

Technology Assessment



**Technology
Assessment Program**

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

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Prepared by:

Minnesota Evidence-based Practice Center
Minneapolis, MN

Investigators:

Howard A. Fink, M.D., M.P.H.
Laura S. Hemmy, Ph.D.
Roderick MacDonald, M.S.
Maureen H. Carlyle, M.P.H.
Carin M. Olson, M.D., M.S.
Maurice W. Dysken, M.D.
J. Riley McCarten, M. D.
Robert L. Kane, M.D.
Indulis R. Rutks, B.S.
Jeannine Ouellette
Timothy J. Wilt, M.D., M.P.H

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The information in this report is intended to help health care decision-makers; patients and clinicians, health system leaders, and policymakers, make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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None of the investigators has any affiliations or financial involvement related to the material presented in this report.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The Centers for Medicare and Medicaid Services requested and provided funding for this report.

The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

Richard Kronick, Ph.D.
Director
Agency for Healthcare Research and Quality
and Quality

Yen-pin Chiang, Ph.D.
Acting Deputy Director
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director, Evidence-based Practice Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Elise Berliner, Ph.D.
Director, Technology Assessment Program
Agency for Healthcare Research and Quality

Kim Marie Wittenberg, M.A.
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

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Peer Reviewers

We wish to acknowledge individuals listed below for their review of this report. This report has been reviewed in draft form by individuals chosen for their expertise and diverse perspectives. The purpose of the review was to provide candid, objective, and critical comments for consideration by the EPC in preparation of the final report. Synthesis of the scientific literature presented here does not necessarily represent the views of individual reviewers.

Rebecca F. Gottesman, MD, PhD
Department of Neurology
Johns Hopkins University School of Medicine
Baltimore, MD

David Knopman, MD
Neurology, Mayo Clinic
Rochester, MN

Lenore Launer, PhD
Neuroepidemiology National
Institute of Health
Bethesda, MD

Ronald Lazar, PhD
Neurology and Neurological
Surgery Columbia University
New York, NY

Robin Varghese, MD, MS
Assistant Professor of Surgery
Department of Cardiothoracic Surgery
Icahn School of Medicine, Mount Sinai Medical Center
New York, NY

Mary Woo, DNSc, RN, FAAN
University of California, Los
Angeles Los Angeles, CA

Wei Zhou
Vascular Surgery
Stanford University and Palo Alto Veterans Affairs Health Care System
Palo Alto, CA

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

Structured Abstract

Objective: To summarize current evidence on intermediate- and long-term cognitive outcomes after coronary and carotid revascularization, cardiac valve procedures, and ablation for atrial fibrillation in older adults, and their association with procedure-related stroke, transient ischemic attack (TIA), and other procedure and patient characteristics.

Data Sources: MEDLINE[®], Cochrane Database of Systematic Reviews, Scopus, and ClinicalTrials.gov electronic databases from 1990 through July 2014; 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/or long-term (>12 months) cognitive outcomes after one or more of the above selected cardiovascular procedures. Cognitive outcomes of interest were clinical diagnoses (e.g., mild cognitive impairment), neuropsychological test results, and incident cognitive impairment derived from a composite of neuropsychological test results. We extracted data, rated individual study risk of bias, and graded strength of evidence (SOE).

Results: Seventeen RCTs and 4 prospective cohort studies were included. Eighty percent of participants were male and mean age was 68 years. Five studies excluded participants for some measure of abnormal baseline cognition. Nevertheless, more than half of studies reported mean baseline scores in the impaired range for at least one neuropsychological test, most frequently with slowing in timed tests. There was no significant difference in post-procedure cognitive function between on- versus off-pump coronary artery bypass grafting (CABG) ($n=6$) (low SOE), hypothermic versus normothermic CABG ($n=3$) (moderate to low SOE), or CABG versus medical management ($n=1$) (insufficient SOE). One trial reported lower risk of incident cognitive impairment at 3 months with minimal versus conventional extracorporeal bypass CABG (RR=0.34 [95%CI=0.16-0.73]). Two trials found no difference between surgical and endovascular carotid revascularization (low to insufficient SOE). One cohort study reported increased cognitive decline after transcatheter versus surgical aortic valve replacement at 3 months (28% versus 6 %, $p=0.04$), but results may have been limited by large selection and outcome measurement biases (insufficient SOE). Because study participants had few strokes and transient ischemic attacks, we could not determine whether these events affected post-procedure cognitive outcomes. We found no evidence from eligible studies about whether patient characteristics such as age and baseline cognitive function modify the association between these cardiovascular procedures and intermediate- or long-term post-procedure cognitive outcomes. This review was limited by the small number of eligible studies for each treatment comparison, including no eligible studies that assessed cognitive outcomes after ablation for atrial fibrillation; heterogeneity of cognitive outcomes; and limited individual study quality. Results may have

limited generalizability to the elderly, women, or individuals with substantial baseline cognitive impairment.

Conclusions: Persistent cognitive impairment attributable to studied cardiovascular procedures in older adults appeared uncommon and may reflect pre-existing cognitive impairment. Specifically, CABG may have little intermediate to long-term cognitive effect in older adults, including numerous comparisons of different versions of CABG versus each other. Intermediate-term cognitive effects may be similar between those who undergo surgical versus endovascular carotid revascularization. Results suggesting better cognition after minimal versus conventional extracorporeal bypass CABG are promising but need confirmation. Confidence in review findings should be tempered by substantial limitations in primary data quantity and quality. Results may not be generalizable to old-old patients, to women, or to patients with substantial baseline cognitive impairment.

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Introduction

Background

Concern about the possible association between cardiovascular procedures and subsequent cognitive outcomes is long standing. Particularly for coronary artery bypass grafting (CABG), and to a lesser extent for other procedures such as carotid endarterectomy (CEA), cardiac valve replacement, and catheter ablation for atrial fibrillation, these concerns have stimulated investigations to try to protect against adverse cognitive outcomes and have raised questions about the relative benefits and harms of these procedures versus alternatives and whether targeting interventions based on patient characteristics such as age and baseline cognitive function could improve patient cognitive outcomes.

Many early studies reported a high but variable incidence of post-CABG cognitive impairment. Etiological factors were thought to include anesthesia, cardiopulmonary bypass, hypoperfusion and embolic stroke, among others. However, these studies may have overestimated the incidence of persistent cognitive impairment attributable to CABG. Many studies did not adequately account 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 early and repeated cognitive testing.¹

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.² A 2012 systematic review of 29 studies that included a mix of older and newer studies reported that psychomotor speed was slightly but significantly impaired for <2 weeks after CABG, but that psychomotor speed, memory and executive functioning were slightly but significantly improved compared to baseline by 3 months.³ In the few studies reporting, these small improvements appeared sustained at 6 to 12 months. That review did not report other neuropsychological domains and did not indicate whether neuropsychological test abnormalities were associated with functional impairment. Further, one-third of included studies had only short-term (<3 months) post-procedure followup and, of the remainder, mean age was <65 years in all but four studies, limiting their relevance to the aging population that is increasingly undergoing CABG.

Although adverse post-CABG cognitive outcomes have been associated with several patient characteristics, including increased age, less education or social support, cerebrovascular or peripheral vascular disease, hypertension, diabetes, and depression,^{1, 4-7} studies of risk factors have not generally included control groups. While multiple reviews have reported no difference in cognitive risk between on and off-pump CABG,^{3, 8} 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. Though many older CEA studies reported cognitive improvements, these studies often lacked a control group and results may have benefitted from practice effects.^{9, 10} Older studies reporting post-CEA cognitive declines also often had only short-term followup, making it difficult to separate out the potential transient effects of anesthesia, pain, medications, sleep deprivation, and other hospital-related illness unrelated to the CEA. Carotid artery stenting (CAS) is a less invasive, percutaneous alternative to CEA for carotid revascularization whose association with cognition has been less studied than CEA, but some studies have raised alarms

by finding a higher frequency of imaging-detected microemboli with CAS than CEA.^{11, 12} Carotid revascularization procedures also could affect cognition by causing an acute clinical stroke or TIA, transiently altering cerebral perfusion, and from the effects of anesthesia, but also by improving cerebral circulation and lowering longer term stroke risk.¹³

In a 2011 systematic review, about half of studies of CEA and/or CAS reported improvement in at least one neuropsychological test and about half reported some decline or no change.¹⁴ The authors suggested that the mixed findings might be explained by variable followup times (including many <1 month), variability in the neuropsychological tests administered, and heterogeneity in patient populations and surgical management. About one-third of included studies also did not compare cognitive changes to those in a control group, a limitation in distinguishing between the effects of the procedure and those of patient characteristics and other causes of cognitive changes. In addition, many of the studies had a limited representation of older adults. Consequently, the review findings may have had limited applicability to the intermediate and long-term cognitive outcomes after carotid revascularization procedures in older adults. Authors suggested that the impact of patient and procedure factors on cognitive outcomes after CEA and CAS needed further examination.

The impact of cardiac valve replacement or repair procedures on intermediate and long-term cognitive outcomes in older adults also is unclear. Studies have consistently reported a high frequency of imaging-detected cerebral emboli, though with only a minority of these abnormalities associated with focal neurologic symptoms. For example, in one review of transcatheter aortic valve replacement (TAVR) studies, while most patients had ischemic defects identified on diffusion-weighted MRI days after the procedure, symptomatic stroke was only identified in about 3 percent of participants.¹⁵ Though cardiac valve procedures could adversely affect cognition through similar mechanisms as those proposed for CABG, cognitive outcomes after these procedures have been less frequently studied, especially beyond the short-term. Studies comparing surgical aortic valve replacement (AVR) and TAVR suggest a higher risk of cerebral emboli and stroke with TAVR, which also could lead to differences in cognitive outcomes, but these have been less consistently reported.¹⁶ Mitral valve procedures have been less studied, but limited data suggest that cognitive outcomes may differ between mitral valve replacement and repair.¹⁷ We have not identified any systematic reviews on cognitive outcomes after cardiac valve procedures, let alone one that addresses more than short-term outcomes and focuses on older adults, who may be at greatest risk for these adverse effects.

Relatively little is known about the cognitive effects of catheter ablation procedures for atrial fibrillation. Risk of periprocedural stroke is about 1 percent, but brain MRI studies have identified new ischemic lesions in 7 to 14 percent of patients overall, with substantial variability by ablation technique.¹⁸ Regarding clinical cognitive outcomes, a large administrative data study reported that patients with atrial fibrillation who underwent catheter ablation were at significantly lower risk for a dementia diagnosis at 1 and 3 years than those with atrial fibrillation who didn't receive ablation and were at similar risk to those without atrial fibrillation.¹⁹ However, these results could have been vulnerable to misclassification and treatment selection bias. Another small study reported that predominately middle-aged individuals who underwent catheter ablation for atrial fibrillation had both more frequent ischemic lesions on post-procedural MRI and relatively more decline in cognitive performance at 3 months in verbal but not nonverbal memory compared to healthy controls.²⁰ However, these results must be interpreted cautiously given the small number of events and the absence of between-group differences in any of the other cognitive domains tested.

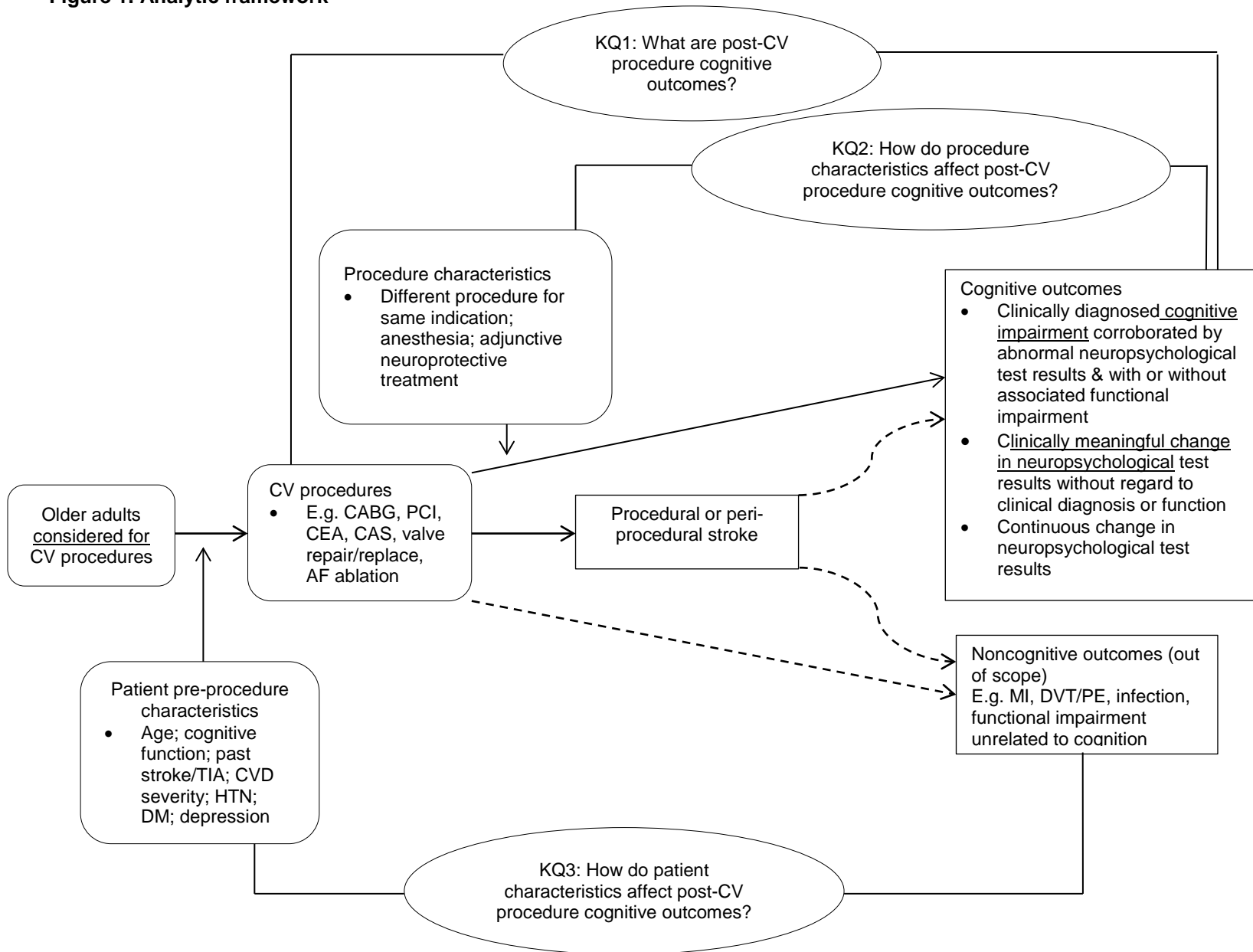
Purpose of Comparative Effectiveness Review

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. These procedures were nominated to the Agency for Healthcare Research Quality (AHRQ) for study by the project nominator, the Centers for Medicare and Medicaid Services (CMS). 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. Improving understanding of the duration, pattern and risk factors for cognitive outcomes attributable to these cardiovascular procedures 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.

Analytic Framework and Key Questions

During this project's topic refinement, AHRQ and CMS 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



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 versus 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)?

Methods

Protocol Development

We followed a formal protocol developed with AHRQ and CMS input (Appendix A).

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 July 2014 to limit the review to studies of cognitive outcomes after cardiovascular procedures that reasonably reflect current clinical practice. Appendix B contains the full search strategy.

Study Inclusion Criteria

Study Design

- We restricted the review to randomized controlled trials (RCTs), nonrandomized comparative trials, and appropriately controlled prospective observational cohort studies. We selected these study designs to minimize comparison group differences other than the cardiovascular procedure, to increase consistency in how the cardiovascular procedures evaluated within each individual study were performed, and ensure that post-procedural cognitive outcomes were assessed prospectively.

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 at least ten patients aged ≥ 65 years).
- We included studies with at least ten 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 one 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).

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 one cognitive outcome at least 3 months after the procedure.

Studies which reported only shorter-term followup were excluded to limit the potentially transient impact of factors other than the cardiovascular procedure on reported cognitive outcomes (e.g., pain, anesthesia, medications, sleep deprivation, and other unrelated hospital-related illness). Our interest in looking at cognitive outcomes measured at >12 months was to assess whether earlier onset cognitive effects persist long-term.

Given the uncertainty about whether and in what manner these cardiovascular procedures impact cognitive outcomes, we did not believe it made sense to prejudge which cognitive domains to consider while excluding others from our review. Therefore, we considered studies eligible if they assessed any measured (i.e. not self-reported) cognitive outcome, but particularly measures focusing on attention, memory, language, executive function, psychomotor speed, or visuospatial function, or a global cognitive screen (e.g. Mini-Mental State Exam [MMSE]).

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.

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 one or more neuropsychological tests that addressed one or more cognitive domains and/or brief global cognitive screening measures, though we included any objectively tested cognitive outcomes studies reported.
- Continuous measure/change in one or more of the above neuropsychological or brief global cognitive screening test results.

Setting

- Studies were eligible regardless of whether the cardiovascular procedure took place in the inpatient or outpatient setting. However, studies in which intermediate- and long-term post-procedure cognitive assessments were available only from within the inpatient setting were excluded. The purpose for this exclusion is the concern that patients who

remain inpatients >3 months after their procedure likely have experienced medical complications unrelated to their procedure that could impact their cognitive function.

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 C).

Data Extraction

For each eligible study, 1 study investigator extracted data onto pre-tested extraction forms/evidence tables. A second investigator double checked extracted data for accuracy. Differences between the two reviewers 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; and post-procedural minus pre-procedural changes in neuropsychological test scores (i.e. mean change from baseline).

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 or post-procedural minus pre-procedural changes were not directly reported by the study, but could be calculated from available data, we performed these calculations, particularly for the most commonly performed neuropsychological tests (i.e. Trail Making A, Trail Making B, Rey Auditory Verbal Learning Test, Grooved Pegboard, Verbal Fluency, Digit Symbol, Digit Span Forward, Digit Span Backward, Boston Naming Test, Vocabulary [WAIS], and Block Design). 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 risk of bias in individual studies according to recommendations from the Cochrane Handbook for Systematic Reviews of Interventions.²¹ Following categorization of studies according to their design as either interventional (RCTs, nonrandomized controlled clinical trials [i.e. controlled clinical trials or CCTs]) 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 (e.g., Alzheimer’s or vascular 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 tool²²: (1) random allocation of the subjects to the treatment groups; (2) adequacy of allocation concealment²³; (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.²⁴ However, we concluded an unclear risk of bias when at least 2 individual criteria were rated unclear and no more than one criterion was rated high-risk.

For prospective cohort studies, we assessed risk of bias using the following criteria from the AHRQ Methods Guide:²⁴ (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 followup 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.²⁴ We concluded an unclear risk of bias when at least 2 individual criteria were rated unclear and no more than one criterion was rated high-risk.

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 followup cognitive assessment (i.e., intermediate-term [3 to 12 months] and long-term [>1 year]).

To pool descriptive data on participant characteristics across multiple studies, we calculated weighted means by multiplying each variable (e.g. age) by its corresponding study sample size (n), and then dividing the sum of the products by the sum of the study sample sizes (N). Therefore, if the study had a larger sample size, it contributed more to the calculated mean of the variable in question.

We used Review Manager (RevMan) version 5.2 software to estimate relative risks and 95 percent confidence intervals for the incidence of dichotomous outcomes and standardized mean differences (effect sizes) and 95 percent confidence intervals for continuous outcomes (e.g., for mean between-group difference in followup scores).²⁵ 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).²⁶ Where possible, outcome measures were quantitatively summarized. However, this was infrequently possible because few studies had clinically comparable patient populations, cardiovascular procedure and comparison groups and reported the same cognitive outcomes in a comparable way.

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 versus 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, 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 AHRQ and the Effective Health Care Program.²⁷

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) 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. For example, in a comparison in which results suggested no statistically significant difference between treatment groups (i.e. effect size 95% confidence intervals straddled zero), results could not exclude a moderate or larger difference between groups in either direction (upper bound of effect size CI ≥ 0.5 or lower bound of CI ≤ -0.5). 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 SOE 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 L.

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.²⁸

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 AHRQ. AHRQ assigned this report to the 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.

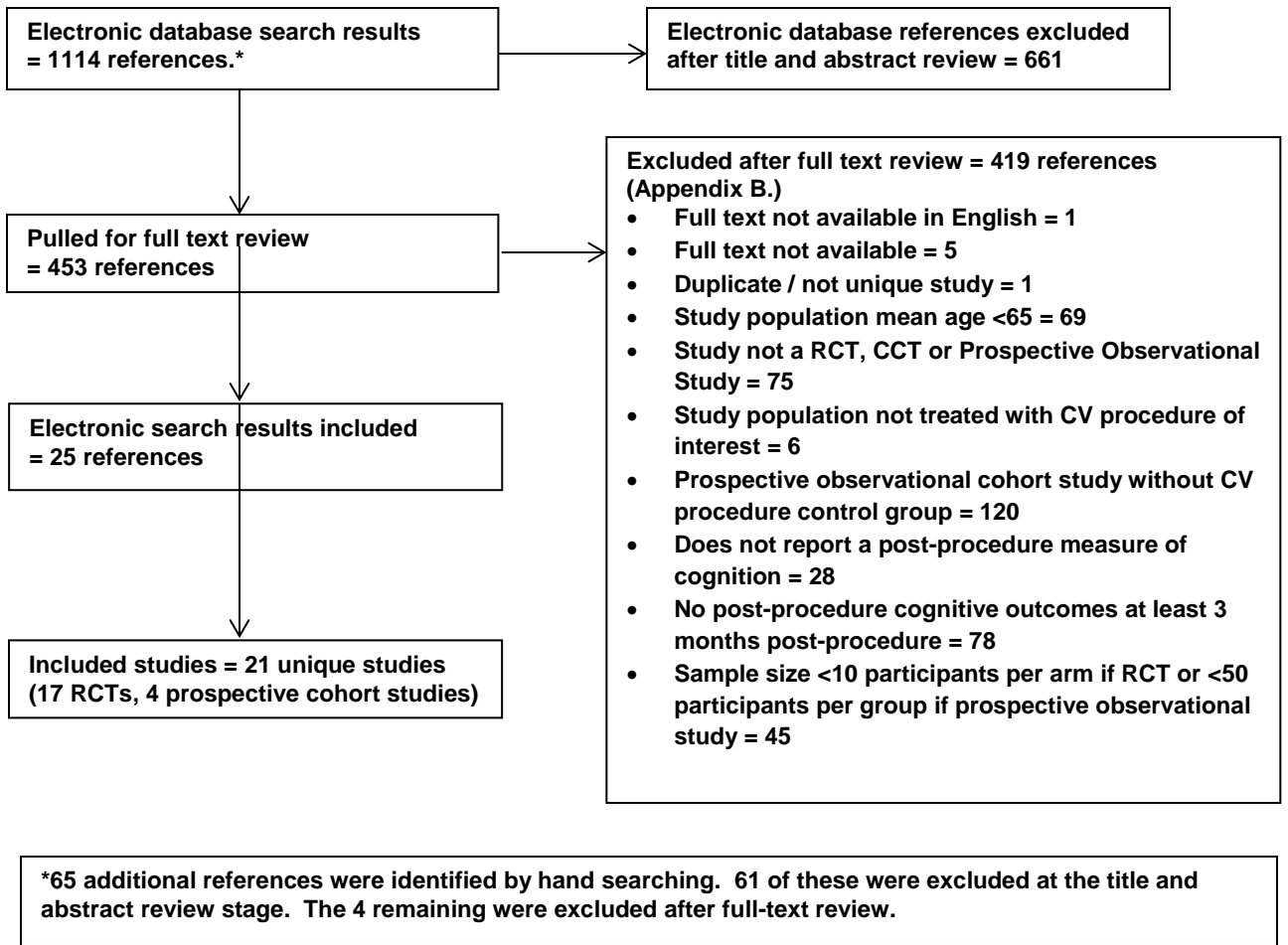
Results

Identification of Eligible Studies

From our primary electronic database search for RCTs, CCTs and prospective cohort studies reporting cognitive outcomes after selected cardiovascular procedures, we identified 563 references from MEDLINE[®], 294 references from Cochrane Central Register of Controlled Trials (CENTRAL), and 538 references from Scopus, for a total of 1114 unique references. Of these, we excluded 661 as ineligible during title and abstract review and 428 as ineligible during full-text review (Figure 2), leaving 25 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 four 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 one as ineligible based on in-depth review. Altogether, including four followup reports of eligible studies,²⁹⁻³² these sources generated 25 reports of 21 unique studies that met eligibility criteria (Figure 2).^{7, 12, 33-51}

All eligible studies were published in peer-reviewed English-language journals.

Figure 2. Literature search flowchart



Study Characteristics

Study Design

Among 21 eligible studies, 17 were RCTs and 4 were prospective cohort studies.^{34, 38, 48, 50} Treatment duration for the RCTs ranged from 3 to 60 months, with only one trial longer than 12 months.³⁰ Treatment duration for the prospective cohort studies duration ranged from 3 to 72 months, with only one study longer than 12 months.³⁸

Treatment Groups

Among eligible studies, most (n=15) evaluated cognitive outcomes after CABG. Of the CABG studies, one observational study compared cognitive outcomes between three 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.³⁸ Each of the other CABG studies were RCTs that compared cognitive outcomes between two different approaches to CABG, including five that compared on- versus off-pump CABG,^{33, 35-37, 39} three that compared CABG performed under hypothermic conditions versus under normothermic conditions,^{37, 41, 42} one that compared on-pump CABG using conventional extracorporeal bypass versus minimal extracorporeal bypass,⁴⁰ one that compared CABG performed under hyperbaric oxygen conditions versus under atmospheric oxygen conditions,⁴³ one that compared CABG using fentanyl versus propofol,⁷ one that compared CABG using high versus low dose fentanyl,⁴⁴ one that compared CABG using cell saver versus using cardiotomy suction,⁴⁵ one that compared CABG with high versus low mean arterial blood pressure maintained during cardiopulmonary bypass,⁴⁶ and one that compared CABG with preoperative angiotensin-receptor blocker treatment versus CABG with pre-operative placebo.⁴⁷

Three eligible studies evaluated cognitive outcomes after carotid artery revascularization, including one RCT that compared CEA versus CAS,⁴⁹ one RCT that compared CEA versus carotid angioplasty,¹² and one prospective cohort study that compared CEA versus laparoscopic cholecystectomy.⁵⁰

Two eligible studies evaluated post-procedural cognitive outcomes between two different approaches to tissue aortic valve replacement (AVR), including one RCT that compared participants assigned to undergo surgical AVR under hypothermic conditions versus under normothermic conditions⁵¹ and one observational study that compared surgical versus transcatheter aortic valve replacement (TAVR).³⁴ Another prospective cohort study compared CABG alone versus surgical cardiac valve repair (aortic or mitral) alone or combined with CABG.⁴⁸

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

Cognitive Outcome Measures

Among the 21 eligible studies, none reported post-cardiovascular procedure incidence of clinical dementia, mild cognitive impairment or any other cognitive-related clinical diagnosis.

All studies reported results for one or more neuropsychological tests in multiple cognitive domains and/or results of global cognitive screening tests. Consistent with the recommendations of a 1995 consensus statement on cognitive testing of patients undergoing CABG,² the most

common cognitive domains and individual tests reported within eligible studies are listed below. A description of the main neuropsychological tests used in eligible studies according to their primary cognitive domain tested follows here, though because many neuropsychological tests assess more than one cognitive domain, results for each neuropsychological test are presented in outcomes tables (Appendix D) for each cognitive domain it addresses.

- **Attention:** n=18 studies (Trail Making Test A, n=16; Digit Span Forward, n=11);
- **Memory:** n=18 (Rey Auditory Verbal Learning Test, n=9; nonverbal memory tests, n=5);
- **Language:** n=12 (verbal fluency tests, n=10; Boston Naming Test, n=4);
- **Executive:** n=20 (Trail Making Test B, n=18; Digit Symbol/Symbol Digit, n=11; Digit Span Backward, n=10)
- **Visuospatial functioning:** n=7 (Block Design, n=2)
- **Psychomotor:** n=14 (Grooved Pegboard, n=10).

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

In addition to the individual neuropsychological test data, 12 studies specified abnormal absolute or change thresholds for each administered neuropsychological test and then defined incident "cognitive impairment" or "cognitive decline" based on whether participants performed abnormally or worsened by some threshold on some minimum number of these tests (Appendix I). The most frequently used definitions were ≥ 20 percent and ≥ 1 SD decline in at least two cognitive tests compared to baseline, respectively. However, some studies didn't define deterioration, others required change in only one test, and no two studies used the same set of neuropsychological tests.

Eight studies administered global cognitive screening tests, including the MMSE (n=6), MoCA (n=3) and 3MS (n=1), though in some cases these measures were only administered at baseline.

Participant Characteristics

Demographics

The 21 eligible studies included 7802 participants (range 46 to 4752). Study participants were predominately male (weighted mean 80 percent) and had a weighted mean age of 68 years (range of means of 65 to 76 years, including means between 65 to 69 years in all but four studies) (Appendix E). In studies that reported data on education, mean years of education was 11 (range 7 to 14 years; 6 studies with 906 participants reporting) and 40 percent of participants attended any post-secondary program (range 13 to 61 percent; 4 studies with 684 participants reporting). In the two trials that reported data on race (574 participants), 92 percent of participants were Caucasian. One study was conducted in both North America and Europe (61 percent of all study participants), six studies were conducted only in North America (17 percent of all study participants), 11 only in Europe (14 percent), and three in Australasia (8 percent).

Comorbid Conditions

Few participants in the CABG studies had a past history of stroke. Mean prevalence was 6 percent (range 0 to 8 percent) in 10 studies reporting. In contrast, in the carotid revascularization

studies, all participants in two studies^{12, 49} and half in one study⁵⁰ had recent symptomatic internal carotid artery stenosis (i.e., ischemic stroke, transient ischemic attack, and/or amaurosis fugax). One of the valve surgery studies excluded patients with prior stroke, while the other two valve studies didn't report data on pre-procedural stroke history. Prevalence of other co-morbidities included diabetes 39 percent (range of means 0 to 47 percent; 20 studies reporting) and myocardial infarction 36 percent (range of means 9 to 73 percent; 13 studies reporting). Two CABG studies excluded participants with depression, while no other studies reported data on prevalence of depression.

Cognitive Function

Four studies excluded participants with dementia or an abnormal baseline cognitive screening test^{29, 41, 47, 50} and two studies excluded participants with mental retardation or a learning disorder.^{43, 50} Within eligible studies, using age, gender and education data to compare individual study populations with normative data, most participants appeared cognitively intact prior to their cardiovascular procedures as measured by IQ, global cognitive screening tests, and neuropsychological memory tests. However, some participants had baseline deficits on timed tests, including of set shifting (Trails B) and motor performance (Grooved Pegboard).

More specifically, for studies that reported IQ estimates (n=5 studies), baseline scores ranged from 95.8 to 115, all within the normal range. For studies that reported global cognitive screening tests, baseline scores for the Montreal Cognitive Assessment (MoCA) (n=3 studies) and Mini Mental State Exam (MMSE) (n=6 studies) ranged from 23.2 to 27.1 and from 25 to 30, respectively. These are within the normal range, with the exception of the lowest reported scores for each test. Baseline raw scores for the Rey Auditory Verbal Learning Test (RAVLT) sum of learning trials and delayed recall (n=9 studies) ranged from 33.6 to 53.9 and from 6.0 to 8.4, respectively. All these scores are in the normal range except for the study with the lowest sum of learning trials score.

For the timed tests, baseline raw scores for Trial Making Test A (n=16 studies) ranged from 34 to 68.8 seconds while those for Trail Making Test B (n=18 studies) ranged from 82 to 163.7. Based on the demographics for their specific study sample, few study mean scores fell in the impaired range for Trails A but approximately half the study means were in the impaired range for Trails B. In addition, Grooved Pegboard scores (n=10 studies) for the dominant and non-dominant hand ranged from 81.3 to 108 seconds and 97.2 to 119 seconds, respectively, with about half the study mean scores falling in the impaired range based on their individual study demographics.

Individual Study Risk of Bias

Among the 17 eligible RCTs, ten were rated as having a moderate risk of bias, and seven were rated as having unclear risk of bias (Appendix F). Risk of bias related to randomization was rated low in 12 trials and was unclear in five trials. Risk of bias related to masking of the outcome assessment was rated low in 13 trials, and was unclear in four trials. Risk of bias related to use of intention-to-treat principles was rated as high in 15 trials (e.g., analyses performed in study completers only) and was unclear in two trials. Risk of bias related to selective reporting of prespecified outcomes was rated low in all eligible trials. Fourteen of the 17 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 four eligible prospective cohort studies, three were rated as having a high risk of bias, and one was rated as having moderate risk of bias (Appendix F). For similarity of prognostic factors between baseline comparison groups and in study accounting for attrition bias, three studies were rated as high risk of bias and one low risk of bias. Risk of bias related to masking of the outcome assessment was rated as low in one study and unclear in three studies. All studies were rated low risk for selective reporting of prespecified outcomes. All prospective cohort studies reported withdrawals, which were 18 to 19 percent at 3 months in two studies reporting, 32 percent at 6 months in one study reporting, 6 to 17 percent at 1 year in two studies, and 47 percent at 3 years and 37 percent at 6 years in one 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

- Only one study in adults aged ≥ 65 years compared a cardiovascular procedure of interest versus medical management and reported intermediate and/or long-term cognitive outcomes and just three compared one of these procedures with a less invasive alternative. All had substantial quality limitations, with either moderate or high risk of bias.
- Based on these data, insufficient strength evidence from one study suggested that CABG was not associated with any decline in cognitive function in older adults for up to 6 years, both compared to patients managed with medical therapy and compared to a pre-surgery baseline.
- Low strength evidence from 1 study suggested that there were no significant differences in cognitive function at 6 months between older adults who underwent CEA versus CAS. While results from a second study also suggested that there were no significant differences at 6 months after CEA versus carotid angioplasty, SOE for this finding was rated insufficient. There appeared no difference within any treatment groups in either of these studies compared to pre-operative levels. Although, risk of incident cognitive impairment appeared lower with CEA than for carotid angioplasty in one small study, this finding was not statistically significant.
- Results from one study suggested that older adults who underwent TAVR were significantly more likely than those who underwent AVR to experience incident cognitive decline at 3 months, but because results may have been attributable to their older age, more limited education, increased morbidity, and differences in outcome definitions between treatment groups, SOE was rated insufficient.

Coronary Artery Revascularization

- Insufficient strength evidence from one observational study (high risk of bias) that compared CABG with medical management in older patients with coronary artery disease reported no statistically significant differences between treatment groups in any reported neuropsychological test at 1 and 6 years. Within the CABG and medical

management groups, there were small to moderate improvements in memory versus baseline at 1 year, but no difference in any cognitive test versus baseline at 6 years.^{31, 32, 38}

- Though statistical power from this one observational study was low and losses to followup could have favorably biased results in favor of the CABG group, the small effect sizes both within and between the CABG and medical management groups suggest that the intermediate and long-term cognitive impact of CABG in these older adults may be small.
- No eligible RCT or CCT compared CABG with medical management in older adults and reported intermediate or long-term cognitive outcomes.
- No eligible RCT, CCT or prospective cohort study compared PCI with medical management in older adults and reported intermediate or long-term cognitive outcomes.
- No eligible RCT, CCT or prospective cohort study compared different types of coronary artery revascularization procedures with each other (e.g., CABG versus PCI) in older adults and reported intermediate or long-term cognitive outcomes.

Carotid Artery Revascularization

- No eligible RCT, CCT or prospective cohort study compared any carotid artery revascularization procedure (i.e., CEA, CAS, or carotid angioplasty) with medical management in older adults and reported intermediate or long-term cognitive outcomes.
- Low strength evidence from one RCT that compared CEA versus CAS in older adults and reported no statistically significant difference between treatment groups for the outcome of change from baseline to 6 months on any individual neuropsychological domain tested.⁴⁹
- Insufficient strength evidence from one RCT that compared CEA versus carotid angioplasty in older adults and reported no statistically significant difference in risk of incident “cognitive impairment” derived from a composite of neuropsychological test measures or in change from baseline or absolute levels at followup in 10 of 11 individual neuropsychological test results at 6 months.¹²
- Although both RCTs had limited statistical power and moderate risk of bias, results suggest that if any intermediate-term cognitive differences exist between CEA and either CAS or carotid angioplasty they may be small.
- Insufficient strength evidence from one observational study that reported that older patients who underwent CEA had a 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.⁵⁰

Cardiac Valve Replacement/Repair

- No eligible RCT, CCT or prospective cohort study compared cardiac valve replacement/repair with medical management in older adults and reported intermediate or long-term cognitive outcomes.
- One prospective cohort study reported that older patients who underwent TAVR were significantly more likely to experience clinically significant cognitive decline at 3 months than those who underwent AVR, but because results may have been attributable to their older age, more limited education, increased morbidity, and differences in how this

outcome was defined between these two treatment groups, SOE for this result was rated insufficient.

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

Ablation for Atrial Fibrillation

- No eligible RCT, CCT or prospective cohort study compared surgical or transcatheter ablation for atrial fibrillation versus each other or versus medical management in older adults and reported intermediate or long-term cognitive outcomes.

Combined CV Procedures

- Insufficient strength evidence from one prospective cohort study that compared CABG alone with aortic or mitral valve surgery alone or valve surgery combined with CABG in older adults and reported no statistically significant difference in 13 of 14 neuropsychological tests at 6 months.⁴⁸

Table 1. Summary of evidence on association of selected cardiovascular procedures versus control group with intermediate and long-term cognitive outcomes in older adults (KQ 1)

Interventions, Studies (Study Quality)	Cognitive Outcomes	Strength of Evidence*
Coronary Artery Revascularization		
CABG vs. Medical Management 1 prospective, observational study, n=326 (high risk of bias) ^{31, 32, 38}	<i>Clinically diagnosed:</i> No results reported. <i>Individual neuropsychological (NP) tests:</i> No statistically significant differences between treatment groups in any absolute test score measured at endpoint (range of effect sizes -0.32 to 0.24). No statistically significant differences between treatment groups in mean change from baseline in selected NP tests.† <i>Composite neuropsychological test cognitive impairment (NPCI):</i> No results reported	Clinical: Insufficient Individual NP Tests: Insufficient Composite NPCI: Insufficient
Carotid Artery Revascularization		
CEA vs. CAS: 1 RCT, n=140 (moderate risk of bias) ⁴⁹	<i>Clinically diagnosed:</i> No results reported. <i>Individual NP tests:</i> No statistically significant differences between treatment groups when comparing mean change from baseline in selected NP tests.† <i>Composite NPCI:</i> No results reported	Clinical: Insufficient Individual NP Tests: Low Composite NPCI: Insufficient
CEA vs. Carotid Angioplasty 1 RCT, n=46 (moderate risk of bias) ¹²	<i>Clinically diagnosed:</i> No results reported. <i>Individual NP tests:</i> No statistically significant differences between treatment groups in any absolute test score measured at endpoint in 10 of 11 measures reported. No statistically significant differences between treatment groups when comparing mean change from baseline in selected NP tests.† <i>Composite NPCI:</i> 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])	Clinical: Insufficient Individual NP Tests: Insufficient Composite NPCI: Insufficient

Interventions, Studies (Study Quality)	Cognitive Outcomes	Strength of Evidence*
CEA vs. Laparoscopic Cholecystectomy: 1 prospective, observational study, n=213 (high risk of bias) ⁵⁰	<i>Clinical cognitive outcomes:</i> No results reported. <i>Individual NP tests:</i> Small but statistically significantly greater improvement from baseline to 12 months in CEA group vs. cholecystectomy group (MMSE [0.3 vs. 0.0, p<.01], and MoCA [1.0 vs. 0.1, p<.01; between group effect size 0.58 ³³]). <i>Composite NPCI:</i> No results reported.	Clinical: Insufficient Individual NP Tests: Insufficient Composite NPCI: Insufficient
Cardiac Valve Replacement/Repair		
CABG vs. Cardiac Valve Replacement with or without CABG: 1 prospective, observational study, n=109 (moderate risk of bias) ⁴⁸	<i>Clinical cognitive outcomes:</i> No results reported. <i>Individual NP tests:</i> No statistically significant between-group difference in proportion of participants rated as having a deficit for 13 of 14 neuropsychological tests at followup. <i>Composite NPCI:</i> No results reported.	Clinical: Insufficient Individual NP Tests: Insufficient Composite NPCI: Insufficient
AVR vs. TAVR: 1 prospective, observational study, n=64 (high risk of bias) ³⁴	<i>Clinical cognitive outcomes:</i> No results reported. <i>Individual NP tests:</i> No direct comparisons between treatment arms were done. <i>Composite NPCI:</i> Lower after AVR compared to TAVR (6% vs. 28%; p=0.04).	Clinical: Insufficient Individual NP Tests: Insufficient Composite NPCI: Insufficient
Ablation for Atrial Fibrillation		
No eligible studies		

Abbreviations: AVR = surgical aortic valve replacement; CABG = coronary artery bypass grafting; CAS = carotid artery stenting; CEA = carotid endarterectomy; CI = confidence intervals; KQ = Key Question; MMSE = Mini-Mental State Exam; MoCA = Montreal Cognitive Assessment; NP=neuropsychological; “NPCI” = cognitive impairment as defined from a composite of neuropsychological test results; RCT = randomized controlled trial; RR = risk ratio; SOE = strength of evidence; TAVR = transcatheter aortic valve replacement.

*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., Two 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

†Selected NP tests included Trail Making A, Trail Making B, Rey Auditory Verbal Learning Test, Grooved Pegboard, and Verbal Fluency. Number of selected NP tests implemented varied between studies and sometimes between intervention groups.

Detailed Findings

Coronary Artery Revascularization

CABG Versus Medical Management

We found no RCTs or CCTs and only one prospective cohort study (n=326) that compared CABG versus medical management and reported cognitive outcomes (Appendix G, Table 1).^{31, 32, 38}

In the cohort study, at both 1 and 6 years of followup, there were only small differences in the absolute test scores between either the on-pump or off-pump CABG and medical management groups for any of the individual neuropsychological tests reported (range of effect sizes -0.32 to 0.24) that were not statistically significant (Appendix J, Table 1). In within group comparisons, compared to their test scores prior to the procedure, both the CABG groups and the medical management group had moderate improvements in the Rey Auditory Verbal Learning Test at 1 year (range of effect sizes -0.39 to -0.57) that were statistically significant but that were

no longer present at 6 years (Appendix M, Table 1). For other neuropsychological tests, there was a general pattern for small not statistically significant improvements from baseline to 1 year that were no longer apparent at 6 years.

Although this study had low statistical power to detect small differences in neuropsychological test results and the greater drop-out rate in the CABG groups may have biased results in their favor if participants with greater cognitive decline were less likely to followup, study results suggested that CABG was not associated with cognitive decline during followup as long as 6 years and that there were no significant differences in intermediate and long-term cognitive function between the CABG and medical management groups. However, primarily because this study was rated as having high risk of bias, SOE for these results was graded as insufficient.

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 H, Table 1; Appendix I, Table 1).

PCI Versus Medical Management

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

CABG Versus PCI

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

Of note, 14 RCTs assigned all participants to CABG and randomized them between two different methods of CABG (e.g., on versus off-pump, surgery under hypothermic conditions versus 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 Versus Medical Management

No eligible studies compared CEA, CAS or carotid angioplasty to medical management of carotid artery disease and reported cognitive outcomes in older adults.

We identified one 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 G, Table 3).⁵⁰ MMSE and MoCA cognitive screening measures were the only cognitive outcomes reported. This study reported statistically significant improvements of mostly small magnitude in the symptomatic CEA group from baseline to both 3 and 12 months (0.4 and 0.3 point improvement on MMSE, respectively, with effect sizes 0.35 to 0.44; 0.9 and 1.0 point improvement on MoCA, respectively, with effect sizes 0.48 to 0.62) (Appendix M, Table 2). These improvements were generally statistically significantly larger than the changes from baseline seen in the laparoscopic cholecystectomy group (e.g. effect sizes for the between-group difference in the mean MoCA changes were 0.52 to 0.58 at 3 months and 0.35 to 0.36 at 12 months) (Appendix J, Table 3). Between the asymptomatic CEA group and the laparoscopic cholecystectomy group, there were no differences in any cognitive measures at any time point, or when comparing change from

baseline to any followup time point. This study did not report results for post-surgical incidence of any cognitive-related clinical diagnosis (Appendix H, Table 3), for incident cognitive impairment as defined by a combination of neuropsychological tests (Appendix I, Table 3), or for any individual neuropsychological tests other than the MMSE and MoCA (Appendix J, Table 3). SOE for findings from this study were graded insufficient.

CEA Versus CAS or Carotid Angioplasty

We identified one eligible RCT that compared CEA versus CAS (n=140)⁴⁹ and one that compared CEA versus carotid angioplasty (n=46) (Appendix G, Table 3).¹² Neither study reported results for post-surgical incidence of any cognitive-related clinical diagnosis (Appendix H, Table 3).

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 I, Table 3). However, 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 J, Table 3). SOE for this latter outcome was graded as low.

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 percent versus 38 percent; RR, 0.47 [95% CI, 0.16 to 1.35]) (Appendix I, Table 3). In addition, no statistically significant difference was found between these treatment groups in change from baseline to 6 months or in absolute scores at 6 months in 10 of 11 individual neuropsychological tests measured (Appendix J, Table 3). SOE for the individual neuropsychological test outcomes was graded as insufficient.

Although these two 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 may be small.

Cardiac Valve Replacement

Cardiac Valve Replacement Versus No Cardiac Valve Replacement

We identified no eligible study that compared either surgical or transcatheter cardiac valve replacement versus cardiac valve repair or medical management and reported cognitive outcomes.

Surgical Versus Transcatheter Cardiac Valve Replacement

We identified no eligible RCTs or CCTs and only one prospective observational cohort study that compared surgical versus transcatheter cardiac valve replacement and reported cognitive outcomes. In this observational study, 17 patients with aortic valve stenosis considered surgical candidates underwent surgical AVR, while 27 with aortic valve stenosis who were significantly older and less educated and at higher surgical risk underwent transcatheter TAVR³⁴ (Appendix G, Table 2). This study did not report results for post-surgical incidence of any cognitive-related clinical diagnosis (Appendix H, Table 2). Both groups completed a battery of neuropsychological tests before and 3 months after the procedure, with the AVR patients administered more tests and only two tests completed by both groups. Based on a study definition for clinically significant cognitive decline as being when the number of tests with

decline (followup score ≥ 1 SD worse than baseline) exceeded the number with improvement (followup score ≥ 1 SD better than baseline) by at least two for the TAVR patients and at least three for the AVR patients, TAVR patients were significantly more likely to experience cognitive decline (28 percent versus 6 percent, $p=0.04$) (Appendix I, Table 2). With respect to individual neuropsychological test results (Appendix J, Table 2), in the TAVR patients who provided followup data (26 percent died at 3 months), there were no statistically significant differences from baseline in any test at 3 months. In the AVR group, there also were no cognitive tests that were impaired at 3 months compared to baseline. Due to the substantial differences in patient populations, outcome measures and followup, direct comparisons of cognitive outcomes between these two treatment groups were subject to considerable bias, as a consequence of which SOE for between-group comparisons was graded as insufficient. Within study group comparisons showed small to moderate differences in neuropsychological test results between baseline and 3 months, none of which were statistically significant, though results were limited by small sample sizes.

Of note, we identified one eligible RCT that compared aortic valve replacement performed under hypothermic conditions versus aortic valve replacement performed under normothermic conditions.⁵¹ 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 in older adults and reported cognitive outcomes.

Combined Cardiovascular Procedures

CABG Versus Cardiac Valve Replacement With or Without CABG

We identified one 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 surgical aortic or mitral valve replacement alone or surgical valve replacement in combination with CABG ($n=109$ participants) (Appendix G, Tables 1 and 2).⁴⁸ This study did not report results for post-surgical incidence of any cognitive-related clinical diagnosis (Appendix H, Tables 1 and 2) or incident “cognitive impairment” as defined by a composite of neuropsychological tests (Appendix I, Tables 1 and 2). In the 68 percent 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 J, Tables 1 and 2). SOE for this between treatment comparison was graded insufficient.

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 versus catheter-based/stenting; anesthesia type; adjunctive neuroprotective treatments)?

Key Findings

Overview

- Because strokes and TIAs were uncommon in eligible studies and risk for these events did not appear different between treatment groups, we could not determine whether risk for adverse intermediate or long-term cognitive outcomes in older adults following these cardiovascular procedures is affected by procedural and peri-procedural stroke or TIA.
- We found low SOE that intermediate and long-term cognitive outcomes are not significantly different between older adults assigned to on versus off-pump CABG.
- We found mostly low to moderate strength evidence that intermediate and long-term cognitive outcomes are not significantly different between individuals assigned to hypothermic versus normothermic CABG, and insufficient strength evidence for no difference between hypothermic versus normothermic AVR surgery.
- We found no evidence from eligible studies enrolling older adults 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 uncommon in eligible studies of older adults (i.e., one or fewer in each treatment group in most of the 10 coronary and carotid revascularization studies that reported strokes and the four 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 SOE from five RCTs that compared on versus off-pump CABG in older adults 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 individual neuropsychological test results or global cognitive screening tests.
- Insufficient SOE from one prospective cohort study that compared on versus off-pump CABG in older adults 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).^{31, 32, 38}
- Low SOE from three RCTs that compared hypothermic versus normothermic CABG in older adults and reported no statistically significant differences between treatment groups in risk of incident “cognitive impairment” defined from a composite of neuropsychological tests and low to moderate SOE that treatment groups did not differ in change from baseline or in absolute levels at followup in individual neuropsychological test results.

- Low SOE from one RCT that, when compared to older adults 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 percent for MECC versus 61 percent for CECC; RR, 0.34 [95 percent CI, 0.16 to 0.73]). Low SOE that participants in the MECC group performed statistically significantly better than those assigned to CECC in six of seven neuropsychological tests reported.⁴⁰
- Insufficient SOE from each of six additional RCTs that compared different versions of CABG in older adults and reported no statistically significant between-group differences in either risk of incident “cognitive impairment” defined from a composite of neuropsychological tests, but a mix of insufficient to low SOE for no difference between these different versions of CABG in any individual neuropsychological test results or global cognitive screening tests.

Effect of Other Procedural Characteristics on Cognitive Outcomes after Carotid Artery Revascularization

- No eligible RCT, CCT or prospective cohort study enrolled older adults 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 SOE from one RCT that compared surgical AVR under hypothermic conditions versus AVR under normothermic conditions in older adults and reported no statistically significant between-group differences in MMSE or Trail Making A tests at up to 4 months.⁵¹
- No eligible RCT, CCT or prospective cohort study enrolled older adults 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 eligible RCT, CCT or prospective cohort study enrolled older adults 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 in older adults (KQ 2)

Interventions, Studies (Study Quality)	Cognitive Outcomes	Strength of Evidence*
Coronary Artery Revascularization†		
On vs. Off-Pump CABG 5 RCTs, n= up to 2349 (3 with moderate risk of bias, 2 with unclear risk of bias); ^{29, 33, 36, 37, 39} and 1 prospective, observational study, n=227 (high risk of bias) ³¹	<i>Clinically diagnosed:</i> No results reported. <i>Individual neuropsychological (NP) tests:</i> No statistically significant difference between treatment groups (n=6 studies) in any absolute followup test score except in 1 of 16 measures in 1 RCT, and in 2 of 24 measures in 1 prospective cohort study. Among all studies, no statistically significant differences between treatment groups in mean change from baseline in selected NP tests,‡ except for in 2 measures in only 1 RCT (Trail Making B and Verbal Fluency). ³⁹ <i>Composite neuropsychological test cognitive impairment (NPCI):</i> No statistically significant difference between treatment groups in 4 RCTs (n=320).	Clinical: Insufficient Individual NP Tests: Low (RCTs), Insufficient (prospective observational study) Composite NPCI: Low (RCTs), Insufficient (prospective observational study)
Hypothermic vs. Normothermic CABG 3 RCTs, n=610 (moderate risk of bias) ^{30, 37, 41, 42}	<i>Clinically diagnosed:</i> No results reported. <i>Individual NP tests:</i> No statistically significant difference between treatment groups (n=3 trials) except in 1 of 17 measures in 1 trial. No statistically significant differences between treatment groups when comparing mean change from baseline in selected NP tests.‡ <i>Composite NPCI:</i> No statistically significant difference between treatment groups.	Clinical: Insufficient Individual NP Tests: Moderate for 3 domains, Low for 2 domains, and Insufficient for 1 domain Composite NPCI: Low
Minimal vs. Conventional Extracorporeal (on-pump) CABG 1 RCT, n=64 (moderate risk of bias) ⁴⁰	<i>Clinically diagnosed:</i> No results reported. <i>Individual NP tests:</i> Statistically significantly better performance in 6 of 7 administered NP tests at 3 months, including those addressing attention, executive, memory, visual/spatial, and psychomotor domains. <i>Composite NPCI:</i> Reduced risk (21 vs. 61%; RR, 0.34 [CI, 0.16 to 0.73])	Clinical: Insufficient Individual NP Tests: Low for all domains except Insufficient for language Composite NPCI: Low
Carotid Artery Revascularization		
No eligible studies		
Cardiac Valve Replacement/Repair		
Hypothermic vs. Normothermic AVR 1 RCT, n=60 (unclear risk of bias) ⁵¹	<i>Clinical cognitive outcomes:</i> No results reported. <i>Individual NP tests:</i> No statistically significant difference between treatment groups in both tests administered (MMSE, Trail Making A) at up to 4 months. <i>Composite NPCI:</i> No results reported.	Clinical: Insufficient Individual NP Tests: Insufficient Composite NPCI: Insufficient
Ablation for Atrial Fibrillation		
No eligible studies		

Abbreviations: AVR = surgical aortic valve replacement; CABG = coronary artery bypass grafting; CI = confidence intervals; KQ = Key Question; MMSE = Mini-Mental State Exam; NP = neuropsychological; NPCI = cognitive impairment as defined from a composite of neuropsychological test results; 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 difference between treatment group differences in either risk of NPCI or in any individual neuropsychological test result.

‡Selected NP tests included Trail Making A, Trail Making B, Rey Auditory Verbal Learning Test, Grooved Pegboard, and Verbal Fluency. Number of selected NP tests implemented varied between studies and sometimes between intervention groups.

Detailed Findings

Impact of Stroke/TIA on Post-Procedural Cognitive Outcomes

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 21 eligible studies, 12 reported data on strokes and four on TIAs occurring during or after the cardiovascular procedure (Appendix K, Tables 1-3). In the studies that reported these events, occurrence was infrequent and was not statistically significantly different between treatment groups. All treatment groups had one or fewer strokes in six studies,^{29, 34, 36, 39, 40, 51} while in a another study stroke incidence was reported to be zero in patients treated with CEA but was not reported for the cholecystectomy control group.⁵⁰ Stroke incidence was ≤ 4 percent and not statistically significantly different between treatment groups in four additional studies.^{7, 33, 38, 44} Last, stroke rate was not reported but was stated to be not significantly different between CEA and CAS in one trial,⁴⁹ and the apparently lower risk of stroke in one trial that randomized 106 patients undergoing CABG to candesartan versus placebo was not statistically significant (4.7 percent versus 11.4 percent; RR, 0.41 [95% CI, 0.08 to 2.00]).⁴⁷ For TIAs, all treatment groups had no TIA in two studies;^{39, 40} TIA incidence was ≤ 4 percent and not significantly different between treatment groups in 1 study;³⁸ and TIA incidence was 2 percent in patients treated with CEA but was not reported for the cholecystectomy control group in an additional study.⁵⁰

Impact of Procedure Characteristics on Cognitive Outcomes

Coronary Artery Revascularization

Fourteen RCTs enrolled older adults undergoing CABG and randomized them with respect to one aspect of the CABG procedure (e.g., on versus off-pump, surgery under hypothermic conditions versus 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 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. The one possible exception came from one small RCT in which older adults randomized to on-pump CABG with minimal extracorporeal bypass performed statistically significantly better on all but one individual neuropsychological test and were less likely to have incident cognitive impairment than those assigned to CABG with conventional extracorporeal bypass.

CABG: On- Versus Off-Pump

We identified five RCTs^{33, 35-37, 39} and one observational study^{31, 32, 38} that compared CABG performed on-pump versus off-pump and reported cognitive outcomes (Appendix G, Table 1). None of the six studies reported post-CABG incidence of clinical dementia, mild cognitive impairment or any other cognitive-related clinical diagnosis (Appendix H, Table 1). All five RCTs reported risk of incident cognitive impairment defined as a composite of individual neuropsychological tests at 3 to 12 months after surgery, and none reported a statistically significant difference in risk between treatment groups (Appendix I, Table 1). There also were no statistically significant differences between treatment groups in change from baseline or in absolute test score at followup for any individual neuropsychological test in any trial except for in one of 16 measures in one trial that favored the off-pump group (Appendix J, Table 1).³⁹ SOE for these results was graded low.

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 H, Table 1; Appendix I, Table 1). There also were no statistically significant differences between treatment groups in change from baseline for any individual neuropsychological test. Within treatment groups, at 12 months memory was statistically significantly improved in both groups, while Trails A and Grooved Pegboard tests were improved only in the on-pump group. At 6 years, by which time there was an additional 20 to 25 percent loss to followup, there were no statistically significant differences from baseline in any neuropsychological test or global cognitive screening test. (Appendix M, Tables 1, 5, 8, 11 and 14). SOE for all between-group outcome comparisons from this cohort study was graded insufficient.

CABG: Hypothermic Versus Normothermic

We identified three RCTs that compared CABG performed under hypothermic conditions versus CABG under normothermic conditions in older adults and reported cognitive outcomes,^{37, 41, 42} one of which compared hypothermic on-pump versus normothermic off-pump CABG (Appendix G, Table 1).³⁷

None of the three trials reported post-CABG incidence of clinical dementia, mild cognitive impairment or any other cognitive-related clinical diagnosis (Appendix H, Table 1). Though all three studies 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 months^{37, 41} and 5 years³⁰ in any of these trials (Appendix I, Table 1). SOE for these results was low.

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 versus -0.3; effect size, 0.44 [95% CI, 0.18 to 0.70]) in one study (Appendix J, Table 1).⁴¹ However, there were no statistically significant between-treatment group differences in mean scores 12 months after surgery,³⁷ or in change between pre-CABG levels and results 3 months to 5 years after surgery^{30, 41} in any other individual neuropsychological measure reported. SOE for these results mostly ranged between low and moderate.

CABG: Anesthetic Regimens

We identified two RCTs that compared cognitive outcomes between patients who underwent CABG performed using one anesthetic regimen versus CABG performed using a different anesthetic regimen (Appendix G, Table 1). One trial reported cognitive outcomes up to 6 months post-procedure between one group randomized to fentanyl and a second group assigned propofol (n=180).⁷ A second trial compared cognitive outcomes up to 12 months post-CABG between groups that received high versus low dose fentanyl, respectively (n=350).⁴⁴ Neither study reported outcomes for any cognitive-related clinical diagnosis (Appendix H, 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 (SOE insufficient) or in any individual neuropsychological test reported (mostly low SOE) (Appendix I, Table 1).

CABG: Miscellaneous Procedure Methods

Five other RCTs each compared one approach to CABG versus another, respectively performing CABG under hyperbaric oxygen conditions versus under atmospheric oxygen conditions (n=64),⁴³ using cell saver versus using cardiotomy suction (n=226),⁴⁵ maintaining high versus low mean arterial blood pressure during cardiopulmonary bypass (n=248),⁴⁶ using preoperative angiotensin-receptor blocker treatment versus pre-operative placebo (n=106).⁴⁷ and on-pump using minimal versus conventional extracorporeal bypass (MECC versus CECC) (n=64) (Appendix G, Table 1).⁴⁰

None of these five trials reported post-CABG incidence of clinical dementia, mild cognitive impairment, or any other cognitive-related clinical diagnosis (Appendix H, Table 1).

Four of the five trials reported results for incident cognitive impairment defined by a study-specific composite of neuropsychological tests and for several individual neuropsychological tests (Appendix I, Table 1; Appendix J, Table 1).^{40, 43, 45, 46} Of these, three reported no statistically significant difference between treatment groups in any of these outcomes.^{43, 45, 46} SOE in these studies was low for several neuropsychological tests/domains in the cell saver versus suction and high versus low blood pressure trials, but otherwise was graded insufficient.

By comparison, participants randomized to MECC scored statistically significantly better than those assigned to CECC on six of seven individual neuropsychological tests.⁴⁰ Further, participants randomized to MECC were significantly less likely than those assigned to CECC to have incident cognitive impairment (20.7 percent versus 61.3 percent; RR, 0.34 [95% CI, 0.16 to 0.73]). Because the criterion for incident impairment was loose (decline by ≥ 1 standard deviation in at least 1 of 7 neuropsychological tests) and there were few total events, the clinical relevance of this result is unclear. SOE for this treatment comparison was rated low.

Carotid Artery Revascularization

We identified no study that enrolled older 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 one eligible RCT that compared aortic valve replacement performed under hypothermic conditions versus aortic valve replacement performed under normothermic conditions in older adults (n=60 participants) (Appendix G, Table 2).⁵¹ This study did not report results for post-surgical incidence of any cognitive-related clinical diagnosis or incident cognitive impairment as defined by a composite of neuropsychological tests (Appendix H, Table 2; Appendix I, 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 J, Table 2). SOE for this treatment comparison was graded insufficient.

We identified no other eligible study that enrolled older adults 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 eligible study that enrolled older adults 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.
- Data 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.

- Limitations in the available data that impeded meta-regression included there being little between-study variability in participant characteristics. For example, the mean age in nearly all studies was 65 to 69 years; with the exception of slowing on some timed tests, participants' baseline cognitive function appeared intact; 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 few treatment comparisons were evaluated by the same cognitive measures reported in the same way in more than one study.

Discussion

Do Selected Cardiovascular Procedures Impact Cognitive Outcomes in Older Adults?

Few eligible studies in older adults compared selected cardiovascular procedures with medical management or compared more versus less invasive cardiovascular procedures and reported intermediate and/or long-term cognitive outcomes.

Single studies of CABG versus medical management, CEA versus CAS, CEA versus carotid angioplasty, and cardiac valve replacement with or without CABG versus CABG alone each found no difference in intermediate and/or long-term cognitive outcomes between treatments. Beyond there being no statistically significant between-group differences in these cognitive outcomes, the small magnitude of both the between-group differences and the within-group change scores suggested that these findings may not be due just to low statistical power. Any intermediate to long-term cognitive differences between these treatments in older adults, if they exist, may be small. One study of AVR versus TAVR reported significantly increased incidence of intermediate-term cognitive impairment in TAVR participants, but because these results could have been biased by substantial between-group differences in cognitive risk factors and by use of different cognitive outcome measures, these results are difficult to interpret.

However, in addition to the small number of studies that were eligible, and the several treatment comparisons for which we identified no eligible studies (e.g. CABG versus PCI; PCI versus medical management; CEA, CAS or carotid angioplasty versus medical management; AVR or TAVR versus medical management; aortic or mitral valve replacement versus valve repair; ablation for atrial fibrillation versus medical management), many of the studies identified had small sample sizes, and all had at least moderate risk of bias. While SOE for the comparison of outcomes between CEA and CAS were mostly graded as low, SOE for these other treatment comparisons was uniformly considered insufficient. Additional studies could substantially change the estimates of effect of these cardiovascular procedures on cognitive outcomes in older adults.

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 or peri-procedural stroke or TIA. This was because, within eligible studies, strokes and TIAs after these cardiovascular procedures were uncommon; risk for strokes and TIAs didn't statistically significantly differ between treatment groups; and risk for post-procedural cognitive outcomes generally didn't 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 concerning this association was clearly inadequate for this conclusion to be definitive. Further, given that few participants in eligible studies other than the carotid revascularization RCTs had a prior history of stroke, the low frequency of procedural and peri-procedural stroke and TIA and lack of association with

cognitive outcomes after these procedures in eligible studies may not be representative of patients at higher stroke risk undergoing these procedures in the community.

Is Any Association Between Selected Cardiovascular Procedures and Cognitive Outcomes in Older Adults Modified by Procedural Characteristics?

For all but two treatment comparisons (on versus off-pump CABG [n=6 studies], and hypothermic versus normothermic CABG [n=3 studies]), there were only single studies that addressed whether differences in how CABG was performed were associated with intermediate or long-term differences in cognitive function in older adults.

For the on versus off-pump CABG and hypothermic versus normothermic CABG comparisons, we found low and low to moderate strength evidence, respectively, that there was no difference in intermediate and/or long-term cognitive function between treatment groups. Beyond there being no statistically significant between-group differences in these cognitive outcomes, the small magnitude of both the absolute between-group differences and the within-group change scores suggested that these findings may not be due just to low statistical power, but that any intermediate to long-term cognitive differences between these treatments in older adults, if they exist, may be small.

Six additional RCTs, each comparing one version of CABG versus another (i.e. different anesthesia regimens, hyperbaric versus atmospheric oxygen, high versus low mean arterial blood pressure, preoperative candesartan versus placebo, use of cell saver versus cardiomy suction), all found no significant difference between treatment groups in intermediate-term cognitive outcomes in older adults. Individually, each of these studies has no better than moderate risk of bias and provides insufficient to low SOE to conclude that its observed outcome accurately reflects the true effect. However, viewed together, and in the context of the negative on versus off-pump CABG, and hypothermic versus normothermic CABG studies, these results are at least suggestive that CABG procedure characteristics may have little to no effect on intermediate to long-term cognitive outcomes in older adults. Alternatively, these results could be explained by the inability of limited quality studies to identify true effects of one or more CABG procedure characteristics on these cognitive outcomes. Or, procedure characteristics don't make a difference in intermediate to long-term cognitive outcomes in older adults because CABG itself doesn't affect these outcomes.

But, none of these explanations may be correct if the results from a single, 3-month RCT in which older adults were randomized to minimal extracorporeal bypass versus conventional extracorporeal bypass are true.⁴⁰ In this small trial (n=64), we found low SOE that risk of incident cognitive impairment was statistically significantly reduced by two-thirds and six of seven individual neuropsychological tests were better at followup in the minimal compared to the conventional bypass group. Because the criterion for incident cognitive impairment was lenient (decline by ≥ 1 standard deviation in at least 1 of 7 neuropsychological tests), it is likely that some individuals met this criterion due to chance. Since there were relatively few total events, the clinical relevance of this result is still unclear. A recent meta-analysis of RCTs comparing minimal versus conventional extracorporeal bypass CABG unrestricted by age reported no statistically significant reduction in neurologic events, but didn't report cognitive outcomes specifically, and noted that available studies were generally small and limited in quality.⁵² A trial comparing minimal versus conventional extracorporeal bypass CABG is now

enrolling participants and aims to randomize 150 participants ages 18 to 80 years, and to follow them for neurocognitive function among other outcomes for up to six months.⁵³ Given the age entry criteria, and the absence of information about whether the study is using more rigorous cognitive outcomes, it is unclear if it will clarify whether minimal extracorporeal bypass truly improves intermediate-term cognitive outcomes in older adults undergoing CABG procedures.

Data on the potential impact of procedural characteristics on the association between cardiovascular procedures and intermediate and/or long-term cognitive outcomes was more limited for other procedures. One RCT found no statistically significant difference in cognitive outcomes at 4 months between older adults randomized to hypothermic versus normothermic AVR. However, we considered the SOE for this comparison insufficient. We found no evidence addressing whether the association between carotid revascularization or atrial fibrillation ablation procedures and cognitive outcomes is modified by procedural characteristics. Consequently, whether any procedural factors affect intermediate or long-term cognitive outcomes after cardiac valvular, carotid revascularization or atrial fibrillation ablation procedures in older adults is far from settled.

Is Any Association Between Selected Cardiovascular Procedures and Cognitive Outcomes in Older Adults Modified by Patient Characteristics?

Increased age, less education or social support, cerebrovascular or peripheral vascular disease, hypertension, diabetes, and depression have been suggested as patient factors that may predict cognitive outcomes after cardiovascular procedures.^{1,4-7} However, these data were derived solely from studies of CABG, many of which were uncontrolled, short-term and/or unrestricted to older adults. We sought to identify evidence about whether they predict intermediate and/or long term cognitive impairment after several different types of cardiovascular procedure in older adults.

Unfortunately, we found no evidence from eligible studies addressing whether any of these patient characteristics 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?

Evidence from our review does not address whether cognitive testing before and after selected cardiovascular procedures improve short-term cognitive outcomes or any noncognitive outcomes. It also does not address whether cognitive screening benefits outweigh harms in any

other population (e.g., older adults not scheduled for these cardiovascular procedures or scheduled for noncardiovascular procedures, younger patients). Some of these important questions have been addressed by recommendations and guidelines by other groups.⁵⁴⁻⁵⁶

The focus of our review was to evaluate whether selected cardiovascular procedures affect intermediate and long-term cognitive outcomes in older adults, including whether this association is impacted by patient characteristics such as baseline cognitive function. A finding that baseline cognitive function predicts differences in intermediate and long-term cognitive outcomes in older adults between one or more cardiovascular procedure and their treatment alternatives could provide guidance in selecting between treatment options. However, studies eligible for this review did not provide data to inform treatment decisions in this way. Additional research will be needed to address this question, such as studies in older adults that report results stratified by or adjusted across a broad range of baseline cognitive function.

A finding that baseline cognitive function predicts intermediate and/or long-term cognitive outcomes in older adults undergoing selected cardiovascular procedures might be used to counsel patients even if it doesn't distinguish these outcomes between different treatment alternatives. For example, patients identified with more baseline cognitive impairment might be counseled that they have an increased risk of intermediate and long-term post-procedure cognitive not caused by the procedure. Again, studies eligible for this review did not provide data to confirm this association.

In sum, we found no direct evidence about whether pre and/or post-procedural cognitive testing may lead to improvement in intermediate and long-term cognitive outcomes in older adults. Valuable future research may address whether cognitive testing before and/or after selected cardiovascular procedures impacts intermediate and long-term cognitive outcomes and other important related outcomes (e.g., patient autonomy related to capacity to consent, complications related to adherence with post-surgical instructions, quality of life, costs).

How May Findings From This Review Inform the Provider-Patient Consent Process for Selected Cardiovascular Procedures?

Our review found limited evidence in older adults addressing whether intermediate and long-term cognitive outcomes after coronary or carotid artery revascularization or cardiac valve replacement are attributable to these procedures. We found low to insufficient strength evidence suggesting that there is no difference in intermediate-term cognitive outcomes between older adults who undergo CEA versus either of two less invasive alternatives, CAS or carotid angioplasty. We found no evidence from eligible studies about whether these cognitive outcomes are attributable to ablation for atrial fibrillation. Other than one provocative but unconfirmed study suggesting intermediate-term cognitive benefits from minimal versus conventional extracorporeal bypass CABG (low SOE), we found 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. While SOE suggesting that there was no difference in longer term cognitive outcomes between on versus off-pump CABG and hypothermic versus normothermic CABG was low and moderate, respectively, SOE for for there being no difference in these cognitive outcomes between other versions of CABG ranged between insufficient and low.

Therefore, it may be appropriate for providers performing consent to inform older patients that though there is substantial uncertainty about the cognitive risk from these procedures in older adults, limited evidence (both in number of studies and study quality) suggests that intermediate and long-term cognitive risks attributable to the CABG, carotid revascularization, and AVR procedures, or to different versions of these procedures may be small. Though assessment of the risk of short-term cognitive impairment after these cardiovascular procedures was outside the scope of our review, our results suggest that if such short-term impairment occurs, there is at least limited evidence that any cognitive effects from the procedure may be transient. It may be more likely that longer lasting cognitive impairment after these cardiovascular procedures reflects cognitive impairment that was present prior to the procedure, whether or not it was fully recognized.

Applicability

No RCT compared a cardiovascular procedure versus medical management. Only two of 17 RCTs compared different cardiovascular procedures with each other, both of which compared CEA versus a less invasive procedure for treatment of carotid stenosis (i.e., versus CAS and carotid angioplasty, respectively). 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 with limited cognitive impairment, and, other than in the carotid artery revascularization studies, pre-procedural history of stroke was rare. Studies also reported very limited information on participant and procedure characteristics, including on race, comorbid conditions, CVD severity, and adjunctive procedures performed to try to prevent adverse cognitive outcomes.

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 more substantial 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 3. Future research recommendations

Research Gaps	Future Research Recommendations
General Issues	
<ul style="list-style-type: none"> No eligible studies reported clinically diagnosed cognitive outcomes (e.g., dementia, mild cognitive impairment) based on an assessment of symptoms, functional ability, and neuropsychological testing. 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 	<ul style="list-style-type: none"> Future studies should report clinically diagnosed cognitive outcomes based on patient/informant history, formal cognitive testing and functional assessment, such as incident dementia or mild cognitive impairment, although the incidence of these outcomes may be very low. Future studies should use a standardized definition of incident cognitive impairment. Ideally, it would represent a clinically meaningful change in cognition from a pre-

Research Gaps	Future Research Recommendations
<p>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). These thresholds do 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.</p> <ul style="list-style-type: none"> • Statistical pooling of results from different studies was impeded by between-study variability in neuropsychological testing performed, 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. • Followup duration in most studies may have been too short to evaluate long-term cognitive effects of these cardiovascular procedures. • This review only considered intermediate (3 to 12 months) and long-term (>12 months) post-procedural cognitive outcomes. The effect of selected cardiovascular procedures on shorter-term cognitive outcomes was outside the scope of this review. • Many studies not included in this review have examined the association between cardiovascular procedures and subsequent cognitive outcomes without reference to a control group. This may have resulted in attribution of post-procedure cognitive impairment to the procedure that was partly or completely due to patient characteristics. 	<p>procedure baseline. 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 (e.g. post-procedure, or change between pre- and post-procedure). Results should be adjusted for multiple comparisons along with determining whether the magnitude of any statistically significant difference exceeds a rigorous threshold.</p> <ul style="list-style-type: none"> • 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. • Future studies should include control groups (e.g. alternative procedure, medical management) in order to better account for the impact of patient characteristics on post-procedure cognitive outcomes.
<p>Key Question 1. In older adults who undergo selected cardiovascular procedures, what are the associated post-procedural cognitive outcomes?</p>	
<ul style="list-style-type: none"> • We found no evidence from eligible studies in older adults addressing whether there is a difference in intermediate or long-term cognitive outcomes after CABG vs. PCI, cardiac valve replacement vs. valve repair vs. medical management, or ablation versus medical management for atrial fibrillation. • We found insufficient strength evidence from 1 observational study in older adults 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. 	<ul style="list-style-type: none"> • 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 coronary and carotid vascular disease, cardiac valve disease, and atrial fibrillation in older adults.
<p>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?</p>	
<ul style="list-style-type: none"> • We could not determine whether risk for adverse intermediate or long-term cognitive outcomes following selected cardiovascular procedures was affected by procedural and 	<ul style="list-style-type: none"> • Future studies of cardiovascular procedures should include older adults at higher risk for stroke and should systematically collect information on procedural and peri-procedural stroke and TIA.

Research Gaps	Future Research Recommendations
<p>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.</p> <ul style="list-style-type: none"> • Though 5 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 in older adults, SOE for this finding is only low. • Though 3 eligible RCTs of hypothermic vs. normothermic CABG in older adults reported no difference in intermediate and long-term cognitive outcomes between these versions of CABG, SOE for this finding is low to moderate. • Based on several comparisons, each reported in only 1 RCT, we found insufficient to low SOE that intermediate and long-term cognitive outcomes after CABG are not significantly different between older patients treated with a limited number of different anesthetic regimens, hyperbaric versus atmospheric oxygen, cell saver versus cardiotomy suction, high versus low blood pressure, or preoperative angiotensin-receptor blocker treatment versus placebo. • Data from 1 small RCT suggested a potentially large reduction in cognitive impairment 3 months after CABG with minimal extracorporeal vs. conventional extracorporeal bypass. However, because the criterion for incident cognitive impairment was lenient (decline by >1 standard deviation in at least 1 of 7 neuropsychological tests) and there were few total events, the clinical relevance of this finding is uncertain. SOE for this finding is low. 	<ul style="list-style-type: none"> • Though additional RCTs of on vs. off-pump CABG and hypothermic vs. normothermic CABG may 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. • A much larger RCT should randomize older adults to minimal extracorporeal vs. conventional extracorporeal bypass CABG and employ more rigorous cognitive outcomes and longer followup. RCTs with broader age ranges should perform stratified analyses by age and facilitate pooled analyses within an older age subgroup.

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

<ul style="list-style-type: none"> • We found no evidence from eligible studies in older adults undergoing selected cardiovascular procedures addressing whether selected patient characteristics (e.g., age; baseline cognitive function; past stroke or TIA, baseline CVD severity; hypertension; diabetes; depression) modify the association between these 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 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 	<ul style="list-style-type: none"> • 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 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).
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Research Gaps	Future Research Recommendations
<p>cognitive testing, eligible studies appeared to include few participants with substantial 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.</p>	
<hr/> <p>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</p>	

References

1. Selnes OA, Gottesman RF, Grega MA, et al. Cognitive and neurologic outcomes after coronary-artery bypass surgery. *N Engl J Med*. 2012 Jan 19;366(3):250-7. PMID: 22256807.
2. Murkin JM, Newman SP, Stump DA, et al. Statement of consensus on assessment of neurobehavioral outcomes after cardiac surgery. *Ann Thorac Surg*. 1995 May;59(5):1289-95. PMID: 7733754.
3. Cormack F, Shipolini A, Awad WI, et al. A meta-analysis of cognitive outcome following coronary artery bypass graft surgery. *Neurosci Biobehav Rev*. 2012 Oct;36(9):2118-29. PMID: 22732162.
4. Lombard FW, Mathew JP. Neurocognitive dysfunction following cardiac surgery. *Semin Cardiothorac Vasc Anesth*. 2010 Jun;14(2):102-10. PMID: 20478950.
5. Dieleman J, Sauer AM, Klijn C, et al. Presence of coronary collaterals is associated with a decreased incidence of cognitive decline after coronary artery bypass surgery. *Eur J Cardiothorac Surg*. 2009 Jan;35(1):48-53. PMID: 19027312.
6. Ho PM, Arciniegas DB, Grigsby J, et al. Predictors of cognitive decline following coronary artery bypass graft surgery. *Ann Thorac Surg*. 2004 Feb;77(2):597-603; discussion PMID: 14759444.
7. Kadoi Y, Kawauchi C, Ide M, et al. Preoperative depression is a risk factor for postoperative short-term and long-term cognitive dysfunction in patients with diabetes mellitus. *J Anesth*. 2011 Feb;25(1):10-7. PMID: 21161290.
8. Alston RP. Brain damage and cardiopulmonary bypass: is there really any association? *Perfusion*. 2011 Sep;26 Suppl 1:20-6. PMID: 21933818.
9. Lunn S, Crawley F, Harrison MJ, et al. Impact of carotid endarterectomy upon cognitive functioning. A systematic review of the literature. *Cerebrovasc Dis*. 1999 Mar-Apr;9(2):74-81. PMID: 9973649.
10. Irvine CD, Gardner FV, Davies AH, et al. Cognitive testing in patients undergoing carotid endarterectomy. *Eur J Vasc Endovasc Surg*. 1998 Mar;15(3):195-204. PMID: 9587331.
11. Lacroix V, Hammer F, Astarci P, et al. Ischemic cerebral lesions after carotid surgery and carotid stenting. *Eur J Vasc Endovasc Surg*. 2007 Apr;33(4):430-5. PMID: 17196846.
12. Crawley F, Stygall J, Lunn S, et al. Comparison of microembolism detected by transcranial Doppler and neuropsychological sequelae of carotid surgery and percutaneous transluminal angioplasty. *Stroke*. 2000 Jun;31(6):1329-34. PMID: 10835452.
13. De Rango P, Caso V, Leys D, et al. The role of carotid artery stenting and carotid endarterectomy in cognitive performance: a systematic review. *Stroke*. 2008 Nov;39(11):3116-27. PMID: 18723423.
14. Goldberg JB, Goodney PP, Kumbhani SR, et al. Brain injury after carotid revascularization: outcomes, mechanisms, and opportunities for improvement. *Ann Vasc Surg*. 2011 Feb;25(2):270-86. PMID: 20926244.
15. Hynes BG, Rodes-Cabau J. Transcatheter aortic valve implantation and cerebrovascular events: the current state of the art. *Ann N Y Acad Sci*. 2012 Apr;1254:151-63. PMID: 22548581.
16. Miller DC, Blackstone EH, Mack MJ, et al. Transcatheter (TAVR) versus surgical (AVR) aortic valve replacement: occurrence, hazard, risk factors, and consequences of neurologic events in the PARTNER trial. *J Thorac Cardiovasc Surg*. 2012 Apr;143(4):832-43 e13. PMID: 22424519.
17. Grimm M, Zimpfer D, Czerny M, et al. Neurocognitive deficit following mitral valve surgery. *Eur J Cardiothorac Surg*. 2003 Mar;23(3):265-71. PMID: 12614792.
18. Healey JS, Nair GM. Does catheter ablation for atrial fibrillation increase or reduce neurological insult? *Curr Opin Cardiol*. 2012 Jan;27(1):36-40. PMID: 22123602.
19. Bunch TJ, Crandall BG, Weiss JP, et al. Patients treated with catheter ablation for atrial fibrillation have long-term rates of death, stroke, and dementia similar to patients without atrial fibrillation. *J Cardiovasc Electrophysiol*. 2011 Aug;22(8):839-45. PMID: 21410581.
20. Schwarz N, Kuniss M, Nedelmann M, et al. Neuropsychological decline after catheter ablation of atrial fibrillation. *Heart Rhythm*. 2010 Dec;7(12):1761-7. PMID: 20691284.

21. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0. In: Collaboration TC, editor. 5.1.0 ed; 2011.
22. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. PMID: 22008217.
23. Schulz KF, Grimes DA. Allocation concealment in randomised trials: defending against deciphering. *Lancet*. 2002 Feb 16;359(9306):614-8. PMID: 11867132.
24. Viswanathan M, Ansari MT, Berkman ND, et al. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. 2008 PMID: 22479713.
25. RevMan RMcPv. Copenhagen: The Nordic Cochrane Centre of the Cochrane Collaboration. 2008.
26. Cohen J. Statistical power analysis for the behavioral sciences (2nd ed.). 2nd ed. ed. Hillsdale, NJ: Erlbaum; 1988.
27. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions—agency for healthcare research and quality and the effective health-care program. *J Clin Epidemiol*. 2010 May;63(5):513-23. PMID: 19595577.
28. Agency for Healthcare Research and Quality. Assessing the Quality and Applicability of Included Studies. In: Agency for Healthcare Research and Quality, ed *Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews*. Rockville, MD: Agency for Healthcare Research and Quality; 2007.
29. Jensen BO, Rasmussen LS, Steinbruchel DA. Cognitive outcomes in elderly high-risk patients 1 year after off-pump versus on-pump coronary artery bypass grafting. A randomized trial. *Eur J Cardiothorac Surg*. 2008 Nov;34(5):1016-21. PMID: 18778948.
30. Nathan HJ, Rodriguez R, Wozny D, et al. Neuroprotective effect of mild hypothermia in patients undergoing coronary artery surgery with cardiopulmonary bypass: five-year follow-up of a randomized trial. *J Thorac Cardiovasc Surg*. 2007 May;133(5):1206-11. PMID: 17467430.
31. Selnes OA, Zeger SL. Coronary artery bypass grafting baseline cognitive assessment: essential not optional. *Ann Thorac Surg*. 2007 Feb;83(2):374-6. PMID: 17257951.
32. Selnes OA, Grega MA, Borowicz LM, Jr., et al. Cognitive outcomes three years after coronary artery bypass surgery: a comparison of on-pump coronary artery bypass graft surgery and nonsurgical controls. *Ann Thorac Surg*. 2005 Apr;79(4):1201-9. PMID: 15797050.
33. Lamy A, Devereaux PJ, Prabhakaran D, et al. Effects of off-pump and on-pump coronary-artery bypass grafting at 1 year. *N Engl J Med*. 2013 Mar 28;368(13):1179-88. PMID: 23477676.
34. Knipp SC, Kahlert P, Jokisch D, et al. Cognitive function after transapical aortic valve implantation: a single-centre study with 3-month follow-up. *Interact Cardiovasc Thorac Surg*. 2013 Feb;16(2):116-22. PMID: 23148084.
35. Jensen BO, Hughes P, Rasmussen LS, et al. Cognitive outcomes in elderly high-risk patients after off-pump versus conventional coronary artery bypass grafting: a randomized trial. *Circulation*. 2006 Jun 20;113(24):2790-5. PMID: 16769915.
36. Lee JD, Lee SJ, Tsushima WT, et al. Benefits of off-pump bypass on neurologic and clinical morbidity: a prospective randomized trial. *Ann Thorac Surg*. 2003 Jul;76(1):18-25; discussion - 6. PMID: 12842506.
37. Lund C, Sundet K, Tennoe B, et al. Cerebral ischemic injury and cognitive impairment after off-pump and on-pump coronary artery bypass grafting surgery. *Ann Thorac Surg*. 2005 Dec;80(6):2126-31. PMID: 16305857.
38. McKhann GM, Selnes OA, Grega MA, et al. Subjective memory symptoms in surgical and nonsurgical coronary artery patients: 6-year follow-up. *Ann Thorac Surg*. 2009 Jan;87(1):27-34. PMID: 19101263.
39. Vedin J, Nyman H, Ericsson A, et al. Cognitive function after on or off pump coronary artery bypass grafting. *Eur J Cardiothorac Surg*. 2006 Aug;30(2):305-10. PMID: 16828295.
40. Anastasiadis K, Antonitsis P, Papakonstantinou C. When is the optimal time to perform neurocognitive assessment after coronary artery bypass surgery? *Ann Thorac Surg*. 2011 Nov;92(5):1933; author reply -4. PMID: 22051305.

41. Boodhwani M, Rubens F, Wozny D, et al. Effects of sustained mild hypothermia on neurocognitive function after coronary artery bypass surgery: a randomized, double-blind study. *J Thorac Cardiovasc Surg.* 2007 Dec;134(6):1443-50; discussion 51-2. PMID: 18023662.
42. Nathan HJ, Wells GA, Munson JL, et al. Neuroprotective effect of mild hypothermia in patients undergoing coronary artery surgery with cardiopulmonary bypass: a randomized trial. *Circulation.* 2001 Sep 18;104(12 Suppl 1):I85-91. PMID: 11568036.
43. Alex J, Laden G, Cale AR, et al. Pretreatment with hyperbaric oxygen and its effect on neuropsychometric dysfunction and systemic inflammatory response after cardiopulmonary bypass: a prospective randomized double-blind trial. *J Thorac Cardiovasc Surg.* 2005 Dec;130(6):1623-30. PMID: 16308008.
44. Silbert BS, Scott DA, Evered LA, et al. A comparison of the effect of high- and low-dose fentanyl on the incidence of postoperative cognitive dysfunction after coronary artery bypass surgery in the elderly. *Anesthesiology.* 2006 Jun;104(6):1137-45. PMID: 16732083.
45. Djaiani G, Katznelson R, Fedorko L, et al. Early benefit of preserved cognitive function is not sustained at one-year after cardiac surgery: a longitudinal follow-up of the randomized controlled trial. *Can J Anaesth.* 2012 May;59(5):449-55. PMID: 22290354.
46. Gold JP, Charlson ME, Williams-Russo P, et al. Improvement of outcomes after coronary artery bypass. A randomized trial comparing intraoperative high versus low mean arterial pressure. *J Thorac Cardiovasc Surg.* 1995 Nov;110(5):1302-11; discussion 11-4. PMID: 7475182.
47. Flesch M, Knipp S, Kessler G, et al. ARTA: AT1-receptor blocker therapy in patients undergoing coronary artery bypass grafting. *Clin Res Cardiol.* 2009 Jan;98(1):33-43. PMID: 18853093.
48. Andrew MJ, Baker RA, Bennetts J, et al. A comparison of neuropsychologic deficits after extracardiac and intracardiac surgery. *J Cardiothorac Vasc Anesth.* 2001 Feb;15(1):9-14. PMID: 11254832.
49. Altinbas A, van Zandvoort MJ, van den Berg E, et al. Cognition after carotid endarterectomy or stenting: a randomized comparison. *Neurology.* 2011 Sep 13;77(11):1084-90. PMID: 21880992.
50. Baracchini C, Mazzalai F, Gruppo M, et al. Carotid endarterectomy protects elderly patients from cognitive decline: a prospective study. *Surgery.* 2012 Jan;151(1):99-106. PMID: 21943640.
51. Fakin R, Zimpfer D, Sodeck GH, et al. Influence of temperature management on neurocognitive function in biological aortic valve replacement. A prospective randomized trial. *J Cardiovasc Surg (Torino).* 2012 Feb;53(1):107-12. PMID: 22231536.
52. Anastasiadis K, Antonitsis P, Haidich AB, et al. Use of minimal extracorporeal circulation improves outcome after heart surgery; a systematic review and meta-analysis of randomized controlled trials. *Int J Cardiol.* 2013 Apr 5;164(2):158-69. PMID: 22325958.
53. Anastasiadis K. Comparison of Minimal Versus Conventional Extracorporeal Circulation in Coronary Surgery. www.clinicaltrials.gov; National Institutes of Health; 2014. NCT01603589.
54. Greer N, Anderson P, MacDonald R, Tacklind J, Rutks I, Wilt TJ. Delirium: Screening, Prevention, and Diagnosis - A Systematic Review of the Evidence. 2011.
55. United States Preventive Services Task Force. Screening for Dementia: Recommendations and Rationale. 2003. <http://www.uspreventiveservicestaskforce.org/3rduspstf/dementia/dementtr.htm>.
56. Chow WB, Rosenthal RA, Merkow RP, et al. Optimal preoperative assessment of the geriatric surgical patient: a best practices guideline from the American College of Surgeons National Surgical Quality Improvement Program and the American Geriatrics Society. *J Am Coll Surg.* 2012 Oct;215(4):453-66. PMID: 22917646.

Abbreviations

ACS	American College of Surgery
AGS	American Geriatrics Society
AHRQ	Agency for Healthcare Research and Quality
AVR	aortic valve replacement
CABG	coronary artery bypass grafting
CAS	carotid artery stenting
CCT	controlled clinical trial
CEA	carotid endarterectomy
CENTRAL	Cochrane Central register of controlled trials
CV	cardiovascular
CVD	cardiovascular disease
KQ	key question
MCI	mild cognitive impairment
MLIS	Masters of Library and Information Science
MMSE	Mini Mental State Examination
MOCA	Montreal Cognitive Assessment
NR	not reported
PCI	percutaneous coronary intervention
RCT	randomized controlled trial
RevMan	Review Manager
RR	risk ratio
SD	standard deviation
SOE	strength of evidence
TAVR	transcatheter aortic valve replacement
TIA	transient ischemic attack