



# Cognitive Outcomes After Cardiovascular Procedures in Older Adults: A Systematic Review

## Disposition of Comments

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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.

Reviewer & Affiliation	Section	Comment	Response
<b>Peer Reviewer #1</b>	General Comments	Unfortunately, the lack of substantial numbers of suitable articles that address the key questions greatly reduces the clinical meaningfulness of the report. I suppose that it is helpful for clinicians to know that there is "insufficient strength evidence" or "no evidence" but ultimately that leaves the clinician to make judgments with whatever information or biases that already exist.	While strength of evidence is insufficient for many outcomes, a substantial portion of the evidence was graded low strength, while results comparing cognitive outcomes between hypothermic and normothermic CABG were graded moderate strength of evidence. Nevertheless, the fact that after a thorough and rigorous review we found only limited available evidence on cognitive outcomes after selected cardiovascular procedures in older adults is an important finding. Available data were often of limited quality or absent, and, as a consequence, additional data could change the observed estimates of effect. Nevertheless, those data included in the review pretty consistently showed no significant difference in intermediate or long-term cognitive outcomes between treatment groups and small magnitude between-group differences and within-group change scores. Based on these results, for those comparisons studied, any intermediate to long-term cognitive differences between these treatments in older adults, if they exist, may be small.

Reviewer & Affiliation	Section	Comment	Response
<b>Peer Reviewer #2</b>	General Comments	The report is very well structured, key questions are articulated and answered in a clear and organized manner. The main conclusion is that almost no data exist on an extremely important unrecognized clinical problem that clearly needs to be investigated.	We appreciate this comment and agree that additional research should be performed to investigate this clinical problem, as discussed in Future Research Needs.

Reviewer & Affiliation	Section	Comment	Response
#3	General Comments	<p>This mss by Fink et al is a systematic review of the literature investigating possible relationships between cardiovascular procedures in patients &gt; 65 years old and subsequent cognitive impairment measured in the intermediate (3-12 months) and long-term (&gt;12 months). The Key Questions related cognitive outcomes to selected cardiovascular procedures; to procedural and peri-procedural stroke/TIA and other procedural characteristics; and to patient characteristics. The general conclusions were that we simply do not have data in this older patient population with regard to procedural and patient characteristics that demonstrate either selective adverse cognitive effects (safety) or provide evidence for improvement in cognition (efficacy). Well-supported recommendations were made based on the existing evidence that meets their criteria for inclusion. The take-home point was that with more procedures being performed on an aging population, questions regarding candidacy based on cognitive risk-benefit are becoming increasingly important, and better quality outcome research is imperative.</p>	We appreciate these comments.

Reviewer & Affiliation	Section	Comment	Response
#4	General Comments	The report is not very meaningful as there was just not enough data to answer the questions posed. As the authors stated, most of the data available is in a younger population. Cognitive impairment regardless of age is important and hence this report likely would have been more impactful had it included all patient ages as this would have allowed for more recent trial data (SYNTAX trial) to be included in the analysis.	We agree that cognitive impairment is important if it occurs in a younger population as well. However, we were concerned that since older adults are at far greater risk than younger patients for cognitive impairment independent of cardiovascular procedures, that results in younger patients may not be generalizable to older adults. For example, results showing no association between cardiovascular procedures and cognitive outcomes in younger patients may not apply to older patients whose brains may be more susceptible to the different surgical factors that might contribute to cognitive impairment (e.g. hypoxia, hypotension, anesthesia effects). We reviewed the main SYNTAX paper, its supplementary appendix, all other available SYNTAX publications. The SYNTAX trial randomized 1800 participants with 3-vessel or left main coronary artery disease to CABG vs. PCI. Mean age of participants was 65.1 years. This study would have been eligible for inclusion in our review based on participant age (mean age $\geq$ 65 years). The reason it was not included in our review is because it did not collect or report any cognitive outcomes.
#5	General Comments	The report is clinically meaningful, but is primarily limited by the limited quality of the source data, which make it difficult to make any useful conclusions.	We agree that the limited quality of the source data limits the conclusions that may be drawn in this review.

Reviewer & Affiliation	Section	Comment	Response
#5	General Comments	The target population and audience are explicitly defined but there is some heterogeneity in the target population (CABG patients, other cardiac procedure patients, and carotid intervention patients) which could be explained a bit more, to help understand why these different types of procedures are grouped together (see below).	The nominator of this topic to AHRQ originally suggested that the review address a much longer list of cardiovascular procedures than the four included in our draft report. A concern was raised that some procedures in this longer list were infrequently done in older U.S. adults, were thought to have little to no cognitive effects, and/or had little to no relevant literature on preliminary searching. Coronary and carotid revascularization procedures and valve repairs were included because they are commonly performed, invasive and/or we already were aware of some literature looking at post-procedure cognitive function. Catheter-based atrial fibrillation ablation was considered less invasive and a preliminary search suggested there may be little literature regarding its association of atrial fibrillation ablation with cognitive outcomes. Nevertheless, it was thought potentially useful to highlight even this finding. As it happens, while repeated literature searching didn't identify any eligible atrial fibrillation studies, we identified some studies that provide contextual information about the possible association between atrial fibrillation ablation and cognitive function. In the revised report, we have tried to better clarify why the addressed procedures were included.

Reviewer & Affiliation	Section	Comment	Response
#5	General Comments	The key questions are appropriately and explicitly stated, although there is a minor wording concern with key question 2, especially regarding stroke and TIA (see comments below).	As stated below in response to this reviewer, we agree that though peri- or post-procedure strokes or TIAs could either mediate or moderate the association between cardiovascular procedures and post-procedure cognitive function, mediation seems more likely. That said, the current wording for key question 2 (“are ...risks for adverse...cognitive outcomes affected by...stroke”) could equally apply to a mediator or moderator relationship and doesn’t require change. Instead, we revised how we discuss the role of stroke/TIA on the association of cardiovascular procedures with cognitive outcomes in the text of the final report.
#5	General Comments	Consider adding "in older adults" to the title, since it is a limited evaluation in older patients, and this should be clear from the start.	We agree with this suggestion and made the recommended change. The revised title is: “Cognitive outcomes after cardiovascular procedures in older adults: a systematic review.”

Reviewer & Affiliation	Section	Comment	Response
#6	General Comments	<p>This review addressed an important issue in cardiovascular intervention and patient care in general. The questions asked are highly relevant in patient management. However, the methodology applied was not designed to target the key questions asked “In older adults who undergo selected cardiovascular procedures, what are the associated postprocedural cognitive outcomes”. For this question, the author excluded studies without the control and largely examined the study comparing invasive and less invasive procedures or those comparing procedures and medical therapy. While this approach determined cognitive difference between various groups, it did not address whether cardiovascular procedures affects cognition. To address the question, the comparison should really be the differences in neurocognitive assessments between pre- and post-procedures using pre-op as the control. Then the author can determine whether cognitive changes differ among various procedures.</p>	<p>In our draft report, we presented cognitive outcomes as reported by the primary papers. Comparing post-procedure cognitive measures between groups provided information about whether any differences between groups in cognitive level at follow-up or in within group changes from baseline to follow-up are due to the procedure and not to patient characteristics. In the revised report, we calculated additional results for within group changes in cognition. These within group analyses cannot isolate the extent to which the procedure vs. patient characteristics caused cognitive changes over time. However, they can show, for example, that it isn’t just that CABG patients didn’t perform worse than medical management patients in tests at 1 and 6 years, but this wasn’t because both groups got worse by similar amounts. Instead, the results suggest that the CABG patients performed at baseline or better at the 1 and 6 year follow-up times.</p>

Reviewer & Affiliation	Section	Comment	Response
#8	General Comments	<p>The report is NOT clinically useful, as the number and quality of the articles reviewed were of limited utility and quality. The target population and audience were well-defined. The key questions were appropriate, but given the paucity of studies which were reviewed, either this report was premature or a wider search and evaluation strategy was needed. The conclusions/clinical implications that the investigators provide at the end of their report are UNJUSTIFIED (i.e., that risks to the elderly in terms of cognitive changes are small). The lack of quantity and quality of the studies reviewed and the inability of the evaluative team to perform a meta-analysis of the data makes this type of subjective, unsubstantiated statement questionable and potentially dangerous.</p>	<p>We agree that the number and quality of articles eligible for our review were limited. However, this occurred despite a broad, deep search, including an updated search during the public posting period (which identified two newly published studies). No reviewers identified missing eligible studies. Regarding the comment that our implication that risks of cognitive changes to the elderly are small is unjustified and potentially dangerous, in the revised report we tried to state our conclusions more precisely and conservatively. In the Discussion we clearly stated that available data were often of limited quality or absent, and that additional data could change the observed estimates of effect. We further stated that existing data pretty consistently showed no significant difference in intermediate or long-term cognitive outcomes between treatment groups and small magnitude between-group differences and within-group change scores. “Small magnitude” was based on effect sizes that commonly were &lt;0.2. Based on these results, we suggested that for studied comparisons “any intermediate to long-term cognitive differences between these treatments in older adults, if they exist, may be small.”</p>

Reviewer & Affiliation	Section	Comment	Response
#9	General Comment	This is an important topic. I found the manuscript unbiased and well written. The results are comforting; but it is also clear that more pre-procedure and post-procedure cognitive testing should be performed before these meta-analysis findings can be fully embraced.	We agree that additional research is warranted to better understand the cognitive outcomes after these cardiovascular procedures.
Peer Reviewer #1	Intro	The Introduction is well written and frames the issues.	We appreciate this comment.
Peer Reviewer #2	Intro	The introduction appropriately defines the problem, reviews existing studies and prior reviews, provides an analytical model describing the inter-relationships among the key questions, and describes how an answer to these questions can inform clinical practice.	We appreciate this comment.
#3	Intro	The Introduction was cogent and clearly stated the need for this review.	We appreciate this comment.
#4	Intro	Clearly outlined. No concerns.	We appreciate this comment.

Reviewer & Affiliation	Section	Comment	Response
#5	Intro	The intro starts with a discussion of the unclear role of dementia/ cognitive screening in the population in general. Although this is a reasonable way to transition to a discussion about screening before procedures, this is not even a primary goal of the systematic review. There should be a mention at an earlier point in the introduction about the importance of cognition in relationship to cardiovascular procedures.	We appreciate this feedback regarding the ordering of the Introduction. We were trying to frame this CER in terms of a “so what” might a clinician do with more information on the association between cardiovascular procedures and cognitive function. While we think it is important to address potential implications (e.g. preprocedural discussions regarding risk; targeting treatments based on patient-specific risks, possibly including baseline cognitive function), we agree that it is more appropriate for the emphasis of the Introduction to match the emphasis of the key questions. We revised the report accordingly.
#5	Intro	In addition to #1, above, the transition from a discussion about CABG to a discussion about carotid revascularization is unclear. In general, why these types of procedures are combined into one review is not clearly explained. It would help to have an introductory statement describing how these are all types of procedures that could be associated with cognitive problems, for varying reasons (for CABG it is because of the past concern about bypass and cognitive change, and for carotid interventions it might be because this directly has a role related to stroke and resultant cognitive changes).	In the revised report, we attempted to better explain the rationale for inclusion of the several cardiovascular procedures in this report.

Reviewer & Affiliation	Section	Comment	Response
#5	Intro	<p>Different cognitive domains are discussed briefly, but without much background about why these different domains might be important. If they are going to be discussed at all, there should be some discussion of what cognitive domains are most frequently associated with vascular disease and why these might be most important to study in these procedures (such as attention, executive function, with less memory involvement typically), and why studying only one test covering only one domain is therefore problematic.</p>	<p>With the uncertainty regarding whether and in what way (i.e. which cognitive domains, what duration) the selected cardiovascular procedures affect cognitive function, we believed it was important to include studies that evaluated any measured (i.e. not self-reported) cognitive domains or tests. Therefore, we considered studies eligible if they assessed measurements of any of the following: attention, memory, language, executive function, psychomotor speed, visuospatial function, or a global cognitive screen (e.g. MMSE). In the revised report, we provided more rationale for consideration of these different cognitive domains.</p>

Reviewer & Affiliation	Section	Comment	Response
#5	Intro	As a general approach to structuring this introduction, because it is hard to follow the relevance of each section, an approach that might work could be: a) stating the category of interventions that are of particular interest, naming all those that will be included in the paper and why they are of concern; b) discussing the general problems with studies of this type: need for pre-procedural cognitive assessment, short- and long-term followup, and older ages; and then c) going over some of the basic findings, as you have done, within each procedure type, including the subgroup/ effect modification info.	We appreciate this comment. Though we did not strictly adapt the suggested structure, we attempted to improve the writing of the Introduction by more clearly conveying the rationale for including the different cardiovascular procedures, reviewing existing data on the association between these procedures and cognitive function, and methodological issues in studying this association.
#5	Intro	Be careful about how the role of stroke/ TIA is discussed. Although prior stroke/ TIA could be a modifier of the procedure/ cognitive change association, a peri- or postoperative stroke/ TIA is more likely to be a mediator of this association.	We agree with the reviewer that prior stroke/TIA could be a modifier of the association between cardiovascular procedure and cognitive outcome, and that peri/post-procedure strokes are more likely to be mediators of the association between cardiovascular procedure and cognitive outcome. We revised how we discussed the role of stroke/TIA on the association of cardiovascular procedures with cognitive outcomes in the text of the final report.
#5	Intro	p.11, analytic framework- under the cognitive outcomes section, "w/or w/o" is unclear; would put a space between "w/" and "or" or write out with.	We revised the analytic framework to eliminate these abbreviations for with and without.

Reviewer & Affiliation	Section	Comment	Response
#5	Intro	Key question 2: see comment #5 above, intermediate outcomes might mediate the procedure/ outcome association, and not just modify it.	As discussed in more detail above, we agree that peri- or post-procedure strokes or TIAs are more likely to mediate than to modify the association between cardiovascular procedures and post-procedure cognitive function. We revised how we discuss the role of stroke/TIA on the association of cardiovascular procedures with cognitive outcomes in the final report.
#6	Intro	well-written	We appreciate this comment.
#8	Intro	9/8-15 Unclear if this paragraph is helpful or should be used as the first paragraph in this section. However, good summary of the problem and current findings in the remainder of the section.	We appreciate this comment.
Peer Reviewer #1	Methods	The methodology is well described and is free from bias.	We appreciate this comment.
Peer Reviewer #2	Methods	The search strategy is appropriate. Due to the lack of data there was no need to develop and implement appropriate statistical analyses.	We appreciate this comment.

Reviewer & Affiliation	Section	Comment	Response
#3	Methods	<p>An important aspect of the Affordable Care Act concerns readmission of Medicare patients within 30 days of discharge. Cognitive impairment may resolve by 90 days in many cases, but may still be apparent at 30 days, as is demonstrated in the literature. Impaired cognition has been found to affect medication compliance, self care, reporting of symptoms and decisions on seeking medical assistance. It would therefore be important for the authors to examine shorter-term outcomes both for clinical and cost-burden reasons. If, say, off-pump CABG has fewer short-term adverse effects, it may influence choice of procedures. The authors noted that they did not include inpatients in their analysis, but exclusion of this patient group is a notable omission.</p>	<p>We agree with the reviewer that short-term cognitive impairments after cardiovascular procedures may be evident within 30 days that are no longer evident by 90 days. We agree also that short-term post-procedure cognitive impairments may have adverse clinical and financial consequences that may influence procedure choice. However, with agreement from the topic nominator, our <i>a priori</i> focus was on outcomes that were present (persisted) at least 90 days after the procedure. The purpose of this decision was to eliminate transient effects on cognition from factors other than the procedure, including pain, anesthesia, medications, sleep deprivation, and hospital-related illness. Further, studies in which post-procedure cognitive assessments are available only from within the inpatient setting were excluded because of the high rate of delirium reported in older hospitalized patients.</p>

Reviewer & Affiliation	Section	Comment	Response
#3	Methods	<p>One of the reasons why there are seemingly few differences between treatment options may relate to the normal performances at baseline. It is well known, for example, that severe coronary artery disease necessitating CABG is associated with intracranial small vessel disease sufficient to produce vascular cognitive impairment. That patients were functioning so well at baselines in this review suggests that they were already selected by investigators based on inclusion/exclusion criteria as having minimal, if any, cognitive impairment. It may be that these patients are at lower risk for cognitive change. It would therefore be important to study consecutive patients undergoing evaluation for cardiac procedures to avoid this bias. The authors should address this selection bias in their analysis.</p>	<p>We agree with the reviewer's point that pre-procedure cognitive impairment is a risk factor for post-procedure cognitive impairment. Participants in the studies included in the review may have had better cognitive function than patients who undergo these procedures in the community. Evidence for this includes the fact that several (though a minority of) studies excluded participants with low MMSE, dementia, learning difficulty and/or poor educational status. Also, baseline neuropsychological testing of included participants was generally good other than some degree of impairment on some timed tests (Trails B, Grooved Pegboard). We have addressed this potential selection bias in Results section of our revised report.</p>
#4	Methods	<p>The methodology used in the study was sound and thorough. It was clearly outlined and indeed logical.</p>	<p>We appreciate this comment.</p>

Reviewer & Affiliation	Section	Comment	Response
#5	Methods	Search strategies are appropriate, as are inclusion and exclusion criteria, although the limitation to an older age group does exclude a number of important papers in this area.	We appreciate this comment. We agree that limitation to the older age group excludes some studies that met other eligibility criteria, but this was necessarily a consequence of our <i>a priori</i> determined focus on this association in older adults.
#5	Methods	Somewhere in the paper a more detailed discussion is needed of the different ways cognitive change/ cognitive impairment might be defined. This is discussed very briefly but it is certainly a major issue when cognitive change is being analyzed. At the very least, a brief discussion of the definitions used in some of the included papers would be helpful.	In the draft report, this issue was discussed in detail in the Future Research Needs section and to a lesser extent in the Results: Study Characteristics: Cognitive Outcome Measures section. In the revised report, we added more detail to this Results section on the methods included studies used to measure cognitive function and define cognitive decline.
#5	Methods	Please define how weighted means were calculated since these are cited in the results.	Weighted means were calculated by multiplying each variable (e.g. age) by its corresponding study sample size (n), and then the sum of the products was divided by the sum of the study sample sizes (N). Therefore, if the study has a larger sample size, it will contribute more to the average of the variable in question. We have clarified this in the Methods section of the revised report.

Reviewer & Affiliation	Section	Comment	Response
#6	Methods	Again, the methodology applied was not designed to target the key questions asked “In older adults who undergo selected cardiovascular procedures, what are the associated postprocedural cognitive outcomes”. To address the question, the comparison should really be the differences in neurocognitive assessments between pre- and post-procedures using pre-op as the control.	As discussed above, in our draft report we reported cognitive outcomes as reported by the primary papers. For some, that was a between-group comparison of post-procedure cognitive function. For others, that was a between-group comparison of the within group pre-post cognitive change. Comparing pre- vs. post-procedural cognitive outcomes within a treatment group provides information about whether cognition changes during this interval, but not whether the change was caused by the procedure versus patient characteristics or other factors. Comparing post-procedure cognitive measures between groups provides information about whether post-procedure cognitive level differs between treatment groups, but may not highlight whether these groups improved, remained stable or worsened. To provide a fuller picture of post-cardiovascular procedure cognitive outcomes, we have revised this report to add results for within group pre- vs. post-procedure cognitive outcomes, and have added appropriate interpretation of the different results.

Reviewer & Affiliation	Section	Comment	Response
#6	Methods	<p>Only 3 studies have evaluated carotid interventions. The rest are all cardiac procedures. Recommend focus the review to only cardiac interventions rather than cardiovascular interventions. The conclusion from only 3 studies is not considered system review. Recommend eliminate the studies assessing cognitive evaluation &gt;12 months. With a rather elderly cohort, the nature progression of cognitive deterioration over time will like bias the results. The cognitive changes occurring &gt;12 months following intervention are unlikely associated with interventions.</p>	<p>A systematic review is defined by the methods of the review and not by the number of eligible studies it identifies. We agree that cognitive changes that first become evident &gt;12 months after a cardiovascular procedure seem more likely related to underlying disease than to the procedure. However, our interest in looking at cognitive outcomes measured at &gt;12 months was to assess whether earlier onset cognitive effects persist long-term. Therefore, we have retained the longer-term cognitive outcomes in the revised report.</p>
#8	Methods	<p>11/figure Confusing figure, how KQ1 doesn't seem to link to anything, authors appear to wish to indicate that it is an overarching concept – figure needs to be re-organized/re-designed and needs a descriptive figure legend (perhaps getting rid of the excessive amount of text in the figure boxes)</p>	<p>KQ1 was intended to link the participants undergoing CV procedures to the cognitive outcomes. To make this more clear, we've revised the figure to extend the brackets to connect the CV procedures and Cognitive outcomes boxes. We also tried to make the abbreviated figure KQ wording more clear and to reduce the amount of text in the figure boxes.</p>
#8	Methods	<p>13/protocol devel very scan/unclear – needs expansion, beyond the single sentence – not helpful</p>	<p>For the revised report, we added the protocol as an appendix.</p>

Reviewer & Affiliation	Section	Comment	Response
#8	Methods	13/20/appendix A list of key words used to perform search strategy in Appendix A is not exactly interesting/useful; unclear why RCTs were a requirement, or what kind of RCT the reviewers were interested in	We agree that the details of our electronic database search strategy are of limited interest to many. However, we believe reporting this information is necessary for transparency and so that others could reproduce our results if desired or understand how our methods could have affected our findings. As detailed elsewhere in the Methods section, we included prospective observational cohort studies in addition to RCTs.
#8	Methods	13/study design28-29 this is not a description of study design – it is a description of what studies they concentrated on – rationale for selection of these types of studies is unclear	The Study Design heading is a subheading under Study Inclusion Criteria. It lists the types of study designs to which we restricted inclusion in our review. We limited inclusion to these study designs to try to minimize bias and so that cognitive function was assessed prospectively after the cardiovascular procedure. We assumed this would better provide evidence regarding a possible causal relationship if we found an association between cardiovascular procedures and subsequent cognitive function. In the revised report, we tried to better explain the rationale for limiting inclusion to these study designs.

Reviewer & Affiliation	Section	Comment	Response
#8	Methods	13/37-38 unclear why concentrated only on studies with only a minimum of 20 subjects in RCTs, while required 50 or more in the only other type of study to be viewed, “prospective observational cohort studies”	We required minimum sample sizes for study eligibility because of our concern that very small studies could significantly increase workload without adding any high quality evidence. Because we thought this risk was higher with non-RCTs, which are more prone to bias than RCTs, we required a larger sample size for non-RCT eligibility.
#8	Methods	16/19-20 this is not really a “qualitative” analysis procedure	We modified the relevant wording in the Abstract and Methods sections.
#8	Methods	16/21-23 Unclear why they assumed/used mean differences, as the data was unlikely to have been normally distributed	We used standard analytic methods for analyzing and reporting of data. We did not have access to individual patient-level data from any studies, so we could not directly test whether outcomes were normally distributed. Where the studies reported the values as means we assumed the data was normally distributed and the study authors tested the normality of the distribution. Some authors noted use of both parametric and non-parametric testing and performed measures to render tests to a normal distribution. Since the data were presented as continuous variables with standard deviations we used standardized mean differences.

Reviewer & Affiliation	Section	Comment	Response
<b>Peer Reviewer #1</b>	Results	Despite the considerable work and diligence of the authors, this is a failed analysis in the sense that on every question, the authors concluded either that there was insufficient evidence or no evidence. The CABG story had the most data, but ultimately there was only one prospective cohort study that the authors deemed insufficient.	We appreciate the reviewer's comment. Though the limited available studies resulted in insufficient strength of evidence to address many treatment comparisons, we found low strength of evidence for a substantial portion of treatment comparisons, and moderate strength of evidence for the comparison of most neuropsychological test outcomes between hypothermic versus normothermic CABG.

Reviewer & Affiliation	Section	Comment	Response
#2	Results	I am not familiar with all the studies that were reviewed (see Appendix B), but there may have been more information obtained from excluded studies that, for instance, factored in hospital-based delirium, but did have post hospital assessments. For instance, ref 314.	We would have included studies that reported both post-procedure delirium and cognitive outcomes at 3 months or later and met other eligibility criteria. However, we would have evaluated only the cognitive outcomes at 3 months or later. Regarding the reviewer's example of reference 314 from our draft report list of excluded studies (Saczynski, J.S., et al., Cognitive trajectories after postoperative delirium. NEJM, 2012;367:30-9.), we reassessed it and found that it was correctly determined to not be eligible for inclusion in our review. However, during our recheck, we found that it was not ineligible for not being an RCT, CCT or prospective observational cohort study as was incorrectly indicated in the draft report appendix. It was ineligible for not having a control group. After finding this error in reporting the reason for ineligibility, we reviewed all 127 references labeled in the draft report as excluded for not being an RCT, CCT or prospective observational cohort study. Some of these were an RCT, CCT or prospective cohort study, but all were ineligible for another reason. We revised the appendix of ineligible studies and the study flow diagram accordingly.

Reviewer & Affiliation	Section	Comment	Response
#3	Results	The amount of detail in the results section was appropriate and the key messages were clear. The Figures and Tables were fine.	We appreciate this comment.
#4	Results	The results were clearly outlined and addressed the key questions posed. The lack of data made the value of the results limited but this was not a result of poor analysis, but more a result of a narrow pre specified age range for patients. (age >65).	We agree that several studies were excluded for not meeting our age criterion that met all other eligibility criteria. Including these studies of younger patients would have provided more data, but results may have had limited applicability to older patients, who are at greater risk of cognitive impairment independent of any potential effect from cardiovascular procedures.
#5	Results	The results section has an appropriate amount of detail- first summarized, both in text and table form, and then given in more detail.	We appreciate this comment.
#5	Results	When a subset of the studies provides information on a specific point (for instance, "In the 2 trials that reported data on race...") it would be helpful to provide the sample size ("In the 2 trials (N=X) that reported data on race...") with data on that specific point.	We agree with this suggestion and have addressed the Demographics section in the revised report accordingly.
#5	Results	More detail on pre procedural cognitive function would be helpful; it is only stated that they are generally "in the normal range".	We have added additional detail on pre-procedural cognitive function to the revised report.

Reviewer & Affiliation	Section	Comment	Response
#5	Results	For overall organization, you might put all the cardiac procedures together (in separate sections, but sequenced after each other; CABG, then valve, etc.), followed by the carotid data.	At the time we sequenced the report, our rationale for this order was that carotid revascularizations had more available data than valve repairs. However, this is a logical suggestion and in retrospect it might be preferable if we were starting again from scratch. However, it is still a bit of a style issue and given the amount of work that would be required to reorder the text, tables, appendix, etc., we do not think this change is warranted.
#5	Results	Appendix G tables are not clearly helpful at all.	Appendix G tables make the point that no studies provided results on incidence of clinically diagnosed cognitive disorders.
#6	Results	Only limited patient and procedure characteristics are reviewed in each included studies. For example microembolization was not included. Recommend to acknowledge that only limited variables were included in the studies.	In the revised report, we more explicitly noted that included studies reported only limited information on patient and procedure characteristics.
#8	Results	The results section had a huge amount of detail, which basically continually reiterated that there were inadequate numbers of studies to evaluate and for most cardiovascular procedures, NO STUDIES were available.	We appreciate this comment.

Reviewer & Affiliation	Section	Comment	Response
#1	Discussion/ Conclusion	<p>The constraints imposed by an evidence based review often seem to lead to equivocal recommendations. Unfortunately, equivocation is not of much use to clinicians. For CABG, you imply, though I wish you had stated it more strongly, that the risk to cognition of CABG seems small. The fact that there was one set of strong studies (McKhann, Selnes) seemed to be minimized because of concerns about bias in baseline differences and dropout. Given that there was nothing better, and given the reality that matching heart disease patients who undergo or dont undergo procedures will inherently result in differences at baseline, it seems unfortunate to dismiss the McKhann &amp; Selnes studies as inconclusive. Yes, this reviewer is aware of the ground rules for evidence-based reviews. But, you pay the price: an inconclusive report that will be ignored.</p>	<p>We agree that the limited available evidence suggests that the intermediate to long-term risk to cognition from CABG versus medical management seems small, but that our confidence in this finding is limited by the high risk of bias in the single eligible cohort study that compared these treatment groups. To supplement our between group comparison, for the revised report we added (still only for appropriately controlled studies) additional analyses calculating and comparing pre- vs. post-procedure cognitive function in studies that didn't report results in this fashion but in which these results could be estimated. These results further suggested that intermediate to long-term risk to cognition from CABG may be small.</p>
#2	Discussion/ Conclusion	<p>Yes, the implications were well laid out as were future research needs.</p>	<p>We appreciate this comment.</p>

Reviewer & Affiliation	Section	Comment	Response
<b>Reviewer #3</b>	Discussion/ Conclusion	<p>Overall, the implication of the major findings is that we do not have sufficiently well controlled studies from which to answer the Key Questions. Thus, their assertion in Future Research Recommendations that the incidence of these outcomes (dementia and mild cognitive impairment) "may be low" is not justified. The analysis of 30-day outcomes may be important in this regard. Also, the authors did not address procedures for the treatment of congestive heart failure, such as implantation of left ventricular assist devices (LVAD) and cardiac transplantation. LVAD is increasingly used as destination therapy among the elderly who are not transplant candidates.</p>	<p>Based on neuropsychological test results, the limited evidence from studies included in this review suggests that these procedures may not adversely impact intermediate and long-term cognitive function. Absent much neuropsychological test decline, incidence of mild cognitive impairment and dementia, which would require development of even greater cognitive decline, would be expected to be low, especially during shorter-term follow-up, such as after 30 days. Analysis of cognitive outcomes 30 days after cardiovascular procedures may be valuable for determining short-term cognitive impacts of these procedures, but our study was designed to focus on intermediate and long-term outcomes. There is a long list of cardiovascular procedures performed in clinical practice. To try to maintain a reasonable scope and focus, we attempted to limit this report to some of the more commonly performed procedures. For those interested in the potential association between excluded cardiovascular procedures and cognitive outcomes, this may be considered a limitation of our report.</p>

Reviewer & Affiliation	Section	Comment	Response
#4	Discussion/ Conclusion	The conclusion is unbiased and clear. It summarizes the results. I did not review all the papers they reviewed, but it did seem like they were thorough in their search.	We appreciate this comment.
#5	Discussion/ Conclusion	It seems that the included cohort has especially low postoperative stroke rates and "normal" cognition at baseline. Can the authors discuss the possibility of selection bias and who was actually included in these studies? It is important both for generalizability but also the likelihood of identifying different subgroups at greatest risk for a bad cognitive outcome.	We agree that within included studies average baseline cognition appeared normal except for slowing in some timed tests. Also, incidence of post-procedure strokes was low. These characteristics and the risk for adverse intermediate or long-term cognitive outcomes may differ between included study participants and patients who undergo these procedures in the community. If this was the case, this could limit generalizability of the results of the review to patients with pre-procedure cognitive impairment. We discussed the potential implications of included studies enrolling predominately cognitively intact participants and having few incident strokes in the Discussion-Applicability and Future Research Needs sections of the draft report.

Reviewer & Affiliation	Section	Comment	Response
#5	Discussion/ Conclusion	<p>The leap from the study questions to the question as to whether there is a role of prep cognitive testing is hard to make- and not clearly relevant. The authors didn't address whether outcomes differed for people with cognitive problems at baseline, for instance. This can be mentioned as an area warranting further study but I don't think trying to extrapolate an answer to this question from the systematic review makes sense.</p>	<p>Key question 3 was: "...are associated risks for adverse post-procedural cognitive outcomes affected by patient characteristics (e.g., ...baseline cognitive function...)?" We anticipated that such data, had we found any, could have indicated whether such patient have a different (e.g. higher) risk for post-procedure cognitive impairment. Such information might have suggested that cognitively impaired patients may be candidates for alternative interventions, adjunctive neuroprotective treatments, etc. And, if such patients may be candidates for different treatment, it might be worthwhile to identify them, which may be accomplished by preprocedure cognitive testing. So, this question about preprocedure cognitive testing is relevant to key question 3. In the revised report, we tried to make this rationale more clear. The draft report already advocated future research on the association between cardiovascular procedures and cognitive outcomes in patients with baseline cognitive impairment and these recommendations remain in the revised report.</p>

Reviewer & Affiliation	Section	Comment	Response
#5	Discussion/ Conclusion	The recommendation that future studies should include clinically diagnosed outcomes might need to be reworded some- there is a concern that some studies might define outcomes as normal/ MCI/ dementia while still only obtaining the same information, when this diagnosis should include more of a functional assessment/ change in function, or informant interview.	In the revised report we clarified that the clinically diagnosed cognitive outcomes should be based on patient/informant history, formal cognitive testing, and functional assessment.
#5	Discussion/ Conclusion	Recommendations for future studies should include re-emphasis of the importance of control groups.	We agree and added this recommendation to the revised report.
#5	Discussion/ Conclusion	In table 3, would avoid giving an example of a threshold. Having one test at a level of just 1 SD below the normative mean is not likely to be meaningful clinical cognitive impairment, and this might be used as a literal recommendation by future investigators. The change from baseline is likely to be highly important, as well.	We didn't mean to suggest an exact definition that would be literally accepted, but to suggest how a definition might be derived. Therefore, in the revised report we removed the example of a threshold. In the revised report, we also were more explicit in referring both to between-group comparisons in post-procedure cognitive levels and in changes in cognitive levels between pre- and post-procedure assessments.
#6	Discussion/ Conclusion	Need to acknowledge that only very limited studies were included for this systemic review. There is insufficient evidence due to lack of valid studies.	In the revised report, we tried to more clearly make this point about there being only a small number of studies to address study questions.

Reviewer & Affiliation	Section	Comment	Response
#8	Discussion/ Conclusion	37/37-41 claim that risks of the procedures to cognition is small is unsubstantiated, based upon the very; small number of studies reviewed, and the lack of coverage of most CV procedures	On review, we agree that our lead Discussion sentence in the draft report didn't adequately acknowledge the difference in the number of eligible CABG studies compared to the number for other cardiovascular procedure types. The evidence suggesting that procedure-related cognitive risks are small is stronger for CABG than for the other cardiovascular procedures covered in this review. In the revised report, we tried to make this distinction more clearly.
	Figures		
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