Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: *Renal Artery Stenosis Management Strategies: An Updated Comparative Effectiveness Review*

Draft review available for public comment from March 25, 2015, to April 28, 2015.

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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
Peer Reviewer #1	General	Quality of the Report: Fair	
Peer Reviewer #1	General	The heterogeneity of these trials and patients makes reaching any conclusion very difficult. You are to be applauded for not including the older balloon angioplasty trials, which are not relevant to today's interventional practice.	Thank you
Peer Reviewer #1	General	I find the paper to be too long and somewhat difficult to read.	The length of the full report is longer than many readers may expect, but there is a large amount of information being convey which needs to be explicated in detail.. The Executive Summary is considerably more concise and readable for the average reader and, we believe, of appropriate length given the topic.
Peer Reviewer #2	General	This is a well-written review about a complicated topic dealing with revascularization of renal artery stenosis.	Thank you
Peer Reviewer #2	General	Clarity and Usability: Yes	Thank you
Peer Reviewer #3	General	I do believe that the report is quite meaningful and well executed. Believe that the key questions are approriate and explicitly stated.	Thank you
Peer Reviewer #3	General	Clarity and Usability: the report is well structured and the main points are clearly presented. The conclusions presented can (and should) certainly be used to inform policy and practice.	Thank you

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	General	General Comments: This is an important update to the previous comparative effectiveness review (years 2006-2007) on management of atherosclerotic renal artery stenosis (ARAS). Of greatest importance is that the update includes data from 3 randomized controlled trials (RCT's - CORAL, ASTRAL, STAR) comparing ARAS revascularization by stenting to medical therapy. Although the newer RCT's have limitations that are well-articulated in the review, they confirm previous observations that stenting does not best medical therapy in typical people with ARAS. An RCT is unlikely to be performed in those with higher risk characteristics, e.g. congestive heart failure/pulmonary edema or rapidly declining kidney function. Thus, we are left with observational studies and case reports from which to draw inferences. Nonetheless, the comparative effectiveness review points to how these types of studies can be improved to inform future practice, e.g. analyses with propensity score matching.	Thank you
TEP Reviewer #1	General	The review is a useful guide to clinical management of ARAS that provides the most complete evidence to-date. I do not believe that any essential studies or topics were missed. The key questions have been voiced clearly and answered as much as possible. My specific comments in the sections below are simple intended to foster clarity and balance.	Thank you
TEP Reviewer #1	General	Clarity and Usability: The report is well-organized and user-friendly. Main points are clearly highlighted with relevant supporting information provided in close proximity. Users will readily be able to find what they seek, and the information is presented in such a way that recommendations should be helpful to clinicians, researchers, and policy-makers.	Thank you
TEP Reviewer #2	General	I focused my review on any aspects that related to regulatory processes or approvals. There were very few mentions of these and they were all accurate. Overall, the report seemed to be comprehensive and with supportable conclusions.	Thank you

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	General	Clarity and Usability: The report was well-organized and informative.	Thank you
TEP Reviewer #3	General	This is a well designed and well articulated comprehensive review of the renal artery stenosis management strategies. The key questions are appropriately stated and the report details the target audience.	Thank you
TEP Reviewer #3	General	Clarity and Usability: This report is well structured and organized. See prior comments above.	Thank you
TEP Reviewer #4	General	Overall, this is a thoughtful, comprehensive review of published comparative trial information regarding renal arterial disease. Comparative trials have been hampered by a dual paradigm, in which the question posed "is renal artery stenting comparable or better than therapy with current medical therapy?" [the primary question posed by recent RCT's] in the same universe where observational reports and experience has been established for many patients for whom "renal revascularization is applied for failed medical therapy" as a successful "rescue therapy". Hence, there is an intrinsic duality that remains unresolved.	Thank you. This is an excellent way of describing the conflict between RCTs and observational studies. We have included this concept in the Discussion of both the Executive Summary and main report.
TEP Reviewer #4	General	This report deals mainly with comparative studies. From 1454 citations, the final analysis was confined t 76 "relevant" studies and 20 case reports.	True.
TEP Reviewer #4	General	Clarity and Usability: There are no major omissions from my perspective.	Thank you
TEP Reviewer #4	General	The usability of this report is limited by the intrinsic ambiguity of the clinical context (see "dual paradigm" above). This is intrinsic to the questions posed. I believe the authors treatment of this effect and the restrictions on interpretation are a major strength of this project.	Thank you
TEP Reviewer #6	General	The report is a very dense read, but the material is complex and difficult to summarize so this is somewhat expected. The figures are very helpful, particularly the point estimates.	Thank you

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #6	General	Clarity and Usability: The report is organized well, but might benefit from an abbreviations section and harmonization of some of the terminology (as mentioned above).	Good idea. We have created an abbreviations page at the beginning of the report.
TEP Reviewer #6	General	The key points are useful, but could they be further condensed?	We believe it is valuable to have the main data in the key points to make them more complete. We have followed the structure of the original report.
TEP Reviewer #6	General	I commend the authors for including excluded studies along with the rationale/justification for exclusion.	Thank you
TEP Reviewer #6	General	Check for typographical erros (page 14, line 20 and page 23, line 10)	These errors have been fixed. Thank you for pointing them out.
TEP Reviewer #7	General	The report is potentially clinically meaningful because it supplies an exhaustive, detailed reference of clinical research focused on standard treatments of ARAS for readers to assess for themselves.	Thank you
TEP Reviewer #7	General	However, the key sections for take-home messages (Abstract and Executive Summary) seem to lack perspective about:•Incremental knowledge, if any, that has actually been obtained since the original 2007 report from comparative effectiveness studies of standard treatment options on well characterized, real-world populations with ARAS. Examples might be the demonstrated safety of ACEis/ARBs in ARAS, and consistently similar long-term outcomes of mortality, RRT and CV event rates for both PTRAS and aggressive medical therapy. ...How treatment trends for ARAS have changed over the years (e.g., rapid upstroke in use of PTRAS in early 2000s without evidence basis). CMS data on renal artery stenting claims would be useful to know, just as has been provided for surgical revascularization on page 2 of Background. ...How the “typical patient” considered for invasive intervention has also changed. …Importance of RCTs over other types of studies--this point gets quickly buried in text that lumps randomized and non-randomized comparative studies.	We have added a section to the Executive summary about incremental knowledge since the first AHRQ review (and have updated the main report section on Comparison with the prior CER). The executive summary does not include references to tables, figures, appendixes, etc. We did not review, and thus do not comment on, changes in treatment trends or who is currently treated.

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TEP Reviewer #7	General	Since the process for grading the strength of evidence underlies all conclusions in this report, some reference to Tables 6-8 (Pages 62-64) should be included upfront for readers to have better insight into how conclusions were drawn. Although described on page 10, it is not clear what weight was given by the study team to each of the factors listed: "number of studies, study design, study limitations, directness of evidence to Key Questions, consistency of study results, precision of estimates of effect, likelihood of reporting bias, other limitations, and overall findings across studies".	At the start of the Results we have added a call-out to the strength of evidence section. We have clarified the description of grading strength of evidence.
TEP Reviewer #7	General	...The percent (estimate) of patients with ARAS who exhibit acute decompensation and may be "effectively excluded" from trials.	We have added in data about the percentage of patients who present with flash pulmonary edema or rapidly declining kidney function. This is also noted in the Discussion.
TEP Reviewer #7	General	The Target audience is well defined in the Preface. Key questions are clearly stated and appropriate.	Thank you
TEP Reviewer #7	General	Minor Comments: •Wording of similar thoughts is not always consistent throughout the report. Example: Abstract, Page iv, "For all outcomes, the strength of evidence is low regarding the relative benefit of PTRAS and (? should be versus) medical therapy alone for patients with ARAS.….There is low strength of evidence that there is no difference in clinically important outcomes (death, CV events, RRT) between PTRAS and medical therapy alone, but this conclusion is most applicable to those patients for whom there is clinical equipoise between the two treatments." This seems unnecessarily wordy compared to Conclusions, page 68: "Overall, the evidence suggests that PTRAS does not provide a benefit over medical therapy alone in patients for whom there is equipoise between the two intervention approaches."	We need to include the strength of evidence in the abstract, but did not want to be overly repetitive. We have tightened up the language some.
TEP Reviewer #7	General	Clarity and Usability: The structure and organization of the report are fine	Thank you

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #7	General	The main points, such as in the conclusions of the Abstract, could be condensed and more clear. For instance, instead of repeating the phrase "There is a low strength of evidence that.." several times, perhaps the different points could be bulleted. Alternatively, just copy and paste the Conclusion section of the manuscript into the abstract. The conclusions have already informed practice decisions, as indicated at top of page 3.	We have not changed the structure or format of the various pieces.
Public Reviewer #1 (Michael Bloch)	General	As a clinician active in the field of clinical hypertension, I welcome this well, performed and authoritative comparative effectiveness review from AHRQ. As is obvious from the introduction, management of atherosclerotic renal artery disease (RAS) remains a vexing clinical problem with a suboptimal database from which to make clinical recommendations. AHRQ should be commended for taking on this challenge.	Thank you.
Public Reviewer #1 (Michael Bloch)	General	I believe that the authors have done an exceedingly competent job of identifying the scope of the problem and the key clinical questions that are both answerable and clinically relevant.	Thank you
Public Reviewer #2 (Alan Matsumoto)	General	Again, I believe the document represents the literature very well, and I do appreciate the chance to make suggestion and provide feedback.	Thank you.
Public Reviewer #3 (Joel Harder/SCAI)	General	However this document in its present format is less accessible to the practitioner. Everyone agrees that the strength of the evidence is low when compared to the type of data we have for coronary artery procedures. Nevertheless the Society is glad that the AHRQ acknowledges that some patients are likely to benefit from renal intervention. SCAI disagrees with the report that the subsets of patients in whom this therapy may be beneficialare unknown. In fact SCAI laid them out in our document and the evidence to support treatment for global renal ischemia in truly treatment resistant hypertension progressive ischemic nephropathy and refractory HFflash pulmonary edema seem to be generally agreed upon.	The systematic review summarizes across all relevant studies. Since there was not consistency across studies and, in many cases, sparse evidence, we cannot conclude that there is high strength of evidence about subpopulations of treatable patients.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #7	Abstract	In formatting the Results in the Abstract, page iv, consider adding a separate category in italics for nonrandomized comparative studies and consider moving each sentence in the subgroup analyses section to its respective study category section to simplify for reader.	We have separated out the RCTs from the nonrandomized studies, but we think it is clearer to have a separate section for subgroup analyses.
TEP Reviewer #7	Abstract	In Exec. Sum., page v, first paragraph, second sentence, "the goals of treatment are reduction in death, cardiovascular events (add these at front of list)...	We have revised the sentence to make the goals more explicit.
Peer Reviewer #1	Introduction	To be clinically meaningful, we must be able to identify obstructive renal artery lesions, and angiography is very imprecise for mild to moderate (50% to 70%) stenoses (which make up the largest amount of clinical trial enrollment). You provide the references and tables, but do not emphasize enough in the text that angiography is a poor discriminator of severity of obstruction in the mid-range of 50% to 70%.	We have added to the introduction about further issues with catheter angiography and with a lack of confirmed correlation with trans-lesional pressure drop, the true hemodynamic problem. (end of page 1) We have also added "Per expert opinion, the Society for Cardiovascular Angiography and Interventions also includes “hemodynamically significant” stenoses to warrant consideration for revascularization , including angiographic stenosis of 50 to 70 percent—only with an abnormal translesional pressure gradient—or stenosis greater than 70 percent." on page 2.
Peer Reviewer #1	Introduction	It is important to understand there are 3 indications for renal intervention: 1 renovascular hypertension; 2 ischemic nephropathy; and 3 cardiac destabilization syndromes (heart failure, flash pulmonary edema, and refractory angina). These should NOT be lumped together, but addressed individually when assessing the benefit of therapy.	Thank you, we have revised the introduction and clarified the indications for renal intervention.
Peer Reviewer #1	Introduction	The weakness of angiography to discriminate over the midrange of lesions (50% to 70%) is over-looked. These moderate lesions must have hemodynamic confirmation of their severity to merit revascularzation.	See response to same comment above.
Peer Reviewer #2	Introduction	The introduction is well written.	Thank you

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Introduction	In both the executive summary and the introduction, the goals of therapy are intially stated as imprving blood pressure, preservation or salvage of kidney function, and improved quality of life. They are later stated (more appropriately and comprehensively) to include prevention of adverse cardiovascular and renal events and improving survival. Would recommend and favor all statements of the goals defaulting to the more comprehensive listing.	We agree. The statement has been revised to: The goals of therapy are improvement in uncontrolled HTN, preservation or salvage of kidney function, prevention or treatment of cardiac syndromes such as pulmonary edema or unstable angina, and ultimately improved survival
TEP Reviewer #1	Introduction	b. Introduction: Page 11/229, line 23-24. The proportion of patients entering dialysis programs with end-stage renal disease due to ARAS is highly speculative and the reference cited is a review article. Since there is not systematic ascertainment for ESRD cause, this statement should be amended to reflect considerable uncertainty.	We have modified the text and added a USRDS and other study reference.
TEP Reviewer #1	Introduction	Pages 11-12/229, lines 57-58 and 1-2. CORAL showed no evidence that RAS blockade accelerated loss of eGFR. That observation can be inferred from the published primary paper. A detailed analysis of kidney function is expected to be published in 2015.	We have toned down the statements and added that the question of whether loss of kidney function differs based on treatment is of interest.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	Introduction	Page 13/229, lines 6-11 I take issue with the statement that the newer RCT's were biased toward lower-risk patients because many clinicians and patients with higher-risk did not agree to randomization to medical therapy. Rather, as one of the investigators and an active clinician, my view is that the trial participants were actually representative of typical people with ARAS. Remember that those who are disappointed with outcomes of a trial often become detractors who bring their own biases to opposing the results with their opinions (not necessarily facts). Please tone down the overly presumptive statements in this section and throughout the document.	We did not state that patients with higher risk were not included in the RCTs, but that the RCTs included "patients for whom there is equipoise between revascularization and medical therapy alone in current clinical practice (since the patients and their clinicians had to agree to the possibility of not having PTRAS)". This is a truism. We do not believe that we downplay the "negative" results of the RCTs. Other reviewers appear to agree. We did change "not necessarily [applicable] to the majority of patients undergoing PTRAS" to "possibly not to many patients undergoing PTRAS". In the Abstract we also changed "limited applicability to typical patients" to "many patients". We also toned down the language in the Executive Summary.
TEP Reviewer #2	Introduction	The introduction covered the scope of the issue at hand very nicely.	Thank you
TEP Reviewer #3	Introduction	The background section is well written and establishes the key controversies regarding management and intervention for renal artery stenosis.	Thank you
TEP Reviewer #4	Introduction	Good summary of older populations with high prevalence of identifiable disease, but limited by imprecise criteria for hemodynamic and clinical significance. While prospective RCT's have been negative, the authors recognized difficulties of enrollment and exclusion of subsets that benefit from salvage revascularization	Thank you
TEP Reviewer #5	Introduction	P1. Would consider adding data on prevalence of RAS in patients with non-dialysis-dependent CKD. Also, need to differentiate between rates of ALL RAS and moderate to severe RAS (generall accepted as >60-80% stenosis) to better understand the actual prevalence of RAS that might be considered relevant for revascularization.	The data on RAS prevalence is poor. We have cited what we believe is the most up to date and complete review, the systematic review by de Galt (reference 2). We have added in that RAS was generally defined as ≥50% stenosis. We found no data on prevalence in the general CKD population. (Dr. Rundback was emailed for any additional references he may know about.

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TEP Reviewer #5	Introduction	P 1. RE: "The value of these non-invasive imaging techniques depend on operator's experience, body habitus, the presence of bowel gas, and they may be less reliable in visualizing distal segments of rental arteries." These limitations only apply to renal duplex ultrasound. MRA and CTA are contraindicated in patients with renal insufficiency, and both studies are compromised by the presence of metallic implants (i.e. aortic endografts).	The description has been modified.
TEP Reviewer #5	Introduction	P 3. There is an important point here. CORAL is in the process of publishing BP data stratified by severity of stenosis, baseline SBP, and translesional pressure gradients. Since this data is soon forthcoming, it may provide critical analyses relevant to this review. We should consider either delaying this review, or acknowledge that an update to this review may be needed in the near future.	AHRQ has decided to proceed with completing this review. We believe it is likely that AHRQ will request a short addendum to this report when the new CORAL analyses are published.
TEP Reviewer #5	Introduction	P4. Another intermediate outcome is preservation of renal mass (Caps, Zierler data)	Renal mass was not agreed upon as an outcome of interest and is not included. We purposely limited intermediate outcomes to kidney function and blood pressure measurements.
TEP Reviewer #5	Introduction	P 4. Re: "High likelihood of poor outcomes": Might elaborate on this more, including such variables as CHF severity or frequency of hospitalization, threatened renal mass, diastolic dysfunction, and other surrogates of CV events, as well as post coronary artery bypass surgery risk of AKI (correlated with RAS).	Thank you. We have elaborated.
TEP Reviewer #6	Introduction	The analytic framework figure is confusing and does not contribute significantly to the reader's understanding. Please consider redesigining this with a more logical organization.	We have revised the analytic framework somewhat.
TEP Reviewer #7	Introduction	Referring to the original AHRQ report, on Page 2, "The review concluded that the evidence did not support one treatment approach over another for the general population with ARAS" should also be incorporated into the final sentence of Background in the Abstract, page iv.	We need to keep the abstract within a page and we do not think this point is more important than items currently in the abstract.

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TEP Reviewer #7	Introduction	Background-All minor comments: If possible, at end of first paragraph on Page 1, include an estimate of percentage of the population with ARAS who exhibit acute decompensation and may be “effectively excluded” from RCTs.	We have added an estimate on page 2 where the AHA criteria are presented. We also added to the description of the RCTs and the discussion.
TEP Reviewer #7	Introduction	...•Second paragraph, second to last sentence “The value of duplex ultrasonography (rather than all of previously mentioned angiographic imaging techniques) depends on operator’s experience, body habitus, etc.	The description has been modified.
TEP Reviewer #7	Introduction	...Third paragraph, first sentence, the goals of therapy are reduction of death and CV events, improvement of uncontrolled HTN, etc. Consider adding after second sentence, "Both options have risks."	Thank you. Added.
TEP Reviewer #7	Introduction	...On Page 2, second paragraph, add CMS stats about trends for PTRAS.	We have added this to the Introduction (on page 3).
Peer Reviewer #1	Methods	Methods: OK	Thank you
Peer Reviewer #2	Methods	The methods are well described and the inclusion/exclusion criteria stated clearly.	Thank you
Peer Reviewer #3	Methods	Believe that the answer to all of these questions are yes with the caveat that a number of investigations meeting the stated criteria and included in the RCT group are very limited studies that employ widely disparate techniques and less scientific rigor than the largest studies.	This aligns with our findings.
TEP Reviewer #1	Methods	The comparative effectiveness review was orchestrated, conducted, analyzed, and reported with an overall rigorous approach. I have no quibbles with the methodology and congratulate the review team on a job well-done.	Thank you
TEP Reviewer #2	Methods	The analyses performed seemed appropriate.	Thank you
TEP Reviewer #3	Methods	The strategies to define different types of studies for renal artery stenosis management are well articulated---as are the outcome measures and statistical methodology to be employed.	Thank you

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TEP Reviewer #4	Methods	Search strategies and methods of evaluation are explicit related to patient characteristics and adverse effects of procedures. The authors acknowledge that adverse effects of medical therapy were generally not published in any of the treatment trials.	Thank you
TEP Reviewer #4	Methods	Outcomes of interest were clearly defined. Inclusion of a limited number of case reports reinforced the "issue of patients excluded from essentially all comparative and almost all single group studies" was important, as it highlights the discrepancies between these populations.	Thank you
TEP Reviewer #5	Methods	P7. All RCTs to date have lacked a parallel registry to evaluate differences in characteristics and outcomes of screened but non-enrolled concurrent patients. This should be a recommendation of future studies to better understand the differences in patient cohorts between those treated with revascularization according to clinical practice and those in whom there was felt to be reasonable therapeutic equipoise for treatment randomization.	We have added a paragraph to Future Research about some possible advantages of a national register.
TEP Reviewer #6	Methods	Suggest mentioning the rationale for including retrospective surgical studies but excluding PTRAS or medical management studies.	The reasons for including retrospective surgical studies is already made in the methods section (page 10), but we have added a justification for including *only* prospective PTRAS studies.
TEP Reviewer #7	Methods	Inclusion of studies other than RCTs has been justified by need to augment the small numbers of RCTs, but this method could potentially dilute high quality data with lesser quality data when grading aggregate evidence. Was there a plan to do a parallel analysis of RCT data only?	We did not separately summarize the strength of evidence for RCTs only. This would only weaken the evidence base.
TEP Reviewer #7	Methods	Exclusion criteria are reasonable. No concern about search strategy. Outcome measures are adequately defined.	Thank you
TEP Reviewer #7	Methods	A statement about study design heterogeneity precluding meta-analysis should be included in the Abstract and Executive Summary.	We have added this to the Executive Summary, but do not think it needs to be in the Abstract.
TEP Reviewer #7	Methods	Report organization might benefit from further breakdown of comparative studies into randomized and nonrandomized.	The comparative studies section has separate sections for RCTs and nonrandomized studies.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1 (Michael Bloch)	Methods	The methodology of study selection and data abstraction was comprehensive and logical. The inclusion of nonrandomized studies and case reports, I believe, is extremely important in this situation where the randomized clinical trials, which are the usual focus of comparative effectiveness reviews, are so obviously flawed.	Thank you
Peer Reviewer #1	Results	Weinberg, I., et al. (2014). "Blood pressure response to renal artery stenting in 901 patients from five prospective multicenter FDA-approved trials." Catheter Cardiovasc Interv 83(4): 603-609.	This study is a pooled analysis of five PTRAS studies, three of which are included (two of which are not eligible). It was missed in our search due to delays by PubMed such that it was not yet searchable. However, we have added the analyses of predictors of BP response to Key Question 2 (Table 1) for PTRAS, with the caveat that the studies are not fully eligible. One study did not meet eligibility criteria because it included patients with ostial restenosis requiring repeat angioplasty (Laird JR, Rundback J, Zierler RE, et al. Safety and efficacy of renal artery stenting following suboptimal renal angioplasty for de novo and restenotic ostial lesions: results from a nonrandomized, prospective multicenter registry. Journal of vascular and interventional radiology : JVIR. 2010 May;21(5):627-37. PMID: 20304680.) One was an unpublished study with no available data that we could find.
Peer Reviewer #1	Results	Results: Do not ignore the power of registry data in assessing treatment efficacy: 1. The heterogeneity of these trials and patients makes reaching any conclusion very difficult. You are to be applauded for not including the older balloon angioplasty trials, which are not relevant to today's interventional practice.	Thank you

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Results	There is a huge difference between the initial treatment of hypertension and renal artery stenosis... i.e. CORAL comparing PTRAS vs MED; and The treatment of patients with significant renal artery stenosis who have failed medical therapy. Two different populations.	We agree. In the Discussion we have added a paragraph about how noncomparative studies are not comparable with each other because of differences in the underlying populations.
Peer Reviewer #2	Results	Yes	Thank you
Peer Reviewer #3	Results	The report is very detailed, possibly bordering on excessive for the most commonly encountered reader.	The length of the full report is longer than many readers may expect, but there is a large amount of information being convey which needs to be explicated in detail.. The Executive Summary is considerably more concise and readable for the average reader and, we believe, of appropriate length given the topic.
Peer Reviewer #3	Results	With that being said, the executive summary is concise and very clearly written to mitigate the previously stated problem. Throughout the key messages are clearly stated and applicable.	Thank you
Peer Reviewer #3	Results	As far as overlooked studies, I do believe that there are additional experiences with embolic protection use that did not meet the proscribed inclusion criteria that present important information (Holden and Hill, Edwards) as do other papers detailing the protective effect of sttain medications in the prevention of restenosis (Corriere).	We acknowledge that our review does not include all evidence that may have a bearing on the topic. It was agreed upon to restrict the review of PTRAS cohort studies to prospective studies. These retrospective cohort studies were, therefore, not eligible.
TEP Reviewer #1	Results	The results are presented in a clear and comprehensive manner. The Forest plots are especially useful to display the data and convey inferences. I believe that the analysis provides a complete report of relevant studies	Thank you
TEP Reviewer #2	Results	This section was very informative. I think the analysis of which patient/lesion characteristics affected outcomes will be especially interesting for readers, and the relevant information was laid out well.	Thank you
TEP Reviewer #3	Results	The investigators present a comprehensive review of randomized control trials, cohort studies, clinical series in case reports and present extensive data in supplemental tables and figures.	Thank you

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TEP Reviewer #3	Results	The authors focus on the randomized control trials for RAS management and conclude that the strength of evidence is low regarding the relative benefits of PTRAS over medical therapy.	Thank you
TEP Reviewer #3	Results	Importantly, they also observed that enrolled patients are "atypical" of those patients likely to benefit from intervention based upon the clinical series--- rapid loss of GFR, severe hypertension, and flash pulmonary edema.	Thank you
TEP Reviewer #4	Results	Studies were presented in reasonable detail, particularly with the benefit of the tables.	Thank you
TEP Reviewer #5	Results	P12. RE Kidney Function: Did these studies include pts with hx of heart failure within 30 days of randomization? This is the group most likely to benefit from revascularization.	We have added that the STAR trial was the only trial to explicitly include patients with CHF (~10%). But this trial didn't have substantially different results than other trials. However, we do not have enough data to make reliable conclusions about the effect on CHF on trial results.
TEP Reviewer #5	Results	P14: It is an important point here that only CORAL utilized an angiographic core lab, and that in general the investigator "visual estimate" of stenosis severity exceeds the core lab determined stenosis severity. By core lab, only 17% of patients in CORAL had stenosis >80%. The disconnect between operator and core-lab assessments as well as the specific disparity in deterimination of stenosis degree in CORAL has been previously presented although not published. At the very least, it may be worthwhile to comment on the lack of core lab measurements in both studies therefore introducing some degree of unreliability regarding the severity of the treated RAS stenosis. In additiona, no study measured plasma renin activity as a direct physiologic correlate of the hemodynamic significance of treated RAS. The lack of physiologic "proof" of renovascular hypertension (although this in itself is an unreliable test) as well the the wide heterogeneity of stenosis in treated and untreated subjects results in a regression to the mean and loss of discrimination of actual treatment effect.	This is a good point. We have added this description to CORAL and included the limitation in that section of the Discussion.

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TEP Reviewer #5	Results	P15, re: "Two included patients with over 50 percent stenosis, one with over 60 percent, and three with over 70 percent stenosis. ARAS was diagnosed in the preoperative period by renal angiography alone in two NRCSs,"Note should be made of the absence of transstenotic pressure measurements in most if not all studies; as a result, there is the possibility that angioplasty was performed on patients without significant stenosis which results in a selection bias limiting the evaluation of PTRA efficacy.	We have added details about reporting of translesional pressure gradient measurements in all main results sections.
TEP Reviewer #5	Results	P15, p 3: However, acute thrombotic events were rarely observed in any of these studies.	We have added this point into the paragraph about prophylaxis
TEP Reviewer #5	Results	P17: CORAL excluded patients who had a history of recent or active CHF and therefore does not evaluate recurrence or severity of CHF following medical or interventional therapy for RAS in patients with unstable cardiac syndromes including recurrent pulmonary edema or unstable angina.	CORAL reports on pulmonary edema or CHF, as we report, though not recurrent or severity.
TEP Reviewer #5	Results	P18: There was a trend towards less decline in inverse serum creatinine following PTRAS in the ASTRAL trial (p=0.06).	We have clarified that the mean slope of 1/SCr revealed a trend towards less decline (p=0.06) but the mean slope of SCr did not (p=0.11).
TEP Reviewer #5	Results	P21: Is there any way to perform an analysis of the characteristics of patients in the NRCSs in whom BP benefit was and or was not observed ... specifically, are there differences with regard to mean patient age, percent diabetic, baseline GFR, and chronicity of CKD in between the studies?	The study results do not allow for this as all but one found no BP benefit.
TEP Reviewer #5	Results	P22, KQ2: Did this discussion include consideration of the mansucripts by Zeller Circulation 2003 and Modral JVS 2011? Both of these manuscripts performed analyses of factors associated with a clinical response following PTRAS.	Zeller 2003 is dicussed under KQ2 of PTRAS studies (in Table 1 on page 42). Modral 2011 was a retrospective study of PTRAS and did not meet eligibility criteria.
TEP Reviewer #5	Results	PSS (22?), KQ3: One manuscript which addressed this was Leesar et al. JACC Vol. 53, No. 25, 2009	Leesar 2009 addresses KQ 2 and is also included in the PTRAS section (Table 1).
TEP Reviewer #5	Results	P28, last p: Mighy consider "breaking out" and reporting results from device PMA studies since these were more vigorously managed and included core-lab evaluations.	We have included all the studies with available data, as per our protocol, including from the FDA database, clinicaltrials.gov, ICTRP (WHO) and conference proceedings.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #6	Results	The term "malignant hypertension" is mentioned but not specifically defined, and seems to be used somewhat interchangably for a subset of factors that define "acute decompensation". It might be good to use consistent terminology and/or define these in the methods section. The same issues apply to the terms "azotemia" versus baseline CKD.	Thank you. We have defined malignant hypertension in the Introduction where mentioned in context of the ACC/AHA guideline. We have removed the poor term azotemia.
TEP Reviewer #6	Results	Suggest a summary of how blood pressure response was measured, as I suspect that there was a large amount of heterogeity across studies (e.g., single clinic measurement versus ambulatory, timing of BP measurement relative to treatment intervention, durability, etc.).	We have added this data in based on what was reported.
TEP Reviewer #6	Results	Were definitions of renal function improvement similar/consistent across studies, or was this defined by the reviewers? Same question applies for cardiovascular events.	This is a good point. We have highlighted the heterogeneity in the PTRAS cohort section and added a paragraph to the limitations portion of the Discussion.
TEP Reviewer #6	Results	It might be worthwhile to summarize the proportion of patients in each study with baseline CKD if renal function was assessed as an outcome.	We have added this information in.
TEP Reviewer #6	Results	Specific to CORAL, it may be worth discussing the run-in phase for standardized antihypertensive medicaiton management, and the fact that many of the participants randomized to PTRAS achieved reasonable BP control before procedural intervention.	We did not find this information in the published article.
TEP Reviewer #7	Results	The level of detail presented was appropriate.	Thank you
TEP Reviewer #7	Results	Studies were well defined in text and tables.	Thank you
TEP Reviewer #7	Results	Minor points: •Consider stating in text how many patients were studied in each broad category, e.g., 2615 patients in comparative studies, 1943 of whom were enrolled in RCTs.	We have added this information in.
TEP Reviewer #7	Results	...•In text summaries of trials, it would be useful to include pre-specified primary and secondary outcomes.	We have added these.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #7	Results	...•In Key Points, page 12, the statement in first bullet, "The RCTs were not representative of patients typically considering or undergoing PTRAS since both they and their clinicians had to have equipoise between PTRAS and continued medical therapy alone, which is sufficiently infrequent that recruitment into the trials was generally difficult", seems overly definitive and may be inaccurate. One message to patients in conducting a comparative effectiveness trial of two standard treatments is that there is a fundamental lack of knowledge about which treatment is better. This was the situation described in the 2007 report, when four of the five RCTs included in the current report were ongoing. Just pointing out that many factors, including lack of equipoise, affect rate of patient recruitment.	We have toned down the language and removed the issue about recruitment.
TEP Reviewer #7	Results	...•In CORAL summary, page 13, might mention that percent stenosis was determined by an angiographic core lab. Use of a distal protection device became optional; the trial was funded primarily by government grants.	This has been added.
Public Reviewer #1 (Michael Bloch)	Results	The results are presented in a fair, balanced, and comprehensive manner. Additionally, the conclusions drawn from the data are appropriately framed given the strength of the evidence from which they are drawn. The consistent and repeated focus on the poor quality of the evidence, particularly the significant inclusion bias of the randomized controlled clinical trials, rather than the results themselves, is refreshing and of crucial importance to clinicians and policy makers.	Thank you

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1 (Michael Bloch)	Results	While some reviewers may suggest that the authors have promoted unorthodoxmethodology in their comparison of the different types of trials, a fair and balanced subjective as well as objective assessment of the primary clinical trials is crucial in comparative effectiveness analyses. Specifically, the inherent hypothesis suggested by the authors that the difference in results between randomized trials and case reports may be due to patient selection rather than study design is of tremendous importance to clinicians and policymakers. Obviously, the basic tenets of evidence based medicine suggest that the results of clinical trials are applicable only to the patient population that was included. The fact that the case reports nearly universally included patients with very high grade stenosis and clear clinical indications for interventions (refractory hypertension, rapidly progressive renal dysfunction, or pulmonary edema) while the randomized clinical trials included very few of these patients, (requiring only a modest degree of luminal obstruction and clinical equipoise on the part of the treating clinician) is a crucial and important point that identifies the way forward for future clinical trials.	Thank you
Public Reviewer #2 (Alan Matsumoto)	Results	Why was there no reference to the STAR trial?	This has been fixed (Star = Bax trial)
Public Reviewer #2 (Alan Matsumoto)	Results	On page 22, second paragraph, last sentence – where it reads, “age> 70 years, or renal artery stenosis > 80 percent”, it should be changed to read, “age > 70 years, or site-reported renal artery stenosis > 80 percent”.	This has been fixed.
Peer Reviewer #1	Discussion/ Conclusion	The conclusions are fair.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Discussion/ Conclusion	We must recognize that the "clinical equipoise" that drives enrollment in clinical trials is completely different than clinical indications to treat patients. A patient with 90% bilateral renal artery stenosis and refractory hypertension to 5 medications, is not the patient who gets randomized. When evaluating the effectiveness of a therapy, there is a role for registry data, to determine effectiveness of interventions.	We agree. This concept has been discussed in summaries and the Discussion.
Peer Reviewer #2	Discussion/ Conclusion	1. There is no discussion about the use of hemodynamic evaluation by measuring trans-lesion pressure gradients as a physiological means to determine the significance of an ARAS. I believe this absence of this discussion is a major weakness of the document. Anatomic assessment of ARAS by measuring percent diameter stenosis is difficult and suffers from marked variability when using a 2 dimensional test such as digital subtraction angiography. I would include some discussion about the use of pressure gradients, by citing both pre-clinical and clinical studies that have shown the importance of measuring pressure gradients in determining the physiologic anda hemodynamic significant of an ARAS. This discussion will emphasis the need to incorporate physiologic, anatomic and clinical data into future studies to demonstrate which subgroup of patients will most likely show a measureable benefit from revascularization.References recommended: References recommended:a. Jones NJ et al. Catheter Cardiovasc Interv 2006; 68: 429-34.b. De Bruyne B et al. J Am Coll 2006; 48:1851-55.c. Mangiocapra F et al. Circ Cardiovasc Interv 2010; 3: 537-42.d. Imanishi et al. Angiology 2002; 43: 933-42.	We have added data about translesional pressure gradients as suggested by several reviewers. We have also further commented on this in the Discussion limitation section.
Peer Reviewer #2	Discussion/ Conclusion	In discussing the RCTs, it should be noted that the CORAL trial was the only RCT that used an independent Angiographic Core Lab to measure percent stenosis.	We have added this point to the discussion (page 73).

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Discussion/ Conclusion	In addition, it should be mentioned that for the CORAL trial, use of an embolic protection device and measurement of trans-lesion pressure gradients were at the discretion of the operators, and the data from those subgroups are being analyzed.	We have added this to the Subgroup and predictor analyses section.
Peer Reviewer #2	Discussion/ Conclusion	The review should note that it did not include stenting of arteries with ARAS in whom there was concern for renal artery compromise during endovascular aortic aneurysm or dissection repairs.	We have added this clarification to the start of the Discussion.
Peer Reviewer #2	Discussion/ Conclusion	Why was there no reference to the STAR trial?	It was included as "Bax". We have fixed this.
Peer Reviewer #2	Discussion/ Conclusion	On page 22, second paragraph, last sentence – where it reads, “age> 70 years, or renal artery stenosis > 80 percent”, it should be changed to read, “age > 70 years, or site-reported renal artery stenosis > 80 percent”	Corrected.
Peer Reviewer #2	Discussion/ Conclusion	Page 66, first paragraph, there is a sentence that notes that after PTRAS, BP generally decrease by about 10-30 mmHg. Since there is good evidence that a decrease in BP by 10-20 mmHg over a long-period of time results in improvement in cardiovascular (CV) outcomes and fewer CV events, it might be helpful to provide some discussion about the postulated reason why none of the trials have shown an improvement in CV outcomes or a reduction in CV events, even with a successful and durable decrease in BP after PTRAS?	We have moved this issue up to the main Summary part of the Discussion. We believe this may have to do with the noncomparability of patients in the different types of studies.
Peer Reviewer #3	Discussion/ Conclusion	The major findings are clearly stated and widely applicable to contemporary practice and future investigation. The limitations of the review are clearly stated with the exception that many of the detailed trials are widely disparate in a multitude of levels of scientific rigor (especially the reported trials involving surgical renal artery revascularization). This latter point is effectively dealt with in multiple sections of the review. Feel that the future research needs are implied strongly throughout and stated clearly in the conclusion; however, feel that addition of a discrete section titled 'future research' would increase clarity and within that section the important questions requiring address could be more explicitly stated.	We have created a separate future research section in the discussion and moved this section to just before the Conclusions.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	Discussion/ Conclusion	Implications and limitations of the comparative effectiveness review are explicitly stated. My major concern is about statements asserting bias toward lower-risk patients in the newer RCT's. As mentioned previously, this assertion should be toned down throughout the report. I appreciate and strongly agree with the suggestion that observational studies can be substantially improved by more advanced analyses such as propensity score matching.	See above response (Page 13/229, lines 6-11). We do not describe these patients as lower risk or excluded patients as higher risk.
TEP Reviewer #2	Discussion/ Conclusion	While this section was well-written and the conclusions point out that PTRAS does not seem to offer a benefit in patients for whom clinical equipoise exists between PTRAS and medical therapy, the fact that there are few robust studies looking at PTRAS in patients for whom equipoise may not exist may be considered a limitation of the available evidence. It may help to call this out more strongly to encourage more evidence development in this area.	A major point made in the Executive Summary Conclusions is "New studies or reanalyses of existing evidence are needed to better understand the comparative effectiveness of PTRAS versus medical therapy for those patients who most commonly undergo PTRAS, namely those who have a "clinical indication" for revascularization under current standard practice." We believe this addresses this point. In the Summary section of the Discussion we have a call for new studies and reanalyses of existing studies.
TEP Reviewer #3	Discussion/ Conclusion	The authors recognize the limited applicability of the results of the RCTs for patients who may or may not benefit from PTRAS for reasons articulated above. They suggest future studies may be needed in patients at higher likelihood of potential benefit---rapid loss of GFR, severe hypertension, or flash pulmonary edema--- and recognize the challenges of recruitment for such studies.	Thank you

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Discussion/ Conclusion	What is not addressed is the challenge for clinicians or guideline committees to recommend RAS management strategies for patients with RAS given the data with limited applicability. It is disconcerting to some that certain subspecialty societies for intervention have published guidelines that do not seem to be in accord with the findings of this report and existing RCT data. This issue deserves comment.	We have added a recommendation that future CPGs be evidence based and should be created in collaboration with various specialties and other interested stakeholders. We have removed the overly strong statement about different subspecialty recommendations. This really pertained to opinion pieces, not guidelines per se. We have also added a section comparing our findings with the 2 main guidelines from ACCF/AHA and SCAI.
TEP Reviewer #4	Discussion/ Conclusion	Key Messages: Major differences between included populations for RCTs and single therapy / observational studies.	True.
TEP Reviewer #4	Discussion/ Conclusion	Reported rates of complications vary considerably and most stringently overseen trials had extremely low procedural complication rates.	This is a good point that we have added to the Summary of findings, in the Discussion.
TEP Reviewer #4	Discussion/ Conclusion	Generally, the description and limitations of these studies are clearly identified.	Thank you
TEP Reviewer #4	Discussion/ Conclusion	The limitations of RCT enrollment place some boundaries on what rationally can be expected from future studies. Single treatment reports certainly reflect selection bias (e.g. for surgery) that is difficult to quantitate. Case reports uniformly reported major clinically beneficial outcomes that imply both selection (and likely publication bias), as the authors acknowledge. Inclusion of these reports offsets the limited, but negative, inferences of RCT data.	Thank you
TEP Reviewer #4	Discussion/ Conclusion	The authors clearly state that the conclusion that no difference exists between medical vs. PTRAS is based on “low strength of evidence”, and most importantly, “is most applicable to those patients for whom there is clinical equipoise between the two treatments”.	Thank you
TEP Reviewer #4	Discussion/ Conclusion	Future research clear? They offer some more detailed analysis of existing data for predictive features, but this is not easily forthcoming.	We agree. We have added in a sentence to the Discussion specifically calling for well-conducted future observational studies. They may be complex, but should be simpler than the recent RCTs.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #6	Discussion/ Conclusion	Suggest including discussion of the implications of including paients with normal baseline renal function in studies where primary endpoint was based on renal function, as this practice (common in many studies) likely results in bias toward the null hypothesis since patients without CKD can experience treatment-induced renal function decline but have no significant chance for improvement.	A reasonable point. We have added this to the limitations; however, we did not find an association between mean baseline kidney function or BP and outcomes.
TEP Reviewer #6	Discussion/ Conclusion	The limitations of number of antihypertensive medicaitons as an outcome (given other indications for many of these medications in the setting of diabetes, CAD, diabetes, etc) may be worthy of mention. The complexity of how number of antihypertensive medications and blood pressure response (i.e., comparing better BP on the same number of meds versus similar BP on fewer meds versus similar BP on lower dose of the same number of meds) may also merit mention as a source of heterogeneity.	We discussed this but have elaborated more fully in the limitations.
TEP Reviewer #6	Discussion/ Conclusion	I would challenge the authors to make more specific reference to evidence gaps or future study designs that they would propose as having the greatest potential to provide meaningful clinical evidence.	We have restructured and added to the Future research section.
TEP Reviewer #7	Discussion/ Conclusion	Discussion is good. Limitations of evidence are addressed. Not aware of any omissions of important literature.	Thank you
TEP Reviewer #7	Discussion/ Conclusion	Future research mention is brief, mainly to reexamine existing databases, consider multi-center observational studies with propensity score adjustment of outcomes based on likelihood of receiving PTRAS.	This has been expanded
TEP Reviewer #7	Discussion/ Conclusion	Better definition of the population for which PTRAS is considered "required" would also be a good aim.	This has been added to the new section on a national registry.
TEP Reviewer #7	Discussion/ Conclusion	Conclusions are stated concisely.	Thank you
TEP Reviewer #7	Discussion/ Conclusion	Minor edits: Would remove "But" from beginning of second sentence and start third sentence with "Nevertheless" instead of "Although".	We agree. Done.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1 (Michael Bloch)	Discussion/ Conclusion	From my point of view, as a clinician (not necessarily a policymaker), the data, as presented here, supports the conclusion that renal artery stenting provides no additional benefit over medical therapy alone among the type of patients primarily included in the randomized clinical trials - those with a moderate degree of stenosis, blood pressure that can be controlled medically, who do not have rapidly progressive renal dysfunction or recurrent pulmonary edema, and in whom the clinician has equipoise concerning management strategy.	Thank you. We have used some of this language to describe the enrolled/applicable patients.
Public Reviewer #1 (Michael Bloch)	Discussion/ Conclusion	While I appreciate the difficulty in abstracting this particular subgroup from the data available, personally I feel that the strength of the evidence for this subgroup is at least moderate. Given the small number of such patients who appear to have been included in the randomized clinical trials, I feel that we are unable to draw any conclusion about the comparative effectiveness of renal artery stenting versus medical management alone in patients who truly have a high degree of stenosis >80% (see discussion below) and/or in the presence of traditional indications for renal artery intervention: hypertension truly refractory to medical management, rapid unexplained renal deterioration or recurrent unexplained pulmonary edema. Clearly future clinical trials are needed in this patient population.	We have added in these descriptions of people for whom it is unclear which treatment is preferred. We are not convinced that trials in these populations are feasible, but analyses of a potential registry and/or propensity score analyses may be reasonable alternatives.
Public Reviewer #1 (Michael Bloch)	Discussion/ Conclusion	The one issue that I feel could be examined and stressed further in this review is that of degree of luminal obstruction. Based upon inclusion criteria, the randomized clinical trials clearly included a large number of patients who did not have hemodynamically significant lesions and as such would be unlikely to derive benefit from stenting. The fact that a high degree of stenosis was present in all included case reports, where benefit was demonstrated, is striking.	We have added data about translesional pressure gradients as suggested by several reviewers. We have also further commented on this in the Discussion limitation section.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1 (Michael Bloch)	Discussion/ Conclusion	The authors may want to consider expanding on their discussion of the change in inclusion criteria for the CORAL study during recruitment as well as the striking difference in the estimated degree of luminal obstruction between the investigator and the core laboratory in CORAL. While formal subgroup analysis did not identify patients with high degree of luminal obstruction as receiving benefit, the discrepancy in measurement (and relatively low utilization of proper pressure gradient measurement) questions whether or not this subgroup was appropriately identified.	The general issue of applicability has been addressed. We have added in a part about the core lab in CORAL. Future subanalyses are also now discussed.
Public Reviewer #1 (Michael Bloch)	Discussion/ Conclusion	Very early in my career I became concerned that the use of renal artery intervention in atherosclerotic renal artery disease was becoming too wide-spread with little data supporting its use and rampant 'indication-creep'. Now, given the popular interpretations of the recent randomized clinical trials that have been widely disseminated, I worry that the pendulum has swung too far in the other direction and we are with-holding a potentially effective treatment from a subset of patients who may significantly benefit from renal artery stenting. I feel that this comparative effectiveness review from AHRQ, if widely disseminated, is critical in helping clinicians and policymakers find their way to sound clinical decision making for patients with atherosclerotic renal artery stenosis.	Thank you

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 (Alan Matsumoto)	Discussion/ Conclusion	There is no discussion about the use of hemodynamic evaluation by measuring trans-lesion pressure gradients as a physiological means to determine the significance of an ARAS. I believe this absence of this discussion is a major weakness of the document. Anatomic assessment of ARAS by measuring percent diameter stenosis is difficult and suffers from marked variability when using a 2 dimensional test such as digital subtraction angiography. I would include somediscussion about the use of pressure gradients, by citing both pre-clinical and clinical studies that have shown the importance of measuring pressure gradients in determining the physiologic anda hemodynamic significant of an ARAS. This discussion will emphasis the need to incorporate physiologic, anatomic and clinical data into future studies to demonstrate which subgroup of patients will most likely show a measureable benefit from revascularization. References recommended: a. Jones NJ et al. Catheter Cardiovasc Interv 2006; 68: 429-34. b. De Bruyne B et al. J Am Coll 2006; 48:1851-55. c. Mangiocapra F et al. Circ Cardiovasc Interv 2010; 3: 537-42. d. Imanishi et al. Angiology 2002; 43: 933-42.	We have added data about translesional pressure gradients as suggested by several reviewers. We have also further commented on this in the Discussion limitation section.
Public Reviewer #2 (Alan Matsumoto)	Discussion/ Conclusion	In discussing the RCTs, it should be noted that the CORAL trial was the only RCT that used an independent Angiographic Core Lab to measure percent stenosis.	This has been added.
Public Reviewer #2 (Alan Matsumoto)	Discussion/ Conclusion	In addition, it should be mentioned that for the CORAL trial, use of an embolic protection device and measurement of trans-lesion pressure gradients were at the discretion of the operators, and the data from those subgroups are being analyzed.	Thank you. This has been added.
Public Reviewer #2 (Alan Matsumoto)	Discussion/ Conclusion	The review should note that it did not include stenting of arteries with ARAS in whom there was concern for renal artery compromise during endovascular aortic aneurysm or dissection repairs.	Thank you. This has been added.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 (Alan Matsumoto)	Discussion/ Conclusion	Page 67, first paragraph, there is a sentence that notes that after PTRAS, BP generally decrease by about 10-30 mmHg. Since there is good evidence that a decrease in BP by 10-20 mmHg over a long-period of time results in improvement in cardiovascular (CV) outcomes and fewer CV events, it might be helpful to provide some discussion about the postulated reason why none of the trials have shown an improvement in CV outcomes or a reduction in CV events, even with a successful and durable decrease in BP after PTRAS?	We have moved this issue up to the main Summary part of the Discussion. We believe this may have to do with the noncomparability of patients in the different types of studies.
Public Reviewer #3 (Joel Harder/SCAI)	Discussion/ Conclusion	Thanks for sharing. SCAI agrees that the conclusions here are not dissimilar to our conclusions stated in the SCAI Expert Consensus Statement for Renal Artery Stenting Appropriate Use.	Thank you, we agree. We have added a section explicitly comparing the findings of the review with the current SCAI and ACCF/AHA guidelines.
Public Reviewer #3 (Joel Harder/SCAI)	Discussion/ Conclusion	Given that the downside risks are low which this report corroborates the treatment of these selected groups of patients is reasonable	We don't makes recommendations
Public Reviewer #3 (Joel Harder/SCAI)	Discussion/ Conclusion	Its important to note that the ACCAHA AUC process has a project on this topic so it might be best to wait for that publication prior to completing this report. Its best to have primary care physicians know the full picture on this vital clinical area.	There are also future CORAL analyses. AHRQ may be interested in conducting an update of the review in the near future.
TEP Reviewer #4	Miscellaneous	Specific comment: p.12: “patient factors” 1 RCT found that patients with flash pulmonary edema…had better outcomes after PTRAS (reference? : The report I am aware of (Ritchie,et.al., was not an RCT, but rather a registry)	Thank you. We have edited this line.
TEP Reviewer #4	Miscellaneous	Note: “Bax 2009” trial should be identified as STAR, for parallel construction to ASTRAL and CORAL.	We have changed the document to identify the STAR trial by its name throughout.
TEP Reviewer #4	Miscellaneous	P. 25: (and Figure 3): Hazard ratios for mortality may be appropriate, but absolute mortality rates in these trials were vastly different (range: 0-53% mortality, average f/u duration: 2.4 years) and emphasize the distinctly different populations enrolled. This section would be improved by identifying this fact (it is mentioned later, but would benefit from inclusion here).	We have added information on differences in included population across NRCSs.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	Miscellaneous	Also p. 25(15): NRCS and reference to Figure 3: Kalra trial does, in fact, report a difference in mortality, contrary to text, does it not?	Thank you. We have corrected the error.
TEP Reviewer #4	Miscellaneous	Occasional grammatical errors: e.g. p. 33 (23) Key points (line 10) missing a verb	These errors have been fixed. Thank you for pointing them out.