Technology Assessment

Cardiovascular Procedures and Subsequent Cognitive Function: a Systematic Review

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Cardiovascular Procedures and Subsequent Cognitive Function: a Systematic Review

Technology Assessment Report

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Cardiovascular Procedures and Subsequent Cognitive Function: a Systematic Review

Structured Abstract

**Objective:** To characterize the intermediate- and long-term cognitive outcomes associated with selected cardiovascular procedures in older adults and the extent to which these associations are modified by procedure-related stroke and/or transient ischemic attack (TIA) and other procedure and patient characteristics.

**Data Sources:** MEDLINE®, Cochrane Database of Systematic Reviews, Scopus, and ClinicalTrials.gov electronic databases; hand searches of references from relevant reviews and eligible studies.

**Review Methods:** We screened abstracts and full text articles of identified references for randomized controlled trials (RCTs) and prospective cohort studies in adults aged ≥65 years that reported intermediate (3 to 12 months) and long-term (>12 months) cognitive outcomes after coronary or carotid artery revascularization, cardiac valve replacement/repair, and/or ablation for atrial fibrillation. Cognitive outcomes of interest were clinical diagnoses (e.g., dementia, mild cognitive impairment), individual neuropsychological test results, and composite measures of “incident cognitive impairment” derived from individual neuropsychological test results. We extracted data, rated individual study risk of bias, and graded strength of evidence. Because available data did not support quantitative synthesis, results were presented qualitatively.

**Results:** From 1099 references identified, we found 19 eligible studies, including 16 RCTs (risk of bias: moderate 14, unclear 2) and 3 prospective cohort studies (risk of bias: moderate 1, high 2). Only 2 studies reported cognitive outcomes >1 year after the cardiovascular procedure. Seventy-eight percent of participants were men, mean age was 65 to 69 years in 17 studies and >70 years in 2 studies, and participants generally performed in the normal range on pre-procedural cognitive testing. No study reported post-procedural clinical cognitive diagnoses. We found no RCT evidence addressing whether any of the selected cardiovascular procedures affect other intermediate or long-term cognitive outcomes of interest when compared to medical management. We found insufficient strength evidence derived solely from 1 prospective cohort study that intermediate and long-term cognitive outcomes are not significantly different between patients who undergo coronary artery bypass grafting (CABG) and those with coronary artery disease treated with medical management. We found insufficient strength evidence from 2 RCTs that intermediate- and long-term cognitive outcomes of interest were not different between participants assigned to carotid endarterectomy versus carotid artery stenting or carotid angioplasty. We found no evidence from other eligible studies addressing whether intermediate- or long-term cognitive outcomes differ after more versus less invasive cardiovascular procedures (e.g., CABG vs. percutaneous coronary intervention, surgical vs. transcatheter cardiac valve repair, or surgical vs. transcatheter ablation for atrial fibrillation). Data from 13 RCTs and 1 prospective cohort study consistently suggested that there is no difference in intermediate- or long-term cognitive differences between different versions of CABG, including on- versus off-pump CABG, and hypothermic versus normothermic CABG. In the subset of studies that
reported data on peri/post-procedure stroke or TIA, occurrence was infrequent (e.g., \( \leq 1 \) stroke in each treatment group in most studies) and not significantly different between treatment groups. Given that intermediate and long-term post-procedural cognitive outcomes also did not differ between treatment groups, we had inadequate statistical power to determine whether risks for these cognitive outcomes are affected by incident stroke or TIA. Last, we found no evidence about whether age, baseline cognitive function, past stroke or TIA, baseline cardiovascular disease severity, hypertension, diabetes, or depression modifies the association between the selected cardiovascular procedures and intermediate- or long-term post-procedure cognitive outcomes.

**Conclusions:** Eligible studies were comprised predominately of cognitively intact older men, with few old-old participants (e.g., aged \( \geq 80 \) years). From these studies, we found insufficient strength of evidence addressing whether coronary or carotid artery revascularization, cardiac valve replacement/repair and/or ablation for atrial fibrillation increase risk for intermediate and long-term clinically diagnosed cognitive impairment. We found low to insufficient strength of evidence that these cardiovascular procedures are not associated with changes in intermediate and long-term neuropsychological test performance compared to medical management or alternative cardiovascular procedures. We found no evidence addressing whether risk for intermediate- and long-term cognitive outcomes after these procedures differs between older patients with and without pre-procedural cognitive impairment as might be identified by pre-procedural cognitive testing. Future research showing a benefit of cognitive testing before and/or after selected cardiovascular procedures on intermediate and long-term cognitive outcomes or on other important patient outcomes (e.g., patient autonomy related to capacity to consent, complications related to adherence with post-surgical instructions, quality of life, costs) may be necessary to justify broad clinical implementation of such cognitive testing.
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Chapter 1. Introduction

Background

In 2003, the U.S. Preventive Services Task Force (USPSTF) concluded that evidence was insufficient to recommend for or against routine screening for dementia in community-dwelling older adults as it was uncertain whether potential benefits of this screening outweighed potential harms.1 A recent systematic review, completed to help update this USPSTF recommendation, reported that though it seems logical that early detection of cognitive impairment would improve patient, family and clinician decision making, and ultimately patient outcomes, little or no empirical evidence supports this position.2

However, whether screening for cognitive impairment (or any condition) is of benefit depends on multiple factors, including the population targeted, the screening setting, and the potential benefits and harms of the screening procedure. In that context, recent American College of Surgery (ACS)/American Geriatrics Society (AGS) Guidelines3 recommend cognitive screening of all adults aged ≥65 years scheduled to undergo surgery. Specifically, they recommend obtaining a cognitive history and administering a brief test of global cognitive function in order to assess each patient’s capacity to understand his/her planned surgery and to estimate his/her risk of post-operative delirium. The ACS/AGS recommendations do not single out cardiovascular surgeries or cite possible benefit on intermediate or long-term post-surgical cognitive function as a justification to perform pre-operative cognitive screening. However, longstanding concerns about the possible association between coronary artery bypass grafting (CABG) and persistent cognitive impairment raises the question of whether cognitive screening may help risk stratify and/or protect older patients undergoing CABG or other cardiovascular procedures from such adverse cognitive outcomes.

Many early studies that evaluated the association of CABG with cognitive outcomes, may have overestimated the incidence of persistent cognitive impairment attributable to CABG. The overestimation may have been due in part to their not accounting for pre-existing cognitive impairment, transient post-procedural cognitive impairment, post-procedural cognitive declines due to underlying systemic disease, and/or test imprecision and practice effects from repeat cognitive testing.4 More recent studies more consistently performed pre-procedural cognitive assessments, compared results from patients receiving CABG with those from a control group, and used a battery of neuropsychological tests recommended by one group for cognitive assessment of these patients.5 A 2012 systematic review of 29 studies that included many of these recent studies reported that psychomotor speed was significantly but slightly impaired for <2 weeks after CABG, but that psychomotor speed, memory and executive functioning were significantly but slightly improved compared to baseline by 3 months.6 In the few studies reporting, these small improvements appeared sustained at 6 to 12 months. That review was limited, however, in that it did not report other neuropsychological domains and did not indicate whether neuropsychological test abnormalities were associated with functional impairment. Further, just two-thirds of included studies had ≥3 months post-procedure follow-up and, of these, mean age was <65 years in all but 4 studies, limiting its relevance to the aging population that is increasingly undergoing CABG and other cardiovascular procedures.

Although adverse cognitive outcomes after CABG have been associated with several patient characteristics, including fewer years of education, limited social support, cerebrovascular or peripheral vascular disease, hypertension, diabetes, and depression, and, perhaps most notably, advanced age,4,7-10 reviews have not previously examined these associations. While multiple

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reviews have reported no difference in cognitive risk between on and off-pump CABG,\textsuperscript{6,11} less is known about the effect of other procedure-related factors on post-CABG cognitive outcomes, including both adjunctive interventions and procedural or peri-procedural stroke or transient ischemic attack (TIA).

The impact of carotid revascularization on persistent cognitive outcomes in older adults also is uncertain. In a recent systematic review not restricted to older patients, about half of studies of carotid endarterectomy (CEA) and/or carotid artery stenting (CAS) reported improvement in at least one neuropsychological test and about half reported some decline or no change.\textsuperscript{12} The authors suggested the mixed findings might be explained by small sample sizes, variable follow-up times (including many <1 month), and variability in the neuropsychological tests administered. About one-third of included studies also did not compare cognitive changes to those in a control group that did not undergo CEA or CAS, another potential source of bias. Even less is known about the effect of procedure and patient characteristics on persistent cognitive outcomes after carotid revascularization procedures in older adults. Uncertainty appears even greater about cognitive outcomes after other cardiovascular procedures in older adults, including cardiac valve replacement/repair and ablation for atrial fibrillation.

Improving understanding of the duration, pattern and risk factors for cognitive outcomes attributable to coronary and carotid artery revascularization, cardiac valve replacement/repair, and ablation for atrial fibrillation in older adults may help guide treatment selection, matching patients to procedures to achieve the best intermediate and long-term cognitive outcomes, and guide informed pre-procedural discussions between clinicians and patients about any longer-term cognitive risks.

**Purpose of Comparative Effectiveness Review**

This systematic review aims to characterize the intermediate and long-term cognitive outcomes attributable to coronary and carotid revascularization procedures, cardiac valve replacement/repair, and ablation for atrial fibrillation, and the extent to which these associations are modified by procedural and patient characteristics and by procedure-related stroke and/or TIA. This review also aims to define the limitations of existing evidence, provide guidance for informed patient-provider discussions about any intermediate and long-term cognitive risks associated with these procedures, and describe the parameters of any future research studies needed to address remaining evidence gaps.

**Analytic Framework and Key Questions**

During this project’s topic refinement, AHRQ and the topic nominator agreed that an independent, comprehensive review of the issues introduced above and as elaborated in the following analytic framework (Figure 1) and Key Questions would provide helpful guidance to clinicians and policymakers about the risks for cognitive outcomes after selected cardiovascular procedures.
Figure 1. Analytic framework

KQ1: Post-CV procedure cognitive outcomes?

KQ2: Procedure characteristics affect post-CV procedure cognitive outcomes?

KQ3: Patient characteristics affect post-CV procedure cognitive outcomes?

Older adults considered for CV procedures

CV procedures
  - E.g. CABG, PCI, CEA, CAS, valve repair/replacement, AF ablation

Patient characteristics
  - Age; baseline cognitive function; past stroke or TIA; baseline CVD severity; HTN; DM; depression

Procedure characteristics
  - Different procedure for same indication; anesthesia type or duration; adjunctive treatment to lower risk of adverse cognitive outcomes

Intermediate outcomes
  - E.g. procedural or peri-procedural stroke; continuous change in neuropsychological test results

Cognitive outcomes
  - Primary: symptomatic cognitive impairments corroborated by abnormal neuropsychological results & w/ or w/o associated functional impairment
  - Secondary: clinically meaningful change in neuropsychological test results (i.e. global cognitive screening measures and/or specific cognitive domain(s))

Noncognitive outcomes (out of scope)
  - E.g. MI, DVT/PE, infection, functional impairment unrelated to cognition

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Key Question 1
In older adults who undergo selected cardiovascular procedures, what are the associated post-procedural cognitive outcomes (e.g., clinical severity; timing/duration; pattern of cognitive domain impairment)?

Key Question 2
In older adults who undergo selected cardiovascular procedures, are associated risks for adverse post-procedural cognitive outcomes affected by procedural and peri-procedural stroke or TIA and other procedural characteristics (e.g., alternative procedures for the same indication, such as surgical vs. catheter-based/stenting; anesthesia type; adjunctive neuroprotective treatments)?

Key Question 3
In older adults who undergo selected cardiovascular procedures, are associated risks for adverse post-procedural cognitive outcomes affected by patient characteristics (e.g., age; baseline cognitive function; past stroke or TIA, baseline cardiovascular disease [CVD] severity; hypertension; diabetes; depression)?
Chapter 2. Methods

Protocol Development
We followed a formal protocol developed with AHRQ and nominator input.

Data Sources
We searched the MEDLINE®, Cochrane Central register of controlled trials (CENTRAL) and Scopus bibliographic databases. An MLIS research librarian experienced in systematic review search methodology and not involved in the project helped refine our bibliographic literature search strategy. To identify additional completed studies, we also reviewed reference lists of included studies, previous systematic and narrative reviews, and ClinicalTrials.gov. We restricted inclusion to studies published from 1990 through January 2013 to limit the review to studies of cognitive outcomes after cardiovascular procedures that reasonably reflect current clinical practice. Appendix A contains the full search strategy. The literature search will be updated while the draft report is under public/peer review.

Study Inclusion Criteria

Study Design
• We restricted the review to randomized controlled trials (RCTs), nonrandomized comparative trials, and prospective observational cohort studies.

Population
• Studies must have included participants who were exclusively or predominately aged ≥65 years (either all participants were ≥65, study mean or median age was ≥65 years, or data were reported from a subgroup of ≥10 patients aged ≥65 years).
• We included studies with at least 10 participants for each treatment arm for RCTs and at least 50 participants in each arm for other eligible study designs.

Interventions
Participants in at least 1 study arm must have undergone at least one of the following cardiovascular procedures:
• Coronary artery revascularization (e.g., CABG, percutaneous coronary intervention [PCI]);
• Carotid artery revascularization (e.g., CEA, CAS, carotid angioplasty);
• Cardiac valve replacement/repair (e.g., surgical or transcatheter, aortic or mitral);
• Ablation for atrial fibrillation (e.g., surgical, transcatheter);
• Combination of any of the above cardiovascular procedures.

Controls
• Studies must have included a control group whose participants did not undergo the cardiovascular procedure of interest or who underwent a modified version of the procedure.
Outcomes

Because the focus of this review was on intermediate-term (3 to 12 months) and long-term (>12 months) cognitive outcomes after cardiovascular procedures, studies must have reported at least 1 cognitive outcome at least 3 months after the procedure. To account for the possible effect of between-group differences in pre-procedural cognitive function on between-group differences in post-procedural cognitive function, all non-RCTs must have performed pre-procedural neuropsychological assessments. Categories of acceptable cognitive outcomes included:

Primary Outcomes

- Clinically diagnosed cognitive impairment based on: (1) the presence of symptoms and/or functional impairment, and (2) abnormal neuropsychological testing based on performance on multiple neuropsychological tests that assessed multiple cognitive domains.

Secondary Outcomes

- Clinically meaningful change in neuropsychological test results regardless of whether symptoms or functional impairment were documented. This could involve 1 or more neuropsychological tests that addressed 1 or more cognitive domains and/or brief global cognitive screening measures.

Intermediate Outcomes

- Continuous measure/change in one or more neuropsychological test results.

Setting

- Studies were eligible regardless of whether the cardiovascular procedure took place in the inpatient or outpatient setting. However, because of the high rate of delirium reported in older hospitalized patients, studies in which post-procedure cognitive assessments were available only from within the inpatient setting were excluded. This restriction was intended to limit the impact of factors other than the cardiovascular procedure on reported cognitive outcomes (e.g., pain, anesthesia, medications, sleep deprivation, and hospital-related illness unrelated to the procedure).

Language

The full text of eligible studies must have been published in English.

Triage

First, two independent investigators reviewed titles and abstracts and categorized them as ‘include,’ ‘exclude,’ or, when a determination could not be made based on title and abstract alone, as ‘full text review needed.’ Differences in triage decisions between the two investigators were resolved by consensus discussion, involving the lead investigator as necessary.

Two independent investigators then reviewed the full texts of all studies rated ‘include’ or ‘full text review needed’ to determine final eligibility. Any differences in their eligibility ratings were resolved by consensus discussion, involving the lead investigator as necessary. Reasons for exclusion of studies during the full text screening stage were recorded (Appendix B).

Data Extraction

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For each eligible study, one reviewer extracted data onto pre-tested extraction forms/evidence tables. A second investigator then double checked the extracted data for accuracy. Differences between the two investigators were resolved by consensus discussion, involving the lead investigator as necessary.

Extracted data fields included author; publication year; study design; cardiovascular procedure and control regimens; anesthesia type and duration; adjunctive treatments intended to lower risk of adverse cognitive outcomes; sample size; participant inclusion and exclusion criteria; participant baseline age; prevalence of hypertension, diabetes, stroke/cerebrovascular disease, and depression; type(s) of pre-procedural neuropsychological assessment (e.g., specific brief global cognitive screening measures and specific cognitive domains tested); N, mean and SD for each reported pre-procedural neuropsychological test score; incidence of procedural and peri-procedural stroke and/or TIA; timing, definition, and event rates/results of clinically diagnosed post-procedural cognitive outcomes and post-procedural neuropsychological tests.

Authors of studies otherwise meeting eligibility criteria, but not reporting mean and SD for pre- and post-procedural neuropsychological testing were contacted in an effort to obtain this information. When these results were not directly reported by the study, but could be calculated from available data, we performed these calculations. For each study, post-procedural cognitive assessments were categorized into those measured at 3 to 12 months (intermediate-term) and those measured >12 months after the procedure (long-term), with only the latest assessment of each cognitive measure within a time period extracted.

**Risk of Bias Assessments for Individual Studies**

We evaluated the risk of bias in individual studies according to recommendations from the Cochrane Handbook for Systematic Reviews of Interventions. Following categorization of studies according to their design as either interventional (RCTs, nonrandomized controlled clinical trials) or prospective observational cohort studies, two investigators reviewed each study for risk of bias for the neuropsychological outcomes, collectively including both the individual neuropsychological test results and the composite “cognitive impairment” outcomes. Because no study reported clinically diagnosed cognitive outcomes (i.e., dementia, mild cognitive impairment), risk of bias could not be assessed for these outcomes.

For interventional studies, we evaluated risk of bias using the following criteria from the Cochrane Risk of Bias tool: (1) random allocation of the subjects to the treatment groups; (2) adequacy of allocation concealment; (3) masking of the outcome assessment (participant, investigator, and/or outcome assessor); (4) use of intention-to-treat principles (i.e., inclusion of all randomized participants in their originally assigned group in outcomes analyses); and (5) selective reporting of prespecified outcomes. Generally, we assumed a low risk of bias when individual interventional studies met all quality criteria, a moderate risk of bias if at least one of the quality criteria was not met, and a high risk of bias if multiple quality criteria were not met. We concluded an unknown risk of bias for the interventional studies with poorly reported quality criteria.

For prospective cohort studies, we assessed risk of bias using the following criteria from the AHRQ Methods Guide: (1) similarity of groups in important prognostic variables; (2) masking of the outcome assessment (outcome assessor); (3) attrition bias (if overall or differential dropout/loss to follow-up or exclusions were a concern, missing data appropriately handled); and (4) selective reporting of prespecified outcomes. Generally, we assumed a low risk of bias when individual prospective observational cohort studies met all quality criteria, a moderate risk of
bias if at least one of the quality criteria was not met, and a high risk of bias if multiple quality criteria were not met. We concluded an unknown risk of bias for the prospective observational studies with poorly reported quality criteria.

Differences in risk of bias assessments between the two investigators were resolved by consensus discussion, involving the lead investigator as necessary.

Data Synthesis

Study results were organized by cardiovascular procedure category, study design, and then by duration between procedure and follow-up cognitive assessment (i.e., intermediate-term [3 to 12 months] and long-term [>1 year]).

Because no 2 studies had clinically comparable patient populations, cardiovascular procedure and comparison groups and reported the same cognitive outcomes in a comparable way, we were unable to perform a quantitative meta-analysis of any cognitive outcomes. Instead, results were qualitatively synthesized. Within individual studies, we used Review Manager (RevMan) version 5.2 software to estimate relative risks and 95% confidence intervals for the incidence of dichotomous outcomes and standardized mean differences (effect sizes) and 95% confidence intervals for continuous outcomes (e.g., for mean between-group difference in follow-up scores). The effect sizes were interpreted using the definition from Cohen of small (≥0.2 to <0.5), medium (≥0.5 to <0.8), and large (≥0.8).

To investigate the possible effect of procedure-related factors on the association between cardiovascular procedures and adverse cognitive outcomes, we had planned to consider the following subgroup analyses: incidence of procedural or peri-procedural stroke or TIA; different procedures for the same clinical indication, such as surgical vs. catheter-based/stenting; anesthesia type and duration; procedure duration; and use of adjunctive neuroprotective treatments. However, available data were insufficient to allow these analyses.

To investigate the possible effect of patient characteristics on the association between cardiovascular procedures and adverse cognitive outcomes, we had planned to consider the following subgroup analyses: age; baseline cognitive function; past stroke or TIA, baseline CVD severity; hypertension; diabetes; and depression. Then, if these subgroup analyses were not possible, we planned to perform random-effects inverse weighted meta-regression on these patient characteristics. However, again, available data were insufficient to allow these analyses.

Grading Strength of Evidence for Individual Outcomes

We graded the overall strength of evidence (SOE) for the studies in this review using methods developed by the Agency for Healthcare Research and Quality (AHRQ) and the Effective Health Care Program.

Within each cardiovascular procedure and control comparison examined, we evaluated SOE for RCTs separately from that for prospective cohort studies. Within each study design category, we rated SOE separately for clinically diagnosed cognitive outcomes (e.g., dementia, mild cognitive impairment), each brief global cognitive screening test, and each of the following cognitive domains (attention, memory, language, executive, visual-spatial functioning, and psychomotor speed). For each cardiovascular procedure and control comparison, we then considered the results from the different study designs together and reported a single SOE for each cognitive outcome. SOE ratings were performed independently by two senior reviewers, with differences between the two investigators resolved by consensus discussion, involving the lead investigator as necessary.
In each case, SOE was evaluated based on the following domains: (1) study limitations (risk of bias or internal validity); (2) directness; (3) consistency; (4) precision; and, when appropriate, (5) reporting bias. Study limitations were rated as low, medium or high based on the study design and risk of bias of individual studies. Directness was rated as direct or indirect based on whether evidence provided a single, direct link between intervention and outcomes. Consistency was rated as consistent, inconsistent, or unknown (e.g., single study) based on the degree to which included studies appeared to have the same direction or magnitude of effect. Precision was rated as precise, imprecise, or unknown based on the degree of uncertainty surrounding the effect estimate that was attributable to insufficient sample size and/or the number of outcome events. An imprecise estimate would be one in which the effect estimate was wide enough to include clinically distinct conclusions. Reporting bias was rated as suspected or undetected based on detection of publication, outcome and/or selective analysis reporting bias. Other factors that were considered in assessing SOE included dose-response relationship, presence of confounders, and strength of association. Based on these factors, the overall SOE was rated qualitatively as:

- **High**: We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable. An overall rating of high strength of evidence would imply that the included studies were RCTs with a low risk of bias, with consistent, direct, and precise domains.
- **Moderate**: We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
- **Low**: We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
- **Insufficient**: We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding judgment.

Detailed SOE ratings are reported in Appendix K.

### Assessing Applicability

Specific study characteristics that may affect applicability were noted on evidence tables. These characteristics may include non-U.S. settings; narrow participant eligibility criteria; participant age, gender, race, or educational level; participant baseline cognitive function and other comorbid characteristics; and use of cognitive assessments not typically used in current U.S. clinical practice.20

### Role of the Funding Source

The Coverage and Analysis Group at the Centers for Medicare and Medicaid Services (CMS) requested this report from The Technology Assessment Program (TAP) at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this report to the following Minnesota Evidence-based Practice Center (EPC) (Contract Number: 290-2007-100641). The scope and Key Questions were developed with input from the AHRQ and the CMS.
Chapter 3. Results

Identification of Eligible Studies

From our primary electronic database search for RCTs and prospective cohort studies reporting cognitive outcomes after selected cardiovascular procedures, we identified 529 references from MEDLINE®, 286 references from Cochrane Central Register of Controlled Trials (CENTRAL), and 454 references from Scopus, for a total of 918 unique references. Of these, we excluded 481 as ineligible during title and abstract review and 414 as ineligible during full-text review (Figure 2), leaving 23 references that met eligibility criteria and were included. An additional 65 references were identified by hand searching reference lists of included articles and review articles; of these, 61 were excluded during title and abstract review and 4 during full-text review. We searched ClinicalTrials.gov for relevant registered and completed trials and identified 116 additional studies potentially meeting eligibility criteria. Of these, we excluded 115 as ineligible based on title review and 1 as ineligible based on in-depth review. Altogether, including 4 follow-up reports of eligible studies, these sources generated 23 reports of 19 unique studies that met eligibility criteria (Figure 2).

All eligible studies were published in peer-reviewed English-language journals.
*65 additional references were identified by hand searching. 61 of these were excluded at the title and abstract review stage. The 4 remaining were excluded after full-text review.
Study Characteristics

Study Design
Among 19 eligible studies, 16 were RCTs and 3 were prospective cohort studies. Treatment duration for the RCTs ranged from 3 to 60 months, with only 1 trial longer than 12 months. Treatment duration for the prospective cohort studies duration ranged from 6 to 72 months, with only 1 study longer than 12 months.

Treatment Groups
Among eligible studies, most (n=14) evaluated cognitive outcomes after CABG. Of the CABG studies, 1 observational study compared cognitive outcomes between 3 groups, patients who underwent CABG with extracorporeal cardiopulmonary bypass (i.e. on-pump), those who underwent CABG without extracorporeal cardiopulmonary bypass (i.e. off-pump), and those treated with medical management. Each of the other CABG studies compared cognitive outcomes between two different approaches to CABG, including 4 that compared on- versus off-pump CABG, 3 that compared CABG performed under hypothermic conditions versus under normothermic conditions, 1 that compared on-pump CABG using conventional extracorporeal bypass versus minimal extracorporeal bypass, 1 that compared CABG performed under hyperbaric oxygen conditions versus under atmospheric oxygen conditions, 1 that compared CABG using fentanyl versus propofol, 1 that compared CABG using high versus low dose fentanyl, 1 that compared CABG using cell saver versus using cardiotomy suction, 1 that compared CABG with high versus low mean arterial blood pressure maintained during cardiopulmonary bypass, and 1 that compared CABG with preoperative angiotensin-receptor blocker treatment versus CABG with pre-operative placebo.

Three eligible studies evaluated cognitive outcomes after carotid artery revascularization, including 1 RCT that compared CEA versus CAS, 1 RCT that compared CEA versus carotid angioplasty, and 1 prospective cohort study that compared CEA versus laparoscopic cholecystectomy.

One eligible study evaluated post-procedural cognitive outcomes between two different approaches to tissue aortic valve replacement, comparing outcomes under hypothermic conditions versus under normothermic conditions. A prospective cohort study compared CABG alone versus cardiac valve repair (aortic or mitral) alone or combined with CABG.

We did not identify any eligible studies that evaluated cognitive outcomes after percutaneous coronary interventions, transcatheter cardiac valve surgery, or surgical or catheter-based ablation for atrial fibrillation.

Cognitive Outcome Measures
Among the 19 eligible studies, none reported post-cardiovascular procedure incidence of clinical dementia, mild cognitive impairment or any other cognitive-related clinical diagnosis. Rather, nearly all studies reported results for 1 or more neuropsychological tests in multiple cognitive domains. Consistent with the recommendations of a 1995 consensus statement on cognitive testing of patients undergoing CABG, the most common cognitive domains and individual tests reported within eligible studies are listed below. A description of the main neuropsychological tests used is in Appendix C.
• **Attention**: n=15 studies (Trail Making Test A, n=14; Digit Span, n=9);
• **Memory**: n=16 (Rey Auditory Verbal Learning Test, n=8; other verbal memory tests, n=13; visuospatial memory test, n=6);
• **Language**: n=11 (Phonemic [letter] verbal fluency, n=8; Boston Naming Test, n=4); executive, n=16 (Trail Making Test B, n=14; Digit Symbol/Symbol Digit Modalities, n=10)
• **Visuospatial functioning**: n=5 (no single visuospatial test was used by >2 studies)
• **Psychomotor speed**: n=12 (Grooved Pegboard, n=10).

Unfortunately, studies often did not report which version of a test was used (e.g., WAIS-R vs. WAIS-III) and/or which specific test score was reported (e.g., Digit span item subscore vs. maximum span) to enable cross-study comparisons or the referencing of participants’ scores with normative information.

In addition to the individual test data, 11 studies defined 1 or more measures of incident “cognitive impairment” from a group of cognitive neuropsychological tests that varied between studies. Most commonly this outcome was reported as a decline versus baseline or a post-procedural deficit exceeding some threshold (dichotomous yes-no) in 2 or more individual cognitive tests.

**Participant Characteristics**

**Demographics**

Among the 19 eligible studies, study participants were predominately male (weighted mean 79 percent) and had a weighted mean age of 68 years (range of means of 65 to 76 years, including range of means of 65 to 69 years in all but 3 studies) (Appendix D). In the few studies that reported data on education, mean years of education was 11 (range of means 7 to 14 years; 6 studies reporting) and 40 percent of participants attended any post-secondary program (range of means 13 to 61%; 4 studies reporting). In the 2 trials that reported data on race, 92 percent of participants were Caucasian. Six studies were conducted in North America (45 percent of all study participants), 10 in Europe (34 percent), and 3 in Australasia (21 percent).

**Comorbid Conditions**

Few participants in the CABG studies had a past history of stroke. Mean prevalence was 3 percent (range 0 to 8 percent) in 9 studies reporting. In contrast, in the carotid revascularization studies, all participants in 2 studies\(^{39,40}\) and half in 1 study\(^{41}\) had recent symptomatic internal carotid artery stenosis (i.e., ischemic stroke, transient ischemic attack, and/or amaurosis fugax). None of the valve surgery studies reported data on pre-procedural stroke history. Prevalence of other co-morbidities included diabetes 26 percent (range of means 0 to 40%; 18 studies reporting) and myocardial infarction 41 percent (range of means 9 to 73%; 12 studies reporting). Two CABG studies excluded participants with depression, while no other studies reported data on prevalence of depression.

**Cognitive Function**

Pre-procedural cognitive functioning was generally in the normal range. Nearly all studies reported mean pre-procedural cognitive test scores by intervention group and the majority reported information to allow comparison of participants’ cognitive function to relevant
normative data (e.g., age, gender, and, less consistently, education). Race and whether participants’ primary language spoken differed from that in which they were tested were not reported. When mean low baseline scores were observed, they most commonly were associated with measures of processing speed and motor performance (for example, Trail Making and Grooved Pegboard tests).

**Individual Study Risk of Bias**

Among the 16 eligible RCTs, 14 were rated as having a moderate risk of bias, and 2 were rated as having unclear risk of bias (Appendix E). Risk of bias related to allocation concealment was rated low in 5 trials and was unclear in 11 trials. Risk of bias related to masking of the outcome assessment was rated high in 1 trial, low in 12 trials, and was unclear in 3 trials. Risk of bias related to use of intention-to-treat principles was rated as high in 14 trials (analyses performed in study completers only) and was unclear in 2 trials. Risk of bias related to selective reporting of prespecified outcomes was rated low in all eligible trials. Fourteen of the 16 trials reported data on withdrawals, which ranged from 6 to 18 percent at 3 months, 5 to 16 percent at 6 months, and 12 to 25 percent at 1 year.

Among the 3 eligible prospective cohort studies, 2 were rated as having a high risk of bias, and 1 was rated as having moderate risk of bias (Appendix E). Two of the studies were rated as high risk of bias and 1 low risk of bias, both in similarity of prognostic factors between baseline comparison groups and in study accounting for attrition bias. Risk of bias related to masking of the outcome assessment was rated as unclear in all 3 studies. All studies were rated low risk for selective reporting of prespecified outcomes. All studies reported withdrawals, which were 18 percent at 3 months in 1 study reporting, 32 percent at 6 months in 1 study reporting, 6 to 17 percent at 1 year in 2 studies, and 47 percent at 3 years and 37 percent at 6 years in 1 study reporting.

**Key Question 1**

In older adults who undergo selected cardiovascular procedures, what are the associated post-procedural cognitive outcomes (e.g., clinical severity; timing/duration; pattern of cognitive domain impairment)?

**Key Findings**

**Overview**

- We found insufficient strength evidence addressing whether there is any difference in older adults in intermediate or long-term, clinically diagnosed or neuropsychological cognitive outcomes between these selected cardiovascular procedures and medical management or between more versus less invasive cardiovascular procedures for the same indication.
- The scant data available reported neuropsychological cognitive outcomes and suggested that there were no differences in these outcomes between treatment groups.

**Coronary Artery Revascularization**

- No RCT compared CABG with medical management and reported intermediate or long-term cognitive outcomes.
No RCT or prospective cohort study compared PCI with medical management and reported intermediate or long-term cognitive outcomes.

No RCT or prospective cohort study compared different types of coronary artery revascularization procedures with each other (e.g., CABG vs. PCI) and reported intermediate or long-term cognitive outcomes.

Insufficient strength evidence from 1 observational study that compared CABG with medical management in patients with coronary artery disease reported no statistically significant differences between treatment groups in any reported neuropsychological test at 1 and 6 years.¹⁹-²¹

**Carotid Artery Revascularization**

No RCT or prospective cohort study compared any carotid artery revascularization procedure (i.e., CEA, CAS, or carotid angioplasty) with medical management and reported intermediate or long-term cognitive outcomes.

Insufficient strength evidence from 1 RCT that compared CEA versus CAS and reported no statistically significant difference between treatment groups on any individual neuropsychological domain tested at 6 months.²²

Insufficient strength evidence from 1 RCT that compared CEA versus carotid angioplasty and reported no statistically significant difference in risk of incident “cognitive impairment” derived from a composite of neuropsychological test measures or in 10 of 11 individual neuropsychological test results at 6 months.²³

Although both RCTs had limited statistical power to detect between-group differences in cognitive outcomes, results suggest that if any differences exist they are small.

Insufficient strength evidence from 1 observational study that reported that patients who underwent CEA had a very small, but statistically significant improvement in mini-mental status exam (MMSE) and Montreal Cognitive Assessment (MoCA) tests of global cognitive function at 12 months versus age and sex-matched individuals who underwent laparoscopic cholecystectomy.²⁴

**Cardiac Valve Replacement/Repair**

No RCT or prospective cohort study compared cardiac valve replacement/repair with medical management and reported intermediate or long-term cognitive outcomes.

No RCT or prospective cohort study compared surgical versus transcatheter cardiac valve replacement/repair and reported intermediate or long-term cognitive outcomes.

No RCT or prospective cohort study compared mitral, tricuspid or pulmonic valve replacement/repair with any control group and reported intermediate or long-term cognitive outcomes.

**Ablation for Atrial Fibrillation**

No RCT or prospective cohort study compared ablation for atrial fibrillation versus medical management and reported intermediate or long-term cognitive outcomes.

No RCT or prospective cohort study compared surgical versus transcatheter ablation for atrial fibrillation and reported intermediate or long-term cognitive outcomes.
Combined CV Procedures

- Insufficient strength evidence from 1 prospective cohort study that compared CABG alone with aortic or mitral valve surgery alone or valve surgery combined with CABG and reported no statistically significant difference in 13 of 14 neuropsychological tests at 6 months.25

Table 1. Summary of evidence on association of selected cardiovascular procedures with intermediate and long-term cognitive outcomes (KQ 1)

<table>
<thead>
<tr>
<th>Interventions, Studies (Study Quality)</th>
<th>Cognitive Outcomes</th>
<th>Strength of Evidence*</th>
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</thead>
<tbody>
<tr>
<td><strong>Coronary Artery Revascularization</strong></td>
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<td></td>
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<tr>
<td>CABG vs. Medical Management</td>
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<tr>
<td>1 prospective, observational study, n=326 (high risk of bias)16-21</td>
<td>Clinically diagnosed: No results reported. Individual neuropsychological (NP) tests: No statistically significant differences between treatment groups in any test measured (range of effect sizes -0.32 to 0.24). Composite neuropsychological test “cognitive impairment” (“NPCI”): No results reported</td>
<td>Clinical: Insufficient Individual NP Tests: Insufficient Composite “NPCI”: Insufficient</td>
</tr>
<tr>
<td><strong>Carotid Artery Revascularization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEA vs. CAS: 1 RCT, n=140 (moderate risk of bias)22</td>
<td>Clinically diagnosed: No results reported. Individual NP tests: No statistically significant differences between treatment groups in any cognitive domain measured. Composite “NPCI”: No results reported</td>
<td>Clinical: Insufficient Individual NP Tests: Insufficient Composite “NPCI”: Insufficient</td>
</tr>
<tr>
<td>CEA vs. Carotid Angioplasty 1 RCT, n=46 (moderate risk of bias)23</td>
<td>Clinically diagnosed: No results reported. Individual NP tests: No statistically significant differences between treatment groups in in 10 of 11 measures reported. Composite “NPCI”: Appeared lower after CEA vs. carotid angioplasty (18% vs. 38%), but this difference was not statistically significant (RR, 0.47 [95% CI, 0.16 to 1.35])</td>
<td>Clinical: Insufficient Individual NP Tests: Insufficient Composite “NPCI”: Insufficient</td>
</tr>
<tr>
<td>CEA vs. Laparoscopic Cholecystectomy: 1 prospective, observational study, n=213 (high risk of bias)24</td>
<td>Clinical cognitive outcomes: No results reported. Individual NP tests: Small but statistically significantly greater improvement from baseline to 12 months in MMSE (0.3 vs. 0.0, p&lt;0.01) and MoCA (1.0 vs. 0.1, p&lt;0.01). Composite “NPCI”: No results reported.</td>
<td>Clinical: Insufficient Individual NP Tests: Insufficient Composite “NPCI”: Insufficient</td>
</tr>
<tr>
<td><strong>Cardiac Valve Replacement/Repair</strong></td>
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<tr>
<td>CABG vs. Cardiac Valve Replacement with or without CABG: 1 prospective, observational study, n=109 (high risk of bias)25</td>
<td>Clinical cognitive outcomes: No results reported. Individual NP tests: No statistically significant between-group difference in proportion of participants rated as having a deficit for 13 of 14 neuropsychological tests. Composite “NPCI”: No results reported.</td>
<td>Clinical: Insufficient Individual NP Tests: Insufficient Composite “NPCI”: Insufficient</td>
</tr>
<tr>
<td><strong>Ablation for Atrial Fibrillation</strong></td>
<td></td>
<td></td>
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<tr>
<td>No eligible studies</td>
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</tbody>
</table>

Abbreviations: CABG = coronary artery bypass grafting; CAS = carotid artery stenting; CEA = carotid endarterectomy; CI = confidence intervals; KQ = Key Question; MMSE = mini-mental status exam; MoCA = Montreal Cognitive Assessment; NP = neuropsychological; “NPCI” = neuropsychological test “cognitive impairment”; RCT = randomized controlled trial; RR = risk ratio; SOE = strength of evidence.

*Examples when evidence is available but SOE may be graded as insufficient include when there is an unacceptably high risk of bias, or there is a major inconsistency that cannot be explained (e.g., 2 studies with the same risk of bias with opposite results and no clear explanation for the discrepancy). In addition, SOE may be graded as insufficient when data are too imprecise. This may be the case when the 95% CI is so wide that it cannot exclude either a clinically significant benefit or harm (e.g., lower CI bound

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Detailed Findings

Coronary Artery Revascularization

CABG vs. Medical Management

We found no RCTs and only 1 prospective cohort study that compared CABG versus medical management and reported cognitive outcomes (Appendix F, Table 1). In follow-up for as long as 6 years (data analyzed at 1 and 6 years), there were only small differences in any individual neuropsychological tests reported (range of effect sizes -0.32 to 0.24) that were not statistically significant between participants who underwent either on-pump (n=152) or off-pump CABG (n=75) and those with coronary artery disease treated with medical management (n=99) (Appendix I, Table 1). Although this study may have had limited statistical power to detect between-group differences in cognitive outcomes, the small absolute differences observed suggest that even if there are real differences in cognitive outcomes between these procedures they are small.

This study did not report results for incidence of any cognitive-related clinical diagnosis or for incident cognitive impairment as defined by results from any combination of neuropsychological tests (Appendix G, Table 1; Appendix H, Table 1).

PCI vs. Medical Management

No eligible studies compared PCI versus medical management and reported cognitive outcomes.

CABG vs. PCI

No eligible studies compared CABG versus PCI or compared different methods of PCI and reported cognitive outcomes.

Of note, 13 RCTs assigned all participants to CABG and randomized them between 2 different methods of CABG (e.g., on vs. off-pump, surgery under hypothermic conditions vs. under normothermic conditions, comparison between different anesthetic agents or doses, or other). These results are presented under Key Question 2.

Carotid Artery Revascularization

CEA, CAS or Carotid Angioplasty vs. Medical Management

No eligible studies compared CEA, CAS or carotid angioplasty to medical management of carotid artery disease and reported cognitive outcomes.
We identified 1 eligible prospective observational study that compared cognitive outcomes at 3 and 12 months between individuals with either symptomatic or asymptomatic carotid artery stenosis who underwent CEA (n=159) and age and sex-matched individuals without diagnosed carotid stenosis who underwent laparoscopic cholecystectomy (n=68) (Appendix F, Table 3). The MMSE and MoCA cognitive screening measures were the only cognitive outcomes reported. This study reported statistically significant but very small differences between the symptomatic CEA group and the laparoscopic cholecystectomy group at baseline (27.4 vs. 28.2 for MMSE and 26.0 vs. 27.1 for MoCA; p<.01 for both comparisons), but not at 3 or 12 months (Appendix I, Table 3). It further reported small, statistically significant differences between the symptomatic CEA group and the laparoscopic cholecystectomy group in change from baseline to 12 months (0.3 vs. 0.0 for MMSE and 1.0 vs. 0.1 for MoCA; p<.01 for both comparisons). There were no differences in any cognitive measures at any time point between the asymptomatic CEA group and the laparoscopic cholecystectomy group. This study did not report results for post-surgical incidence of any cognitive-related clinical diagnosis (Appendix G, Table 3), or for any individual neuropsychological tests other than the MMSE and MoCA (Appendix I, Table 3).

CEA vs. CAS or Carotid Angioplasty

We identified 1 eligible RCT that compared CEA versus CAS (n=140) and 1 that compared CEA versus carotid angioplasty (n=46) (Appendix F, Table 3). Neither study reported results for post-surgical incidence of any cognitive-related clinical diagnosis (Appendix G, Table 3). Though the trial of CEA versus CAS did not report results for incident post-procedural cognitive impairment as defined by a composite of neuropsychological tests (Appendix H, Table 3), it reported that there were no statistically significant differences between treatment groups in change from baseline to 6 months in any individual neuropsychological domain tested (Appendix I, Table 3).

In the trial of CEA versus carotid angioplasty, risk for incident cognitive impairment at 6 months (as defined by a composite of neuropsychological tests) appeared lower after CEA than after carotid angioplasty. However, this difference was not statistically significant (18% vs. 38%; RR, 0.47 [95% CI, 0.16 to 1.35]) (Appendix H, Table 3). In addition, no statistically significant difference was found between these treatment groups in change from baseline to 6 months in 10 of 11 individual neuropsychological tests measured (Appendix I, Table 3).

Although these 2 studies were small and may have had limited statistical power to detect between-group differences in cognitive outcomes, available results nevertheless suggest that any differences in 6 month cognitive outcomes between these procedures are small.

Cardiac Valve Replacement

Cardiac Valve Replacement vs. No Cardiac Valve Replacement

We identified no eligible study that compared either surgical or transcatheter cardiac valve replacement versus no cardiac valve replacement (e.g., medical management) and reported cognitive outcomes.

Surgical vs. Transcatheter Cardiac Valve Replacement
We identified no eligible study that compared surgical versus transcatheter cardiac valve replacement and reported cognitive outcomes.

Of note, we identified 1 eligible RCT that compared aortic valve replacement performed under hypothermic conditions versus aortic valve replacement performed under normothermic conditions. These results are presented under Key Question 2.

**Ablation for Atrial Fibrillation**

We identified no eligible study that compared either surgical or transcatheter ablation for atrial fibrillation versus any comparison group and reported cognitive outcomes.

**Combined Cardiovascular Procedures**

**CABG vs. Cardiac Valve Replacement with or without CABG**

We identified 1 study that compared a combination of any the above cardiovascular procedures with a control group and reported cognitive outcomes. This was a prospective cohort study that compared participants who underwent CABG alone versus a group that included participants who underwent either aortic or mitral valve surgery alone or valve surgery in combination with CABG (n=109 participants) (Appendix F, Tables 1 and 2). This study did not report results for post-surgical incidence of any cognitive-related clinical diagnosis (Appendix G, Tables 1 and 2) or incident “cognitive impairment” as defined by a composite of neuropsychological tests (Appendix H, Tables 1 and 2). In the 68% of enrollees reporting results 6 months after surgery, there was no statistically significant between-group difference in the proportion of participants rated as having a deficit for 13 of 14 individual neuropsychological tests (Appendix I, Tables 1 and 2).

**Key Question 2**

In older adults who undergo selected cardiovascular procedures, are associated risks for adverse post-procedural cognitive outcomes affected by procedural and peri-procedural stroke or TIA and other procedural characteristics (e.g., alternative procedures for the same indication, such as surgical vs. catheter-based/stenting; anesthesia type; adjunctive neuroprotective treatments)?

**Key Findings**

**Overview**

- We could not determine whether risk for adverse intermediate or long-term cognitive outcomes in older adults following any of these cardiovascular procedures is affected by procedural and peri-procedural stroke or TIA.
- We found low to insufficient strength evidence that intermediate and long-term cognitive outcomes are not significantly different between individuals assigned to on versus off-pump CABG, hypothermic versus normothermic CABG, or hypothermic versus normothermic aortic valve replacement surgery.
We found no evidence whether procedure characteristics modify the association between carotid revascularization or ablation for atrial fibrillation and intermediate and long-term cognitive outcomes.

**Association of Incident Stroke/TIA with Cognitive Outcomes**

- Procedural/peri-procedural stroke and TIA were infrequent (i.e., ≤1 in each treatment group in most of the 10 coronary and carotid revascularization studies that reported strokes and the 4 that reported TIAs) and incidence was not statistically significantly different between treatment groups. Also taking into account findings from this review that risk for intermediate and long-term cognitive outcomes didn’t appear to differ between cardiovascular procedure treatment groups, we could not determine from eligible studies whether strokes and TIAs impact risk for these cognitive outcomes.

**Effect of Other Procedural Characteristics on Cognitive Outcomes after Coronary Artery Revascularization**

- Low strength of evidence from 4 RCTs that compared on versus off-pump CABG and reported no statistically significant differences between treatment groups in either risk of incident “cognitive impairment” defined from a composite of neuropsychological tests or in any individual neuropsychological test results except for in 1 of 16 individual neuropsychological tests in 1 trial.\(^{26}\)

- Insufficient strength of evidence from 1 prospective cohort study that compared on versus off-pump CABG and reported no statistically significant difference between treatment groups in incident “cognitive impairment” defined from a composite of neuropsychological tests or in 22 of 24 individual neuropsychological tests (2 of 24 individual tests favored the off-pump group).\(^{19-21}\)

- Low strength of evidence from 3 RCTs that compared hypothermic versus normothermic CABG and reported no statistically significant differences between treatment groups in risk of incident “cognitive impairment” defined from a composite of neuropsychological tests or in any individual neuropsychological test results except for in 1 of 17 individual neuropsychological tests in 1 trial that favored the hypothermic group.\(^{27}\)

- Low strength of evidence from 1 RCT that, when compared to individuals randomized to on-pump CABG with conventional extracorporeal bypass (CECC), those assigned to on-pump CABG with minimal extracorporeal bypass (MECC) had a significantly lower risk of incident “cognitive impairment” defined from a composite of neuropsychological tests (21% for MECC vs. 61% for CECC; RR, 0.34 [95% CI, 0.16 to 0.73]). Insufficient strength of evidence from this trial that participants in the MECC group performed better than those assigned to CECC in 2 psychomotor tests among the 7 individual neuropsychological tests reported.\(^{28}\)

- Insufficient strength of evidence from each of 6 additional RCTs that compared different versions of CABG and reported no statistically significant between-group differences in either risk of incident “cognitive impairment” defined from a composite of neuropsychological tests or in any individual neuropsychological test results.
Effect of Other Procedural Characteristics on Cognitive Outcomes after Carotid Artery Revascularization

- No RCT or prospective cohort study enrolled participants undergoing any method of carotid artery revascularization and compared intermediate or long-term cognitive outcomes between those randomized with respect to another procedural characteristic (e.g., anesthetic regimen) or reported stratified results as a function of this procedural characteristic.

Effect of Other Procedural Characteristics on Cognitive Outcomes after Cardiac Valve Replacement

- Insufficient strength of evidence from 1 RCT that compared aortic valve replacement under hypothermic conditions versus aortic valve replacement under normothermic conditions and reported no statistically significant between-group differences in MMSE or Trail Making A tests at up to 4 months.\(^{29}\)
- No RCT or prospective cohort study enrolled participants undergoing any method of cardiac valve replacement/repair and compared intermediate or long-term cognitive outcomes between those randomized with respect to another procedure characteristic (e.g., anesthetic regimen) or reported stratified results as a function of this procedure characteristic.

Effect of Other Procedural Characteristics on Cognitive Outcomes after Ablation for Atrial Fibrillation

- No RCT or prospective cohort study enrolled participants undergoing ablation for atrial fibrillation and compared intermediate or long-term cognitive outcomes between those randomized with respect to another procedure characteristic (e.g., anesthetic regimen) or reported stratified results as a function of this procedure characteristic.
Table 2. Summary of evidence on effect of procedure characteristics on association of selected cardiovascular procedures with intermediate and long-term cognitive outcomes (KQ 2)

<table>
<thead>
<tr>
<th>Interventions, Studies (Study Quality)</th>
<th>Cognitive Outcomes</th>
<th>Strength of Evidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coronary Artery Revascularization†</strong></td>
<td></td>
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</tr>
<tr>
<td>On vs. Off-Pump CABG</td>
<td>Clinically diagnosed: No results reported. Individual neuropsychological (NP) tests: No statistically significant difference between treatment groups (n=5 studies) except in 1 of 16 measures in 1 RCT, and in 2 of 24 measures in 1 prospective cohort study. Composite neuropsychological test “cognitive impairment” (“NPCI”): No statistically significant difference between treatment groups.</td>
<td>Clinical: Insufficient Individual NP Tests: Low (RCTs), Insufficient (prospective observational study) Composite “NPCI”: Low</td>
</tr>
<tr>
<td>4 RCTs, n=374 (moderate risk of bias); 26, 31-33 and 1 prospective, observational study, n=227 (high risk of bias)19,21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothermic vs. Normothermic CABG</td>
<td>Clinically diagnosed: No results reported. Individual NP tests: No statistically significant difference between treatment groups (n=3 trials) except in 1 of 17 measures in 1 trial. Composite “NPCI”: No statistically significant difference between treatment groups.</td>
<td>Clinical: Insufficient Individual NP Tests: Low Composite “NPCI”: Low</td>
</tr>
<tr>
<td>3 RCTs, n=610 (moderate risk of bias) 27, 33-35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal vs. Conventional Extracorporeal Bypass</td>
<td>Clinically diagnosed: No results reported. Individual NP tests: Statistically significantly better performance in attention, executive, memory, visual/spatial, and psychomotor tests among individual neuropsychological tests at 3 months. Composite NP test “impairment”: Reduced risk (21 vs. 61%; RR, 0.34 [CI, 0.16 to 0.73])</td>
<td>Clinical: Insufficient Individual NP Tests: Low for all domains except language, (Insufficient) Composite NPCI: Low</td>
</tr>
<tr>
<td>1 RCT, n=64 (moderate risk of bias)28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotid Artery Revascularization</td>
<td>No eligible studies</td>
<td></td>
</tr>
<tr>
<td>Cardiac Valve Replacement/Repair</td>
<td>No eligible studies</td>
<td></td>
</tr>
<tr>
<td>Hypothermic vs. Normothermic Aortic Valve Replacement</td>
<td>Clinical cognitive outcomes: No results reported. Individual NP tests: No statistically significant difference between treatment groups in both tests administered (MMSE, Trail Making A) at up to 4 months. Composite “NPCI”: No results reported.</td>
<td>Clinical: Insufficient Individual NP Tests: Insufficient Composite “NPCI”: Insufficient</td>
</tr>
<tr>
<td>1 RCT, n=60 (moderate risk of bias)29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ablation for Atrial Fibrillation</td>
<td>No eligible studies</td>
<td></td>
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</table>

Abbreviations: CABG = coronary artery bypass grafting; CI = confidence intervals; KQ = Key Question; MMSE = mini-mental status exam; NP=neuropsychological; “NPCI” = neuropsychological test “cognitive impairment”; RCT = randomized controlled trial; RR = risk ratio; SOE = strength of evidence.

*Examples when evidence is available, but SOE may be graded as insufficient include when there is an unacceptably high risk of bias, or there is a major inconsistency that cannot be explained (e.g., 2 studies with the same risk of bias with opposite results and no clear explanation for the discrepancy). In addition, SOE may be graded as insufficient when data are too imprecise. This may be the case when the 95% CI is so wide that it cannot exclude either a clinically significant benefit or harm (e.g. lower CI bound <0.5 and upper CI bound >2).

†Six additional RCTs that each compared different versions of CABG, with no common comparison between the 6 trials, reported no statistically significant between treatment group differences in either risk of incident “cognitive impairment” defined from a composite of neuropsychological tests or in any individual neuropsychological test results.

**Detailed Findings**

**Impact of Stroke/TIA on Post-Procedural Cognitive Outcomes**

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We could not determine from available data whether risk for adverse intermediate or long-term cognitive outcomes following coronary or carotid artery revascularization, cardiac valve replacement/repair, and/or ablation for atrial fibrillation in older adults is impacted by procedural and peri-procedural stroke or TIA. This was because within eligible studies strokes and TIAs after CV procedures were uncommon, risk for strokes and TIAs didn’t appear to differ between treatment groups, and risk for post-procedural cognitive outcomes also didn’t appear to differ between treatment groups.

Among 19 eligible studies, only 10 reported data on strokes and 4 on TIAs occurring during or after the cardiovascular procedure (Appendix J, Tables 1-3). In the studies that reported these events, occurrence was infrequent and generally not different between treatment groups. All treatment groups had 1 or fewer strokes in 5 studies, while in a sixth study stroke incidence was reported to be zero in patients treated with CEA but was not reported for the cholecystectomy control group. Stroke incidence was ≤4% and not significantly different between treatment groups in 3 additional studies. Last, stroke rate was not reported but was stated to be not significantly different between CEA and CAS in 1 trial, and the apparently lower risk of stroke in 1 trial that randomized 106 patients undergoing CABG to candesartan versus placebo was not statistically significant (4.7% vs. 11.4%; RR, 0.41 [95% CI, 0.08 to 2.00]). For TIAs, all treatment groups had no TIA in 2 studies; TIA incidence was ≤4% and not significantly different between treatment groups in 1 study; and TIA incidence was 2% in patients treated with CEA but was not reported for the cholecystectomy control group in an additional study.

Impact of Procedure Characteristics on Cognitive Outcomes

Coronary Artery Revascularization

Thirteen trials enrolled participants undergoing CABG and randomized them with respect to one aspect of the CABG procedure (e.g., on vs. off-pump, surgery under hypothermic conditions vs. under normothermic conditions, comparison between different anesthetic agents or doses, or other) and reported cognitive outcomes. However, none reported cognitive-related clinical diagnoses. For the outcomes of incident cognitive impairment as defined by a composite of individual neuropsychological tests and of the individual neuropsychological tests, almost all of the limited available data suggested that there were no cognitive differences between any of the different versions of CABG compared, including on versus off-pump CABG, CABG under hypothermic conditions versus under normothermic conditions, CABG using minimal extracorporeal bypass versus conventional extracorporeal bypass, CABG performed under hyperbaric oxygen conditions versus under atmospheric oxygen conditions, CABG using fentanyl versus propofol, CABG using high versus low dose fentanyl, CABG using cell saver versus using cardiotomy suction, CABG with high versus low mean arterial blood pressure maintained during cardiopulmonary bypass, and CABG with preoperative angiotensin-receptor blocker treatment versus CABG with pre-operative placebo.

CABG: On- vs. Off-Pump

We identified 4 RCTs and 1 observational study that compared CABG performed on-pump versus off-pump and reported cognitive outcomes (Appendix F, Table 1).
None of the 5 studies reported post-CABG incidence of clinical dementia, mild cognitive impairment or any other cognitive-related clinical diagnosis (Appendix G, Table 1). The 4 trials that compared on versus off-pump CABG reported no statistically significant difference between treatment groups in incident cognitive impairment defined as post-procedural declines/deficits in a composite of individual neuropsychological tests at 3 to 12 months after surgery (Appendix H, Table 1).

As for individual neuropsychological test results, in the 4 on versus off-pump trials, there were no statistically significant differences between treatment groups in any individual neuropsychological test in any trial except in 1 of 16 measures in 1 trial that favored the off-pump group (Appendix I, Table 1).29

The prospective cohort study did not report results for incidence of any cognitive-related clinical diagnosis or for any definition of incident “cognitive impairment” (Appendix G, Table 1; Appendix H, Table 1). There were no statistically significant differences between the on and off-pump treatment groups in any individual neuropsychological test results at 1 year post-CABG (Appendix I, Table 1). Further, at 6 years, by which time there was an additional 20-25% loss to follow-up, there still were no statistically significant differences between treatment groups in 9 of 11 individual neuropsychological measures. However, the off-pump group scored significantly better than the on-pump group in the Grooved Pegboard nondominant hand (99 vs. 116.3 seconds; effect size 0.54; p=0.02) and the Rey Auditory Verbal Learning Test (RAVLT) retention task (84.5 vs. 70; effect size 0.45; p=0.004).

**CABG: Hypothermic vs. Normothermic**

We identified 3 RCTs that compared CABG performed under hypothermic conditions versus CABG under normothermic conditions and reported cognitive outcomes,27, 31, 32 one of which compared hypothermic on-pump versus normothermic off-pump CABG (Appendix F, Table 1).27

None of the 3 trials reported post-CABG incidence of clinical dementia, mild cognitive impairment or any other cognitive-related clinical diagnosis (Appendix G, Table 1). Though all 3 reported outcomes for incident cognitive impairment defined as post-procedural declines/deficits in a study-specific composite of individual neuropsychological tests, there was no statistically significant difference between treatment groups in these outcomes at any time point between 3 months27, 31 and 5 years22 in any of these trials (Appendix H, Table 1).

As for individual neuropsychological test results, compared to participants randomized to normothermic conditions those assigned hypothermic conditions had greater improvement at 3 months versus baseline on the WAIS-R Digit Span backwards (0.5 vs. -0.3; effect size, 0.44 [95% CI, 0.18 to 0.70]) in 1 study (Appendix I, Table 1).31 However, there were no statistically significant between-treatment group differences in mean scores 12 months after surgery,27 or in change between pre-CABG levels and results 3 months to 5 years after surgery22, 31 in any other individual neuropsychological measure reported.

**CABG: Anesthetic Regimens**

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We identified 2 RCTs that compared cognitive outcomes between patients who underwent CABG performed using one anesthetic regimen versus CABG performed using a different anesthetic regimen (Appendix F, Table 1). One trial reported cognitive outcomes up to 6 months post-procedure between 1 group randomized to fentanyl and a second group assigned propofol (n=180).10 A second trial compared cognitive outcomes up to 12 months post-CABG between groups that received high versus low dose fentanyl, respectively (n=350).34 Neither study reported outcomes for any cognitive-related clinical diagnosis (Appendix G, Table 1); and both reported no statistically significant difference between treatment groups in risk of incident “cognitive impairment” as defined by a composite of individual neuropsychological tests or in any individual neuropsychological test reported (Appendix H, Table 1).

CABG: Miscellaneous Procedure Methods

Five other RCTs each compared one approach to CABG versus another, respectively performing surgery under hyperbaric oxygen conditions versus under atmospheric oxygen conditions (n=64),33 using cell saver versus using cardiotomy suction (n=226),35 maintaining high versus low mean arterial blood pressure during cardiopulmonary bypass (n=248),36 using preoperative angiotensin-receptor blocker treatment versus pre-operative placebo (n=106).37, and on-pump using minimal versus conventional extracorporeal bypass (MECC vs. CECC) (n=64) (Appendix F, Table 1).30

None of these 5 trials reported post-CABG incidence of clinical dementia, mild cognitive impairment, or any other cognitive-related clinical diagnosis (Appendix G, Table 1). Four of the 5 trials reported results for incident “cognitive impairment” defined by a study-specific composite of neuropsychological tests and for several individual neuropsychological tests (Appendix H, Table 1; Appendix I, Table 1).30, 33, 35, 36 Of these, 3 reported no statistically significant difference between treatment groups in any of these outcomes.33, 35, 36 By comparison, participants randomized to MECC were significantly less likely than those assigned to CECC to have incident “cognitive impairment” (20.7% vs. 61.3%; RR, 0.34 [95% CI, 0.16 to 0.73]). Further, participants randomized to MECC scored significantly better than those assigned to CECC on 2 psychomotor tests (Digit Span backward and Symbol Digit Modalities) (large effect sizes of 0.94 [95% CI, 0.41 to 1.48] to 1.08 [95% CI, 0.53 to 1.62], respectively) among 7 individual neuropsychological tests reported.30

Carotid Artery Revascularization

We identified no study that enrolled participants undergoing carotid artery revascularization and compared cognitive outcomes between those randomized with respect to another procedure characteristic (e.g., anesthetic regimen) or that reported stratified results as a function of this procedure characteristic.

Cardiac Valve Replacement
We identified 1 eligible RCT that compared aortic valve replacement performed under hypothermic conditions versus aortic valve replacement performed under normothermic conditions (n=60 participants) (Appendix F, Table 2).42 This study did not report results for postsurgical incidence of any cognitive-related clinical diagnosis or incident cognitive impairment as defined by a composite of neuropsychological tests (Appendix G, Table 2; Appendix H, Table 2). Authors reported only that there were no between group differences in MMSE or the Trail Making A test for up to 4 months after surgery, but provided no analyzable data (Appendix I, Table 2).

We identified no other study that enrolled participants undergoing cardiac valve replacement/repair and compared cognitive outcomes between those randomized with respect to another procedure characteristic (e.g., anesthetic regimen) or that reported stratified results as a function of this procedure characteristic.

Ablation for Atrial Fibrillation

We identified no study that enrolled participants undergoing ablation for atrial fibrillation and compared cognitive outcomes between those randomized with respect to another procedure characteristic (e.g., anesthetic regimen) or that reported stratified results as a function of this procedure characteristic.

Key Question 3

In older adults who undergo selected cardiovascular procedures, are associated risks for adverse post-procedural cognitive outcomes affected by patient characteristics? (e.g., age; baseline cognitive function; past stroke or TIA, baseline CVD severity; hypertension; diabetes; depression)

Key Findings

• We found no evidence from eligible studies addressing whether age, baseline cognitive function, past stroke or TIA, baseline CVD severity, hypertension, diabetes, or depression modify the association between any of these cardiovascular procedures and intermediate or long-term cognitive outcomes in older adults.
• No study reported risks for cognitive outcomes after cardiovascular procedures compared to risks in a control group (e.g., alternative cardiovascular procedure, medical management) as a function of patient characteristics, either as reported within specific study subgroups or in analyses adjusted for specific patient characteristics.
• Date were insufficient to perform meta-regression analyses to evaluate whether any between study differences in the association of cardiovascular procedures with cognitive outcomes relative to control differed as a function of between-study differences in selected patient characteristics.
  o Limitations in the available data that impeded meta-regression included little between-study variability in participant characteristics. For example, the mean age in nearly all studies was 65 to 69 years; baseline cognitive function appeared intact in nearly all participants; there were very few patients with prior stroke or TIA (other than in studies involving carotid revascularization); there was limited reporting of certain patient covariates (e.g., depression); and, lastly, few comparisons were evaluated by the same cognitive measures in more than 1 study.

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Chapter 4. Discussion

Do selected cardiovascular procedures impact cognitive outcomes in older adults?

In sum, the scant available data that compared selected cardiovascular procedures with medical management or compared more versus less invasive cardiovascular procedures suggest that these procedures have little to no effect on intermediate and long-term cognitive outcomes. Though the strength of evidence for these findings is insufficient and additional studies could substantially change these estimates, these conclusions are based on our finding no RCT evidence addressing whether coronary or carotid artery revascularization, cardiac valve replacement/repair, or ablation for atrial fibrillation impacts intermediate- or long-term cognitive outcomes when compared to medical management in older adults. We found insufficient strength evidence from 1 prospective cohort study that intermediate and long-term cognitive outcomes are not significantly different between patients who undergo CABG versus patients with coronary artery disease who are treated with medical management.

We found no RCT or prospective cohort study evidence addressing whether there is a difference in intermediate or long-term cognitive outcomes after more versus less invasive procedures for coronary artery revascularization (i.e., CABG vs. PCI), cardiac valve disease (i.e., replacement vs. repair, surgical vs. transcatheter), or ablation for atrial fibrillation (i.e., surgical vs. transcatheter). We found insufficient strength evidence from 2 RCTs that intermediate and long-term cognitive outcomes are not significantly different between patients assigned to CEA versus CAS or between CEA versus carotid angioplasty, respectively.

Is any association between selected cardiovascular procedures and cognitive outcomes in older adults attributable to procedure-related strokes and/or TIAs?

We could not determine from available data whether risk for adverse intermediate or long-term cognitive outcomes following coronary or carotid artery revascularization, cardiac valve replacement/repair, and/or ablation for atrial fibrillation in older adults is affected by procedural and peri-procedural stroke or TIA. This was because, within eligible studies, strokes and TIAs after cardiovascular procedures were uncommon; risk for strokes and TIAs didn’t statistically significantly differ between treatment groups; and, with rare exceptions, risk for post-procedural cognitive outcomes didn’t statistically significantly differ between treatment groups. While data from eligible studies don’t suggest that procedure-related stroke or TIA cause intermediate and/or long-term cognitive impairment, statistical power from these studies concerning this association was clearly inadequate for this conclusion to be definitive.

Is any association between selected cardiovascular procedures and cognitive outcomes in older adults modified by procedural characteristics?

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Available data suggest that using on versus off-pump CABG or hypothermic versus normothermic CABG does not make a difference in intermediate and long-term cognitive outcomes. Other modifications to CABG and these other cardiovascular procedures were too little studied to draw anything but tentative conclusions concerning their effect on intermediate and long-term cognitive outcomes.

These conclusions are based on our findings of low strength evidence from RCTs (and insufficient evidence from 1 prospective cohort study) that intermediate and long-term cognitive outcomes after CABG are not significantly different between patients assigned to on-pump versus off-pump surgery or between patients assigned to surgery under hypothermic versus normothermic conditions. We found insufficient evidence that intermediate and long-term cognitive outcomes after CABG are not significantly different between patients treated with a limited selection of anesthetic regimens, or between patients treated with hyperbaric versus atmospheric oxygen, cell saver versus cardiotomy suction, high versus low blood pressure, or preoperative angiotensin-receptor blocker treatment versus placebo.

We found insufficient strength evidence from 1 RCT addressing whether intermediate and long-term cognitive outcomes after aortic valve replacement surgery are impacted by whether the surgery is performed under hypothermic versus normothermic conditions. We found no evidence addressing whether the association between carotid revascularization or atrial fibrillation procedures and cognitive outcomes is modified by procedural characteristics.

Is any association between selected cardiovascular procedures and cognitive outcomes in older adults modified by patient characteristics?

We found no evidence from eligible studies addressing whether any of the patient characteristics we sought to investigate (age; baseline cognitive function; past stroke or TIA, baseline CVD severity; hypertension; diabetes; depression) modify the association between coronary or carotid artery revascularization, cardiac valve replacement/repair, and/or ablation for atrial fibrillation and intermediate or long-term post-procedural cognitive outcomes in older adults. Further, because eligible studies were mostly comprised of men, had a low prevalence of stroke, and included few old-old participants, it may not have been possible to evaluate the impact of variability in these patient characteristics on intermediate and long-term post-procedural cognitive outcomes from these studies.

While older individuals, who are increasingly undergoing these cardiovascular procedures, would be expected to have a higher prevalence of baseline cognitive impairment, higher risk of cognitive decline unrelated to any cardiovascular procedures, and, potentially, greater vulnerability to cognitive decline related to cardiovascular procedures, this could not be determined from eligible studies. This is an important research gap.

What are the benefits and harms of cognitive testing before and after selected cardiovascular procedures?

The focus of our review was to evaluate whether selected cardiovascular procedures affect intermediate and long-term cognitive outcomes. In this context, evidence from this review is relevant to whether cognitive testing before and after selected cardiovascular procedures improves intermediate and long-term post-procedural cognitive outcomes. Evidence from our review does not directly address whether cognitive testing before and after selected
cardiovascular procedures improve any other outcomes (e.g., delirium, noncognitive), or whether
cognitive screening benefits outweigh harms in any other population (e.g., community-dwelling
older adults, older adults scheduled for noncardiovascular procedures). Some of these important
questions have been addressed by recommendations and guidelines by other groups.1,3,43

That said, we found mostly insufficient strength evidence from RCTs and prospective cohort
studies suggesting little to no association between coronary or carotid artery revascularization,
cardiac valve replacement/repair, and/or ablation for atrial fibrillation and subsequent
intermediate and long-term cognitive outcomes. Our review found no evidence addressing
whether risk for intermediate and long-term cognitive outcomes after these procedures differs
between all or targeted patients with and without pre-procedural cognitive impairment as might
be identified by broad or targeted pre-procedural cognitive testing. Therefore, we found no
evidence addressing whether pre and post-procedural cognitive testing may lead to improvement
in intermediate and long-term cognitive outcomes. Future research showing benefit of cognitive
testing before and/or after selected cardiovascular procedures on intermediate and long-term
cognitive outcomes or on other important patient outcomes (e.g., patient autonomy related to
capacity to consent, complications related to adherence with post-surgical instructions, quality of
life, costs) may be necessary to justify broad clinical implementation of such cognitive testing.

How may findings from this review inform the provider-
patient consent process for selected cardiovascular
procedures?

Our review found very limited evidence addressing whether intermediate and long-term
cognitive outcomes after coronary or carotid artery revascularization or cardiac valve
replacement/repair are attributable to these procedures, no evidence about whether these
cognitive outcomes are attributable to ablation for atrial fibrillation, and limited evidence that
there is no significant difference in intermediate and long-term cognitive outcomes between
different versions of CABG and between different methods of carotid artery revascularization.
Therefore, it may be appropriate for providers performing consent to inform patients that though
there is substantial uncertainty about the cognitive risk from these procedures, limited evidence
suggests that intermediate and long-term cognitive risks attributable to the procedures or to
different versions of these procedures, if present, are likely to be small.

Applicability

No trial compared a cardiovascular procedure versus medical management. Only 2 of 16
trials compared different cardiovascular procedures with each other, both of which compared
CEA versus a less invasive procedure (i.e., CAS and carotid angioplasty, respectively) for
treatment of carotid stenosis. Most trials were limited to individuals undergoing CABG and
compared different versions of the CABG procedure. Most participants in these studies were
men. By design, our review was limited to studies in which most or all participants were aged
≥65 years, but most studies appeared to include few old-old participants (e.g., aged ≥80 years).
Studies appeared to enroll predominately participants who were cognitively intact, and, other
than in the carotid artery revascularization studies, pre-procedural history of stroke was rare.
Studies also reported very limited data on the prevalence of certain participant characteristics,
including race, comorbid conditions, and CVD severity
Taking these trial characteristics into account, results from this review may have limited generalizability to the oldest patients who undergo these cardiovascular procedures in the community, to women, to patients with baseline cognitive impairment, or to those with past stroke. Further, results may not be generalizable to patients with comorbid conditions not reported (though not explicitly excluded in most cases) in eligible studies (e.g., depression).

Future Research Recommendations

Table 3 summarizes the areas needing future research based on the gaps identified in this review.

<table>
<thead>
<tr>
<th>General Issues</th>
<th>Future Research Recommendations</th>
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<tbody>
<tr>
<td>No eligible studies reported clinically diagnosed cognitive outcomes (e.g., dementia, mild cognitive impairment) based on the presence of symptoms and/or functional impairment plus abnormal neuropsychological testing.</td>
<td>Future studies should report clinically diagnosed cognitive outcomes, such as incident dementia or mild cognitive impairment, although the incidence of these outcomes may be very low.</td>
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<td>Though many studies reported an outcome of incident “cognitive impairment,” defined by a study-specific combination of 1 or more individual neuropsychological tests meeting a study-specific threshold for abnormality or decline, the meaning of this outcome is unclear. There was no standard definition across studies, either in how many tests were assessed, which tests were assessed, how tests were scored, how many tests must have been abnormal, or in how abnormal was defined (e.g., decline of 20% 0.5 SD, or 1 SD). This does not appear to equate to a clinically meaningful change in these continuous neuropsychological tests. In fact, because criteria could have been met based on sometimes modest abnormalities in a small proportion of administered tests, some participants may have met criteria due solely to chance variation in test performance.</td>
<td>Future studies should use a standardized definition of incident cognitive impairment. Ideally, it would represent a clinically meaningful change in cognition. It should be based on standardized scoring of a standard battery of individual neuropsychological tests sensitive to cognitive changes over time but that minimize learning effects. One possible approach would be to perform between-group statistical significance testing of continuous neuropsychological test scores adjusted for multiple comparisons along with determining whether the magnitude of any statistically significant difference exceeds a rigorous threshold (e.g., &gt;0.5 or 1 SD).</td>
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<tr>
<td>Statistical pooling was impeded by between-study variability in neuropsychological testing, including use of different tests, use of different versions of the same test, and unclear reporting about what tests were used and how test results were derived.</td>
<td>Studies should identify a primary neurocognitive outcome and use it to calculate a sample size sufficient to detect a clinically meaningful difference between treatment groups.</td>
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<td>Follow-up duration in most studies may have been too short to evaluate long-term cognitive effects of these cardiovascular procedures.</td>
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<td>This review only considered intermediate (3 to 12 months) and long-term (&gt;12 months) post-procedural cognitive outcomes. The effect of selected cardiovascular procedures on shorter-term cognitive outcomes was outside the scope of this review.</td>
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Key Question 1. In older adults who undergo selected cardiovascular procedures, what are the associated post-procedural cognitive outcomes?

- We found no evidence from eligible studies addressing whether there is a difference in intermediate or long-term cognitive outcomes after more versus less invasive procedures for coronary artery revascularization (i.e., CABG)
- Future studies (prospective cohorts, RCTs where appropriate considering noncognitive outcomes) should compare intermediate and long-term cognitive outcomes associated with more versus less invasive procedures (including medical management) for treatment of
vs. PCI), cardiac valve disease (i.e., replacement vs. repair, surgical vs. transcatheter), or ablation for atrial fibrillation (i.e., surgical vs. transcatheter).

- We found limited evidence from 1 observational study of no intermediate or long-term differences in multiple individual neuropsychological tests between patients who underwent CABG and those with coronary artery disease treated with medical management.

**Key Question 2.** In older adults who undergo selected cardiovascular procedures, are associated risks for adverse post-procedural cognitive outcomes affected by procedural and peri-procedural stroke or TIA and other procedure characteristics?

- We could not determine whether risk for adverse intermediate or long-term cognitive outcomes following selected cardiovascular procedures was affected by procedural and peri-procedural stroke or TIA because, within eligible studies, strokes and TIAs were uncommon, risk for strokes and TIAs didn’t appear to differ between treatment groups, and risk for post-procedural cognitive outcomes also didn’t appear to differ between treatment groups.

- Though 4 eligible RCTs and 1 eligible observational study of on vs. off-pump CABG reported no difference in intermediate and long-term cognitive outcomes between these versions of CABG, strength of evidence for this finding is only low.

- Though 3 eligible RCTs of hypothermic vs. normothermic CABG reported no difference in intermediate and long-term cognitive outcomes between these versions of CABG, strength of evidence for this finding is only low.

- Based on several comparisons each reported in only 1 RCT, we found insufficient evidence that intermediate and long-term cognitive outcomes after CABG are not significantly different between patients treated with a limited number of different anesthetic regimens, hyperbaric versus atmospheric oxygen, cell saver versus cardiomyotomy suction, high versus low blood pressure, or preoperative angiotensin-receptor blocker treatment versus placebo.

- Future studies of cardiovascular procedures should systematically collect information on procedural and peri-procedural stroke and TIA.

- Though additional RCTs of on vs. off-pump CABG and hypothermic vs. normothermic CABG would be likely to refine the relative estimates of effect for their associated intermediate and long-term cognitive outcomes, the difference between these pairs of treatments is likely to be small, if any, and future research efforts may better be directed to studying the intermediate and long-term cognitive impacts of other less investigated versions of CABG.

- In addition to reporting results for post-procedural cognitive outcomes overall, future studies should report results stratified by and/or adjusted for any procedure characteristics that are allowed to vary between participants as they may be important predictors of these post-procedural cognitive outcomes.

**Key Question 3.** In older adults who undergo selected cardiovascular procedures, are associated risks for adverse post-procedural cognitive outcomes affected by patient characteristics?

- We found no evidence from eligible studies addressing whether any of selected patient characteristics (e.g., age; baseline cognitive function; past stroke or TIA, baseline CVD severity; hypertension; diabetes; depression) modify the association between these selected cardiovascular procedures and intermediate or long-term post-procedural cognitive outcomes.

- Eligible studies appeared to include few old-old participants (i.e., aged 80 years or older). Since the cardiovascular procedures of interest in this report are increasingly common in the old-old...

- Future studies (RCTs, controlled clinical trials (CCTs), prospective cohort studies) comparing intermediate and long-term cognitive outcomes between cardiovascular procedures should be conducted in patients with older ages and/or baseline cognitive impairment. Such patients have the highest risk for developing intermediate and long-term cognitive impairment after these procedures, and may also have larger differences in risk of these cognitive outcomes between different cardiovascular procedures.

- Future studies (RCTs, CCTs, prospective cohort studies) should enroll diverse patient populations and, in addition to reporting results for post-procedural cognitive outcomes in...
population, and this population is likely to be at greater risk for adverse cognitive outcomes, our findings may not be generalizable to this population.

- Based on reported results of pre-procedural cognitive testing, eligible studies appeared not to include many participants with baseline cognitive impairment, who are likely to be at greater risk for adverse cognitive outcomes after cardiovascular procedures, so our findings may not be generalizable to this population.

the population overall, they should also report results stratified by and/or adjusted for patient characteristics that may be important predictors of these post-procedural outcomes, or explore effect modification by these characteristics (e.g., age; baseline cognitive function; past stroke or TIA, baseline CVD severity; hypertension; diabetes; depression).

**Abbreviations:** CABG=coronary artery bypass grafting; CCT=controlled clinical trial; CVD=cardiovascular disease; PCI=percutaneous coronary intervention; RCT=randomized controlled trial; SD=standard deviation; TIA=transient ischemic attack
References


### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACS</td>
<td>American College of Surgery</td>
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<tr>
<td>AGS</td>
<td>American Geriatrics Society</td>
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<td>AHRQ</td>
<td>Agency for Healthcare Research and Quality</td>
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<tr>
<td>AVR</td>
<td>aortic valve replacement</td>
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<tr>
<td>CABG</td>
<td>coronary artery bypass grafting</td>
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<td>CAS</td>
<td>carotid artery stenting</td>
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<tr>
<td>CCT</td>
<td>controlled clinical trial</td>
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<tr>
<td>CEA</td>
<td>carotid endarterectomy</td>
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<tr>
<td>CENTRAL</td>
<td>Cochrane Central register of controlled trials</td>
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<tr>
<td>CV</td>
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<td>key question</td>
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<td>RR</td>
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<tr>
<td>SOE</td>
<td>strength of evidence</td>
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<tr>
<td>TIA</td>
<td>transient ischemic attack</td>
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