findings. Perhaps it would useful to include a short but definitive table of findings with regard to the major outcomes such as death and myocardial infarction for each of the domains studied. This would be incomplete of course vis a vis the rest of the analysis, but it would make the critical points easier to access.	Noted. AHRQ will decide whether to create shorter summaries of the major findings of this report for clinicians and consumers.
Peer Reviewer 4	General: Clarity/usability	I would like to see the executive summary shortened. I would also like to see the flow diagrams expanded. The authors are obviously limited by the types of data that are available for this kind of analysis, but it would be useful to precede Figure A with a broader diagram that includes the readily available strategies that were not or could not be analyzed in this report.	This report is a focused review of key questions that could be answered within the scope of this project. It is not intended to be a guideline or clinical summary of all the treatment options available for UA/NSTEMI.
Peer Reviewer 4	General: Clarity/usability	While the findings of this report are useful in formulating clinical decisions, constraints in the nature of the data (for example, the absence of current data on some of the therapeutic options and combinations that are available) and the rapidity with which the field has been advancing make it rather hazardous to formulate policy based on the current analysis. In addition, the SOE criteria are appropriately rigorous, however, the SOE reported by the authors is frequently less than high, which would complicate policy formulation but might be adequate for clinical decision-making.	We acknowledge that the SOE ratings are frequently less than high in this CER report, which means that more research is needed for many of the comparisons studied and the outcomes assessed.
Peer Reviewer 5	General	clinically meaningful, methodically researched, meticulously referenced.	Thank you.
Peer Reviewer 5	General: Quality of the report	Superior	Thank you.
Peer Reviewer 5	General: Clarity/usability	well organized, nicely presented despite its heft	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 6	General	I commend the authors for a very extensive and comprehensive review of the literature on this topic. The report is very clinically meaningful and timely as decision-making around antiplatelet agents and anticoagulants has become more complex with newer agents on the market and indications for different clinical scenarios. Additionally these newer agents are often tested against an existing standard of care, but not in head to head comparisons including both the standard and new drug options. The separation of the evidence synthesis based on the treatment algorithm (conservative, early invasive, and post-discharge) makes this report clinically applicable as these are the important scenarios of care where drug choice decisions are made.	Thank you.
Peer Reviewer 6	General	The target population – individuals hospitalized or post-discharge with unstable angina and/or non-ST segment elevation MI (NSTEMI) – is well-defined. One comment is that unstable angina and NSTEMI can be a very heterogeneous population given that there can be subjectivity in a clinician's definition or differing thresholds for cardiac biomarkers, etc. The background defines unstable angina and NSTEMI using a standard definition referenced in the literature. Is this the definition used for purposes of this report? It was unclear if an a priori definition was used or if it was based on the how a study identified in the search strategy defined the conditions.	The search strategy was based on the terms outlined in the Appendix. We accepted the definition of UA and NSTEMI as defined by the study authors.
Peer Reviewer 6	General	The other question that arose for me in the early part of the executive summary was whether or not the target population was a population of patients with unstable angina/NSTEMI that were status post PCI or all-comers with UA/NSTEMI. It became clearer to me that PCI was not a requirement for the target population as I read on, but perhaps a clarification early in the document will prevent this confusion. The target population also becomes complicated in the results section when it is explained on p17 that some of the studies reviewed included acute coronary syndrome patients, but did not differentiate ST-segment elevation MI from unstable angina or NSTEMI patients. The explanation and how it was handled was well-described for the reader and seemed appropriate. However, it raises the question of whether the intent is to also apply the report to the ACS population as long as it includes unstable angina and NSTEMI.	This report focuses on the UA/NSTEMI population. In the Methods section, we report the eligibility criteria, and in the introduction of the Results section, we discuss the expansion to ACS studies that included UA/NSTEMI.

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Peer Reviewer 6	General	There is some description of a target audience in the description of the Effective Health Care Program. However, perhaps a more precise description of audience and how different audiences can use the report could be appropriate – care providers, researchers, grantmakers, and regulators, for example. The implications sections of the report on p.188-189 offers an opportunity to make this clearer.	AHRQ evidence reports are often translated into other documents (e.g., Consumer summary, Clinician summary) for different audiences. The text to explain those other documents generally is not included in the CER report.
Peer Reviewer 6	General	The key questions are excellent and well-stated. Including the key questions on the treatment algorithm and the analytic framework diagrams is immensely helpful. It makes it clear where the questions arise in clinical decisionmaking.	Thank you.
Peer Reviewer 6	General	Related to this, is a question on the treatment algorithm diagram (p.5). In the Plan for early invasive approach where KQ 1a, 1c are listed, there are potentially two different interpretations of the information in the box. One is a strategy of anticoagulant plus oral antiplatelet versus a strategy of intravenous GP 2b/3a. The other interpretation is anticoagulant plus either an oral antiplatelet or GP 2b/3a. Perhaps this could be clarified in the diagram.	The diagram can be interpreted in many ways since different combinations of antiplatelet and anticoagulant are used in clinical practice. The purpose of the diagram is to show all the possible combinations—not to restrict the presentation to only a few.
Peer Reviewer 6	General: Quality of the report	Superior	Thank you.
Peer Reviewer 6	General: Clarity/usability	The main points are clearly presented; however, there is a lot of information presented in this report. It is very helpful to have the framework diagrams as well as an orientation to the layout at the beginning of each section. The key questions drive the organizational layout of the document. However, the questions and sub-questions are framed differently than the subtopic headings that are report in the results. Further, there are results reported for each outcome of interest and for each topic, there may not be data for each outcome of interest. This could make for some confusion as the reader may need to return to the key questions to understand how the results relate to the original search objectives. Is there a way to construct a diagram that includes the key questions and their relationship to the individual topics reported out in the results?	We have added the specific subquestion of each Key Question in parentheses next to the comparison.
Peer Reviewer 6	General: Clarity/usability	The conclusions are very helpful to inform practice decisions. The relationship of the findings to current guidelines makes it easier to understand how to plug these findings into evidence-based care as well as helps to identify where there are gaps in evidence for practice decisions. Additionally, the conclusions nicely point out for researchers where more research is needed really focused on head-to-head comparisons of the newer agents alongside the more established ones as well as combinations of therapy.	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP Member 1	General	All exceedingly well done.	Thank you.
TEP Member 1	General: Quality of the report	Superior	Thank you.
TEP Member 1	General: Clarity/usability	In a structured review of this type it is often common to feature repetition (executive summary, followed by results, followed by a more in depth explanation of the results). It would be useful for clinicians to have a very slimmed down executive summary of "the bottom line" findings. Interestingly, the few specific conclusions drawn at the end of the narrative are perhaps too filtered (including only the strongest evidence.) Idea would be a page of approximately 15-20 take home points.	AHRQ usually generates a clinician summary for each CER after the CER is finalized.
TEP Member 2	General	This is an extremely large and comprehensive effort, which generally is of very high quality. It probably represents the most thorough, complete, qualitatively excellent evidence review available in this area. However, limitations are mostly those of the evidence base itself, which is incomplete in many respects. It could perhaps better take into account biological rationale and statistical consistency. For example, the high degree of residual confounding likely affecting the observational studies of PPIs and the lack of differential effects among PPIs in keeping with biochemical interactions (i.e., where omeprazole should have greater interaction) could be noted. Potential confounding in general could be given more attention throughout the article.	We have modified this section to present the adjusted or propensity-scored results to account for confounding. However, we cannot exclude the possibility that residual confounding still exists in the observational studies.
TEP Member 2	General	Another point: where an overall composite endpoint is significant, the intervention is likely effective for its individual components and for subgroups if their point estimates are similar and not heterogeneous statistically, given lower power for these. This doesn't come out in the analyses. A more transparent approach to the designation of SOE low vs. insufficient (and the hypothesis tested—superiority vs non-inferiority) is needed. (Note that I concentrated mostly on the initial, executive summary section, given the enormous length of the report.)	Our justifications for the SOE ratings are described in the full report text and detailed SOE tables. We created summary SOE tables in the Executive Summary to simplify the presentation.
TEP Member 2	General	Updates on Trilogy ACE and ATLAS-ACS should be included.	We have included the Trilogy ACS update; however, the ATLAS-ACS study was excluded from this report since we did not have a Key Question regarding the use of oral anticoagulation (without an indication for long-term anticoagulation).
TEP Member 2	General: Quality of the report	Superior	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP Member 2	General: Clarity/usability	Report is well structured and organized. Main points are clearly presented and re-emphasized in the multiple sections of the report. Conclusions are useful and mostly in keeping with current GL recommendations, although in some instances, they are superficially, at least, divergent, indicating a need for clarification/adjustment/reanalysis of GL as well as methodology used in this report.	Noted.
TEP Member 3	General	A very-well researched and authoritative report. I do not not have substantive comments. My only concern is the speed at which this field is evolving and the ability of such documents to keep pace with the latest developments.	Noted.
TEP Member 3	General: Quality of the report	Superior	Thank you.
TEP Member 3	General: Clarity/usability	Very well-organized.	Thank you.
TEP Member 4	General	The key questions are clear and well defined. The results clearly delineate the data but the clinical implications and how these results differ from the current recommendations and what changes in clinical practice are not highlighted	We have text describing this in the main report discussion under the heading “Findings in Relation to What is Already Known”
TEP Member 4	General: Quality of the report	Good	Thank you.
TEP Member 4	General: Clarity/usability	The conclusions are clearly presented and the report is well structured. I have attached a detailed review of some of the issues identified.	Thank you.
TEP Member 5	General	Key questions are clinically meaningful and appropriate, but difficult to answer and in many cases there is adequate support in terms of available high quality studies.	Noted.
TEP Member 5	General	The report does an excellent job outlining the que4stions and the methods; because there are so many embedded questions (infinite possibilities for dosing and timing) within each question, clear answers are not possible. Under these circumstances, the report does a good job of categorizing the issues and attempting to evaluate the evidence.	Thank you.
TEP Member 5	General	There are a number of minor corrections that need to be made. For example, on p. ES-14 the bottom two bullets say essentially the same thing.	We have gone through the report and made corrections.
TEP Member 5	General	Table D, ES-17 has one HR for a three-way comparison. I didn’t check each result for consistency and logic.	The studies were not three-way comparisons. We have reworded this section header to state “clopidogrel vs. ticagrelor **or** prasugrel.”
TEP Member 5	General: Quality of the report	Good	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP Member 5	General: Clarity/usability	The report is well structured and organized. However it is difficult to obtain a "bottom line."	Noted.
TEP Member 5	General: Clarity/usability	The abstract is dense and difficult to absorb. It might better be displayed as a table.	Thank you for the suggestion, but we are constrained by AHRQ formatting requirements.
TEP Member 5	General: Clarity/usability	The grey shading on tables, indicating insufficient evidence, is good. Bolding the results with SOE=high or moderate would help – there appear to be few of these.	Noted.
TEP Member 5	General: Clarity/usability	An additional table containing all results with SOE=high or moderate across all three questions would put the results in better context prior to the overall conclusions.	We thank the reviewer for their suggestion but have chosen not to include this additional table. Instead, we have highlighted those SOE ratings which are not rated insufficient in the summary tables (non greyed out rows) and we also highlight these findings in the key points and in the abstract for the report.
TEP Member 5	General: Clarity/usability	With so many results arising from so many comparisons, the strength of evidence becomes blurred. It is difficult to determine without the above mentioned table which conclusions can be used to inform policy or practice.	Noted.