Supplement: Evidence-based Practice Center Systematic Review Protocol

I. Background and Objectives for the Systematic Review

Among possible adverse outcomes following cardiovascular (CV) procedures in older adults, including heart attacks (MI), blood clots (DVT/PE), infectious complications, strokes, and delirium, there also has long been a concern regarding possible nontransient adverse cognitive outcomes. Although investigators sought to establish a consensus for cognitive assessment methods following coronary artery bypass grafting (CABG),\(^1\) most early reports are now believed to have overestimated the incidence of adverse cognitive outcomes attributable to these procedures.\(^2\) Though results were based on formal neuropsychological testing, i.e. the standardized administration and qualified interpretation of selected cognitive tests, these studies often did not account for pre-procedure cognitive impairments, transient post-procedure impairments, post-procedure impairments attributable to underlying disease, limitations in cognitive test precision, and the practice effects of repeat cognitive testing.

To address the limitations of these older studies, more recent studies have incorporated pre-procedure cognitive assessments, non-procedure control groups, and limitations on the timing of post-procedure cognitive assessments. A recent systematic review limited to studies reporting results for pre- and post-procedure neuropsychological tests that were recommended in a 1995 consensus paper\(^1\) found that psychomotor speed may be impaired compared to baseline very early after CABG (<2 weeks), but is, along with memory and executive functioning, improved compared to baseline by 3 months and remains so 6-12 months after the procedure.\(^3,\,4\) This review was limited, however, in that it did not evaluate other neuropsychological domains, longer term neuropsychological test results, or whether neuropsychological test abnormalities were associated with symptoms or functional impairment. This is an important consideration since patients are likely to be more concerned about procedure-related cognitive risks that are not just measurable on neuropsychological testing, but also are associated with symptoms they recognize and even moreso that adversely impact their social, occupational or other daily functioning.
Several patient characteristics have been associated with adverse cognitive outcomes after CABG, including advanced age, fewer years of education, limited social support, cerebrovascular or peripheral vascular disease, hypertension, diabetes, and depression.\textsuperscript{2,5-8} However, we are unaware of any systematic reviews that have examined these associations. With regard to the possible impact of procedure-related factors on post-CABG cognitive outcomes, multiple reviews suggest no increased cognitive risk with on-pump versus off-pump CABG.\textsuperscript{3,9} However, less is known about the impact of other procedure-related factors on cognitive outcomes, including from procedural or peri-procedural stroke or TIA.

In a recent systematic review\textsuperscript{10} of 47 studies of carotid revascularization (carotid endarterectomy [CEA] and/or carotid artery stenting [CAS]), about half reported improvement in at least one cognitive measure after the procedure, and about half reported some decline or no change. Authors suggested that the variable findings could be explained by the small sample size of many studies (about one-fourth had fewer than 25 participants with CEA or CAS), variable follow-up times (including about one-fourth with follow-up of <1 month), and different neurocognitive tests administered. In addition, about one-third of included studies did not compare cognitive changes to those in a control group that did not undergo CEA or CAS, another potential source of bias.

Clarifying the true association between CEA and CAS and post-procedure cognitive outcomes will require a more selective consideration of available studies, distinguishing between those most and least likely to provide biased results. This will be a first step before the impact of procedure-related factors and patient characteristics on post-CEA and post-CAS cognitive outcomes can be evaluated.

Data on cognitive outcomes after other CV procedures, including open and transcatheter cardiac valve replacement/repair and atrial fibrillation ablation appear more limited. We are unaware of any review addressing the degree to which these procedures cause adverse cognitive outcomes, including their clinical severity, duration, and pattern of neurocognitive domain impairment.

Though recent American College of Surgery/American Geriatrics Society Guidelines recommend pre-operative cognitive screening of all patients aged >65 years, including a
history and a formal cognitive assessment, such as with the brief, mini-Cog screening measure, the extent to which this occurs in current practice is unknown. Current uncertainties regarding the course, severity, and pattern of cognitive outcomes attributable to CABG, CEA, CAS, cardiac valve replacement/repair, and atrial fibrillation ablation limit pre-procedure discussions between clinicians and patients regarding what cognitive risks may be associated with these procedures. Enhanced understanding of these issues has the potential to inform these discussions and potentially lead to safer and more targeted use of these procedures. The proposed systematic review will comprehensively characterize the cognitive outcomes associated with these CV procedures, and the extent to which these associations are modified by procedure and patient characteristics.

Our findings should provide information about the characteristics and predictors of any cognitive outcomes associated with these CV procedures. Further, they should define the limitations of existing evidence and the parameters of any future RCTs or other research studies that are needed to address remaining evidence gaps.

II. The Key Questions

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

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

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

• Population(s):
• For all 3 key questions:
  1. Older adults undergoing selected CV procedures. There will be no limitations on the basis of cardiac or cerebrovascular disease severity, comorbidities or patient demographics other than age.
  2. We do not anticipate that participant inclusion/exclusion criteria for any eligible studies will exactly match Medicare eligibility. To maximize our report findings to the majority of Medicare enrollees, those aged 65 years or older, as a first step we will include studies that are entirely comprised of individuals aged 65 years or older or that report subgroup data from at least 10 patients in this age stratum. However, we anticipate that these criteria alone would exclude data from many study participants in this older age range who enrolled in studies that also include some younger participants and didn’t report stratified data by age. Therefore, we also will include studies that reported that at least half of participants were 65 years or older, or that reported either a mean or median age of 65 years or older. We do not plan to search for studies that enrolled participants with ESRD or Medicare qualifying disabilities.
• For key question 3 only:
  1. To evaluate whether impact of CV procedures on cognitive outcomes differs according to patient characteristics, we will evaluate results for subgroups defined by selected participant characteristics that may increase risk of adverse cognitive outcomes. Identification of patient characteristics associated with adverse post-procedure cognitive outcomes may help predict individual patient risks. Identifying the subset of these predictors that are potentially modifiable may identify targets for future interventions to reduce these risks. Potential patient characteristics to be evaluated may include: age; baseline cognitive function; past stroke or TIA, baseline CVD severity; hypertension; diabetes; and
depression.

- **Interventions (Procedures):**
  - We will evaluate each of the 3 key questions separately for each of the following CV procedures:
    1. Coronary artery revascularization (e.g. coronary artery bypass grafting [CABG], percutaneous coronary intervention [PCI])
    2. Carotid artery revascularization (e.g. carotid endarterectomy [CEA], carotid artery stenting [CAS])
    3. Cardiac valve replacement/repair (e.g. surgical or transcatheter, aortic or mitral)
    4. Atrial fibrillation ablation (e.g. surgical, catheter)
      *Also including combined coronary and carotid artery revascularizations
  - For key question 2 only:
    1. To evaluate whether impact of CV procedures on cognitive outcomes differs according to procedure characteristics, we will compare whether results differ as a function of whether patients had a procedural or peri-procedural stroke or TIA; between different procedures used for the same clinical indication, such as surgical vs. catheter-based/stenting; and as a function of procedure time, anesthesia time or type, or use of adjunctive neuroprotective treatment..

- **Comparators:**
  - For randomized controlled trials of CV procedures, comparison subjects may include those assigned to placebo, usual care, or active control (e.g. nonprocedure medical management, or an alternative CV procedure, including possible percutaneous procedures).
  - For observational studies, in an effort to limit potential selection bias, we will only include studies that compare the procedure group to an appropriate control group. This control group may be a matched
comparison group of patients who did not undergo the specific CV procedure within the past year or another group in which analyses accounted for differences in underlying CVD severity and other factors between patients who did and did not undergo CV procedures (e.g. age, CVD risk factors, other comorbidities, baseline cognitive function, past stroke or TIA).

- Historical controls will not be considered eligible because of our concern that CVD treatment, including surgical and catheter-based techniques and adjunctive therapy may have changed over time. Even the types of patients who undergo these procedures may have changed over time. All these changes may affect the risk of post-procedure cognitive impairment. Therefore, it would not be possible from studies that use historical controls to accurately assess whether changes in post-procedure cognitive outcomes are due to the procedures or to historical trends in health care and/or populations enrolled. This could result in biased findings.

- **Outcome measures for all questions:**
  
  - **Primary outcomes**
    
    Our two primary outcomes both involve new onset, post-procedure symptomatic changes in cognition. In both cases, these adverse cognitive symptoms, such as poor short-term memory or language abilities, may be recognized by the patient, informant, or both. However, because self-report of cognitive symptoms is not always accurate or reliable, at least in part due to the high prevalence of impaired insight among patients with cognitive impairment, we also will require that studies confirmed these symptoms with neuropsychological testing. Neuropsychologically confirmed cognitive symptoms may or may not be severe enough to be associated with functional impairment (e.g. occupational, social, activities of daily living). Post CV-procedure functional impairments unrelated to cognition (e.g. attributable to impaired CV function, strength, and/or coordination) will be considered out of scope for this review.

  1. **Confirmed symptomatic cognitive impairment associated with**
**functional impairment.** Patients with impairment in memory plus at least one other cognitive domain, who have associated functional impairment, meet DSM-IV criteria for dementia. Patients with impaired function, but with a different pattern of neuropsychological impairment (e.g. only one impaired cognitive domain, only nonmemory domain(s) impaired) may be considered for alternative diagnoses (e.g. possible dementia).

2. **Confirmed symptomatic cognitive impairment not associated with functional impairment.** Patients with impairment limited to one or two cognitive domains, who have no associated functional impairment meet Peterson criteria for mild cognitive impairment (MCI). Patients with intact function, but with a different pattern of neuropsychological impairment (e.g. impairment in three or more cognitive domains) may be considered for alternative diagnoses (e.g. cognitive impairment no dementia [CIND], cognitive impairment etiology unknown).

Within these two primary outcome categories, we also will record if studies report specific etiologies and/or apply specific diagnostic labels for cognitive impairment outcomes (e.g. dementia, vascular dementia, cognitive impairment not dementia secondary to cerebrovascular disease, MCI). However, if studies report these etiologies/diagnostic labels without indicating how they were confirmed by neuropsychological testing (e.g. study reported ICD-9 administrative codes only), we will report diagnostic information derived from these studies separately.

- **Secondary outcomes**

  Our secondary outcome will be **clinically meaningful magnitude of change in neuropsychological test performance.** This will be defined as weighted mean differences (between group differences in change from baseline to follow-up) of at least small effect size in one or more neuropsychological tests, independent of whether these test results were correlated with clinical symptoms or functional impairment. These neuropsychological tests are performance-based and include both brief,
global cognitive screening measures (e.g. mini-mental status exam [MMSE], mini-Cog, MOCA) and more narrow measures that evaluate one or more specific cognitive domains (i.e. attention, memory, language, executive, visual-spatial functioning, and psychomotor speed).

- **Intermediate outcomes**

Measures of continuous change in neuropsychological test performance are of uncertain clinical importance and will not be considered outcomes for the purpose of this report. Procedural and peri-procedural stroke and TIA also will not be considered outcomes in themselves for the purpose of this report. Instead, they will be considered as possible mediators in the causal pathway between CV procedures and the primary and secondary cognitive outcomes listed above.

- **Timing:**
  - **Pre-procedure**
    1. All eligible cohort studies must have performed neuropsychological testing prior to the CV procedure. Randomized controlled trials may be eligible without pre-procedure neuropsychological testing.
  - **Post-procedure**
    1. All eligible studies must have performed cognitive evaluations at least 3 months after the CV procedure in an effort to eliminate transient effects on cognition from factors other than the procedure, including pain, anesthesia, medications, sleep deprivation, and hospital-related illness. In addition, results from testing performed this soon after pre-procedure testing may be influenced by practice effects.
    2. We will extract and separately report cognitive outcomes measured 3 to 12 months after the CV procedure (intermediate-term), and those measured >1 year after the procedure (long-term). For each study, data for a given outcome will only be extracted for the latest available time point within each of these two time periods. We
suspect that in most cases changes reported as present between 3 to 12 months post-procedure were present earlier but persisted, sometimes after resolution of superimposed, transient, nonprocedure-related factors. We will evaluate cognitive outcomes reported >1 year after the CV procedure to look at duration of cognitive changes that were reported 3 to 12 months after the procedure, progression of these earlier changes, and to identify cognitive outcomes that first became evident >1 year after the procedure. Use of RCTs or observational studies with well-matched control groups will be essential for distinguishing the extent to which cognitive changes first reported >1 year after the procedure and progression of earlier cognitive changes were caused by the CV procedure and the extent to which they were attributable to progression of an unrelated underlying disease.

- **Settings:**
  - Studies will be eligible regardless of whether the CV procedure took place in the inpatient or outpatient setting. However, because of the high rate of delirium reported in older hospitalized patients, studies in which post-procedure cognitive assessments are available only from within the inpatient setting will be excluded. This restriction is intended to limit the impact of factors other than the CV procedure on reported cognitive outcomes (e.g. pain, anesthesia, medications, sleep deprivation, and hospital-related illness unrelated to the procedure). Studies may be limited to those conducted in Western settings (or stratified on this factor) to increase the applicability of findings to U.S. practices and outcomes.
Figure 1. AF = atrial fibrillation; CABG = coronary artery bypass grafting; CAS = carotid artery stenting; CEA = carotid endarterectomy; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; DVT = deep venous thrombosis; HTN = hypertension; PCI = percutaneous coronary intervention; PE = pulmonary embolism; TIA = transient ischemic attack
IV. Methods

A. Criteria for Inclusion of Studies in the Review

- Study design: Randomized controlled trial (RCT), nonrandomized comparative trial, prospective observational cohort study, or systematic review that reports separable results for these study types only.

- Population:
  1. Participants must have been older adults. As discussed above, we will include studies whose participants are all aged >65 years, have a mean or median age >65 years, or that report subgroup data from >10 patients aged >65 years.
  2. Participants in at least one intervention or observation arm underwent one of the CV procedures of interest
     a. Coronary artery revascularization (e.g. coronary artery bypass grafting [CABG], percutaneous coronary intervention [PCI])* 
     b. Carotid artery revascularization (e.g. carotid endarterectomy [CEA], carotid artery stenting [CAS])* 
     c. Cardiac valve replacement/repair (e.g. surgical or transcatheter, aortic or mitral) 
     d. Atrial fibrillation ablation (e.g. surgical, catheter) 
     *Also including combined coronary and carotid artery revascularizations

- Minimum sample size of >10 participants in each treatment arm for RCTs and >50 participants in each arm for nonrandomized comparative studies and prospective cohort studies.

- Publication date range: To limit the review to evaluating cognitive outcomes after CV procedures that reasonably reflect current clinical practice, all studies must have been published since 1990.

- As stated earlier, nonrandomized comparative studies and prospective cohort studies must have performed pre-procedure neuropsychological assessments, including possibly brief global cognitive screening measures.
RCTs may be included whether or not they performed pre-procedure neuropsychological assessments.

- As stated earlier, all eligible studies must have reported at least one primary or secondary cognitive outcome at least 3 months after the procedure that was measured outside of the acute inpatient setting.
- As stated earlier, all studies must have included a nonhistorical control group that did not undergo the CV procedure of interest or that underwent a modified version of the procedure.
- All studies must have been published in English language.

**B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions**

We will identify evidence for this review by searching relevant bibliographic databases. Bibliographic database searching will utilize MEDLINE, the Cochrane Central register of controlled trials (CENTRAL), and Scopus to identify RCTs published 1990 to the present. See Supplement Figure 2 for full MEDLINE search strategy. An MLIS research librarian experienced in systematic review search methodology and not involved in the project has peer reviewed and helped refine our bibliographic literature search strategy. Bibliographic database searches will be supplemented with hand searching of reference lists of included studies, and previous systematic reviews. The literature search will be updated while the draft report is under public/peer review.

Additionally, we will search ClinicalTrials.gov to identify relevant registered and completed trials. These sources will be used to identify trials not previously identified. Published and registered trials will be compared to assess potential outcomes reporting bias. Trials registered but not published will be evaluated qualitatively to comment on the potential publication bias relevant to this topic.
Screening of studies identified in our initial and updated literature searches, and of any studies identified during public and peer review will occur in two stages. First, search results will be preliminarily triaged. Titles and abstracts will be reviewed by two independent investigators and marked ‘include,’ ‘exclude,’ or ‘full text needed’ if a determination cannot be made based upon available information. Differences in triage decisions between the two investigators will be resolved by consensus discussion, involving the lead investigator as necessary. Full text will be obtained for articles identified as potential includes during initial triage. These studies will be distributed among investigators for secondary screening and data extraction. Full text will be evaluated by two investigators to ensure that the study meets inclusion criteria. We will document the inclusion and exclusion status and reason for exclusion in the project library of citations.

**Figure 2. Electronic Database Literature Search Strategies**

**MEDLINE**

Database: Ovid MEDLINE(R) <1946 to January Week 3 2013>

Search Strategy:

--------------------------------------------------------------------------------
1 comprehension/ (6633)
2 cognition disorders/ (44130)
3 auditory perceptual disorders/ (909)
4 memory/ (49313)
5 memory, episodic/ (472)
6 memory, long-term/ (371)
7 memory, short-term/ (13113)
8 mental recall/ (25327)
9 retention, psychology/ (7518)
10 memory disorders/ (13433)
11 exp Neuropsychological Tests/ (61191)
exp Executive Function/ (3065)
exp Psychometrics/ (49676)
exp Psychomotor Disorders/ (10067)
exp Psychomotor Performance/ (78939)
Dementia/ or Alzheimer disease/ or aphasia, primary progressive/ or dementia, vascular/ or frontotemporal lobar degeneration/ or lewy body disease/ (90697)
pick disease of the brain/ (351)
mild cognitive impairment/ (762)
central nervous system dysfunction.mp. (498)
neuropsychological impairment.mp. (860)
(Cognitive decline or cognitive dysfunction or cognitive tests or cognitive assessment or cognitive function or cognitive evaluation or cognitive performance or cognitive change or cognitive problem or cognitive outcome or cognitive sequelae).mp. (33149)
(Neuropsychologic* decline or neuropsychologic* dysfunction or neuropsychologic* tests or neuropsychologic* assessment or neuropsychologic* function or neuropsychologic* evaluation or neuropsychologic* performance or neuropsychologic* change or neuropsychologic* problem or neuropsychologic* outcome or neuropsychologic* sequelae).mp. (62490)
or/1-22 (364408)
Randomized controlled trials as topic/ (82496)
Randomized controlled trial/ (337448)
Random allocation/ (75972)
Double blind method/ (117175)
Single blind method/ (16885)
Clinical trial/ (472549)
Clinical trial, phase i.pt. (12507)
Clinical trial, phase ii.pt. (20105)
Clinical trial, phase iii.pt. (7375)
Clinical trial, phase iv.pt. (759)
Controlled clinical trial.pt. (84963)
Randomized controlled trial.pt. (337448)
Multicenter study.pt. (149119)
Clinical trial.pt. (472549)
exp clinical trials as topic/ (259816)
(clinical adj trial$).tw. (174974)
((singl$ or doubl$ or treb$ or trip$) adj (blind$3 or mask$3)).tw. (114747)
Randomly allocated.tw. (14024)
(allocated adj2 random$).tw. (16356)
or/24-42 (1021274)

Epidemiologic studies/ (5512)
exp cohort studies/ (1215732)
(cohort adj (study or studies)).tw. (64056)
Cohort analy$.tw. (2848)
(follow up adj (study or studies)).tw. (33441)
(Observational adj (study or studies)).tw. (32538)
Longitudinal.tw. (112860)
or/44-50 (1316456)

Meta analysis/ (36638)
Meta analys$.tw. (41461)
literature review.mp. (35019)
(systematic adj (review or overview)).tw. (30248)
or/52-55 (106130)

43 or 51 or 56 (2182597)

Case report.tw. (170277)
letter/ (758034)
limit 69 to humans (1980119)
limit 70 to yr="1990 -Current" (1694926)
limit 71 to english language (1521263)
limit 72 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)") (423582)
72 not 73 (1097681)

exp Myocardial Revascularization/ (75825)
exp percutaneous coronary intervention/ (32327)
Heart bypass, right/ (576)
Coronary revascularization.mp. (4172)
(coronary artery bypass graft or CABG).mp. (14519)
(percutaneous coronary intervention or PCI).mp. (15273)
coronary stent*.mp. (4595)
coronary angioplast*.mp. (11666)
or/75-82 (89913)
74 and 83 (28370)

exp Endarterectomy, Carotid/ (6306)
(carotid endarterectomy or CEA).mp. (20384)
(carotid artery stenting or CAS).mp. (54374)
carotid surg*.mp. (1111)
or/85-88 (76271)

74 and 89 (6030)

Heart valve prosthesis/ (26828)
exp Heart Valve Prosthesis Implantation/ (11217)
Cardiac valve annuloplasty/ (137)
(aortic valve replacement or AVR).mp. (8953)
(mitral valve replacement or MVR).mp. (5610)
(aortic valve repair or mitral valve repair).mp. (2378)
(aortic valve surg* or mitral valve surg*).mp. (2156)
or/91-97 (41284)

74 and 98 (5753)

exp Catheter Ablation/ (18600)
exp Ablation Techniques/ (82421)
100 or 101 (82421)

exp Atrial Fibrillation/ (30442)
atrial fibrillation ablation.mp. (446)
103 or 104 (30482)

102 and 105 (5004)
107  74 and 106 (1659)

108  23 and 84 (396)

109  23 and 90 (112)

110  23 and 99 (40)

111  23 and 107 (4)

112  or/108-111 (527)

COCHRANE

#1  MeSH descriptor: [Comprehension] this term only
#2  MeSH descriptor: [Cognition Disorders] this term only
#3  MeSH descriptor: [Auditory Perceptual Disorders] this term only
#4  MeSH descriptor: [Memory] this term only
#5  MeSH descriptor: [Memory, Episodic] this term only
#6  MeSH descriptor: [Memory, Long-Term] this term only
#7  MeSH descriptor: [Memory, Short-Term] this term only
#8  MeSH descriptor: [Mental Recall] this term only
#9  MeSH descriptor: [Memory Disorders] this term only
#10 MeSH descriptor: [Neuropsychological Tests] explode all trees
#11 MeSH descriptor: [Executive Function] explode all trees
#12 MeSH descriptor: [Psychometrics] explode all trees
#13 MeSH descriptor: [Psychomotor Disorders] explode all trees
#14 MeSH descriptor: [Psychomotor Performance] explode all trees
#15 MeSH descriptor: [Dementia] this term only
#16 MeSH descriptor: [Alzheimer Disease] this term only
#17 MeSH descriptor: [Aphasia, Primary Progressive] this term only
#18 MeSH descriptor: [Dementia, Vascular] explode all trees
MeSH descriptor: [Frontotemporal Lobar Degeneration] explode all trees
MeSH descriptor: [Lewy Body Disease] explode all trees
MeSH descriptor: [Pick Disease of the Brain] explode all trees
MeSH descriptor: [Mild Cognitive Impairment] explode all trees
central nervous system dysfunction
neuropsychological impairment
Cognitive decline or cognitive dysfunction or cognitive tests or cognitive assessment or cognitive function or cognitive evaluation or cognitive performance or cognitive change or cognitive problem or cognitive outcome or cognitive sequelae
Neuropsychologic* decline or neuropsychologic* dysfunction or neuropsychologic* tests or neuropsychologic* assessment or neuropsychologic* function or neuropsychologic* evaluation or neuropsychologic* performance or neuropsychologic* change or neuropsychologic* problem or neuropsychologic* outcome or neuropsychologic* sequelae
#27 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #19 or #21 or #22 or #23 or #24 or #25 or #26
MeSH descriptor: [Myocardial Revascularization] explode all trees
percutaneous coronary intervention
MeSH descriptor: [Heart Bypass, Right] this term only
coronary revascularization
coronary artery bypass graft or CABG
percutaneous coronary intervention or PCI
coronary stent*
coronary angioplast*
#28 or #29 or #30 or #31 or #32 or #33 or #34 or #35
#27 and #36
MeSH descriptor: [Endarterectomy, Carotid] explode all trees
carotid endarterectomy or CEA
carotid artery stenting or CAS
carotid surg* OR #38 or #39 or #40 or #41 OR #27 and #42 OR MeSH descriptor: [Heart Valve Prosthesis] this term only OR MeSH descriptor: [Heart Valve Prosthesis Implantation] explode all trees OR MeSH descriptor: [Cardiac Valve Annuloplasty] this term only OR aortic valve replacement or AVR OR mitral valve replacement or MVR OR aortic valve repair or mitral valve repair OR aortic valve surg* or mitral valve surg* OR #44 or #45 or #46 or #47 or #48 or #49 or #50 OR #27 and #51 OR MeSH descriptor: [Catheter Ablation] explode all trees OR MeSH descriptor: [Ablation Techniques] explode all trees OR #53 or #54 OR MeSH descriptor: [Atrial Fibrillation] explode all trees OR atrial fibrillation ablation OR #56 or #57 OR #55 and #58 OR #27 and #59 OR #37 or #43 or #52 or #60

Scopus

1. (KEY(cognit*) AND KEY(cardiovascular surgical procedures) AND LANGUAGE(english))

2. (KEY(cognit*) OR KEY(dementia) AND LANGUAGE(english) AND KEY(cardiovascular surgical procedures)) AND DOCTYPE(ar)
3. (KEY(cognit*) OR KEY(dementia) AND LANGUAGE(english) AND KEY(cardiovascular surgical procedures)) AND DOCTYPE(ar) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND (LIMIT-TO(EXACTKEYWORD, “Aged”))

4. The results of these 3 searches were then combined and duplicate references were removed.

C. Data Abstraction and Data Management

Two investigators will act as primary and secondary abstractor/evaluators, respectively, for their assigned studies. Data fields to be extracted will be determined for each key question/subquestion. Data elements likely will include author; year of publication; CV procedure intervention and control regimens; anesthesia type and duration; description of adjunctive treatments intended to lower risk of adverse cognitive outcomes; sample size; subject inclusion and exclusion criteria; participant baseline age, prevalence of hypertension, diabetes, stroke/cerebrovascular disease, and depression; type(s) of pre-procedure neuropsychological assessment (e.g. specific brief global cognitive screening measures and specific cognitive domains tested); N, mean and SD for each reported pre-procedure neuropsychological test; incidence of procedural and peri-procedural stroke and/or TIA; timing and definition of clinical post-procedure cognitive outcomes; event rates for clinical post-procedure cognitive outcomes (n/N reporting these outcomes, clearly designating drop-outs); and timing, type, n/N reporting, mean and SD for each post-procedure neuropsychological test.

Authors of studies otherwise meeting eligibility criteria, but not reporting mean and SD for pre- and post-procedure neuropsychological testing will be contacted seeking this additional information. When these results are not directly reported by the study, but can be calculated from available data, we
will perform these calculations. The primary abstractor/evaluator will extract relevant data from studies meeting inclusion criteria onto pre-tested extraction forms/evidence tables. These extraction forms/evidence tables will be reviewed and verified for accuracy by the secondary abstractor/evaluator. Differences in abstraction between the two investigators will be resolved by consensus discussion, involving the lead investigator as necessary. As discussed above, timing of post-procedure cognitive assessments will be categorized into those measured at 3 to 12 months (intermediate-term) and those measured >1 year after the procedure (long-term). For each study, we will record all time points at which post-procedure cognitive assessments were performed, but will report results for only the latest assessment of each cognitive outcome within each of these two time periods.

D. Assessment of Methodological Risk of Bias of Individual Studies

We will evaluate the risk of bias in individual studies according to recommendations from the Cochrane Handbook for Systematic Reviews of Interventions.\textsuperscript{14} Following categorization of studies according to their design as either interventional (RCTs, nonrandomized controlled clinical trials) or prospective observational cohort studies, a primary and secondary abstractor/evaluator will independently review study risk of bias for up to two outcomes per study, with one collective rating for clinical outcomes (for confirmed symptomatic cognitive impairment with and without associated functional impairment considered together) and one collective rating for neuropsychological test outcomes.

For interventional studies, we will evaluate risk of bias using criteria from the Cochrane Risk of Bias tool:\textsuperscript{15} (1) random allocation of the subjects to the treatment groups; (2) adequacy of allocation concealment, based on the approach by Schulz and Grimes;\textsuperscript{16} (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 outcomes
analyses); and (5) selective reporting of prespecified outcomes. Generally, we will assume a low risk of bias when individual interventional studies meet all quality criteria, a moderate risk of bias if at least one of the quality criteria is not met, and a high risk of bias if multiple quality criteria are not met. We will conclude an unknown risk of bias for the interventional studies with poorly reported quality criteria.

For prospective observational cohort studies, we will assess risk of bias using criteria suggested in the AHRQ Methods Guide: (1) selection bias (use of appropriately comparable control group, design/analysis accounted for important confounding and modifying variables); (2) masking of the outcome assessment (outcome assessor); (3) use of intention-to-treat principles (i.e. inclusion of all comparison group participants in outcomes analyses); (4) attrition bias (if overall or differential dropout/loss to follow-up or exclusions a concern, missing data appropriately handled); and (5) selective reporting of prespecified outcomes. Generally, we will assume a low risk of bias when individual prospective observational cohort studies meet all quality criteria, a moderate risk of bias if at least one of the quality criteria is not met, and a high risk of bias if multiple quality criteria are not met. We will conclude an unknown risk of bias for the prospective observational studies with poorly reported quality criteria.

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

E. Data Synthesis

When the patient populations, CV procedures, study designs, and outcomes are clinically comparable, we will perform a quantitative meta-analysis of results for confirmed symptomatic cognitive impairment with associated functional impairment, confirmed symptomatic cognitive impairment without associated functional impairment, and possibly for the outcomes of dementia,
MCI, vascular dementia, and for cognitive impairment not dementia secondary to cerebrovascular disease. Under similar conditions, we also will perform a quantitative meta-analysis of results for each brief global cognitive screening test and for up to one neuropsychological test within each cognitive domain. We will analyze data using Review Manager (RevMan) version 5.1 software. We will use random effects models to generate pooled estimates of relative risks and 95% confidence intervals for the incidence of the primary outcomes, and weighted mean differences (between group differences in change from baseline to follow-up) and corresponding effect sizes and 95% confidence intervals for the neuropsychological test outcomes. We will summarize statistical heterogeneity by using the I^2 statistic (50 percent indicates moderate heterogeneity and 75 percent or greater indicates high heterogeneity).

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

To investigate the possible effect of patient characteristics on the association between CV procedures and adverse cognitive outcomes, we will consider the following subgroup analyses: age; baseline cognitive function; past stroke or TIA, baseline cardiovascular disease [CVD] severity; hypertension; diabetes; and depression.
We will consider random-effects inverse weighted meta-regression on drop-out rate, and, when subgroup analyses are not possible, on the patient characteristics listed above.

Within each CV procedure category, results will first be organized by study design (RCT, nonrandomized comparative studies, prospective observational cohort). Within each type of study design, results will be organized by cognitive outcome, with the primary outcomes reported first, followed by the neuropsychological test results organized by brief global cognitive screening tests and specific cognitive domains (attention, memory, language, executive, visual-spatial functioning, psychomotor speed). Results for each cognitive outcome then will be organized into intermediate- (3 to 12 months) and long-term (>1 year) post-procedure assessments and summarized qualitatively.

Next, results for the primary outcomes will be summarized using weighted risk differences and 95% confidence intervals. These results will be derived by comparing the group-specific incidence of participants reaching these endpoints from among all those in each comparison group. Results for clinical diagnoses not supported by documented neuropsychological test results will not be pooled with studies reporting these outcomes supported by neuropsychological test results or with each other.

Results for the different neuropsychological test results will be summarized by type using weighted mean differences and corresponding standard effect sizes and 95% confidence intervals. These results will be derived by comparing the difference between the intervention and comparison groups in pre- versus post-procedure mean (+/-SD) scores.

Risk of bias ratings may be utilized to conduct sensitivity analysis of results, such as by including and excluding studies with an overall poor rating to assess the influence of poor studies on results of the systematic review.
F. Grading the Strength of Evidence (SOE) for Individual Outcomes

The overall SOE for the studies included in this review will be evaluated using methods developed by the Agency for Healthcare Research and Quality (AHRQ) and the Effective Health Care Program\textsuperscript{19} and currently being updated.

Within each CV procedure comparison examined, we will evaluate SOE separately for RCTs, nonrandomized comparative studies, and prospective observational cohort studies. For each of these study types with eligible data, SOE will be evaluated separately for the following clinical outcomes: confirmed symptomatic cognitive impairment with associated functional impairment, confirmed symptomatic cognitive impairment without associated functional impairment, and for each brief global cognitive screening test and each of the following cognitive domains (attention, memory, language, executive, visual-spatial functioning, and psychomotor speed). We then will consider the results from the different study designs together and report a single SOE for each of these cognitive outcomes for each examined CV procedure. SOE ratings will be 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, strength of the evidence will be evaluated based on the following domains: (1) study limitations (risk of bias or internal validity); (2) directness; (3) consistency; (4) precision; and, when appropriate, (5) reporting bias. Study limitations will be rated as low, medium or high based on the study design and risk of bias of individual studies. Directness will be rated as direct or indirect based on whether evidence provides a single, direct link between intervention and outcomes. Consistency will be rated as consistent, inconsistent, or unknown (e.g. single study) based on the degree to which included studies appear to have the same direction or magnitude of effect. Precision will be rated as precise, imprecise, or unknown based on the degree of uncertainty surrounding the effect estimate that is attributable to insufficient sample size.
and/or the number of outcome events. An imprecise estimate would be one in which the effect estimate is wide enough to include clinically distinct conclusions. We will consider rating reporting bias only for RCT evidence and only when the potential SOE for a comparison otherwise is moderate or high. Reporting bias will be rated as suspected or undetected based on detection of publication, outcome and selective analysis reporting bias. Other factors that may be considered in assessing SOE include dose-response relationship, the presence of confounders, and strength of association.

Based on these factors, the overall evidence will be rated qualitatively as:

i. **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.

ii. **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.

iii. **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.

iv. **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.

An overall rating of high strength of evidence would imply that the included studies were RCTs with a low risk of bias, with consistent, direct, and precise domains.

**G. Assessing Applicability** While some conditions that affect applicability of studies to clinical practice are used as exclusion criteria in study selection
(i.e., cognitive assessment not done long enough after the CV procedure), others may only be identified through detailed review of the studies. Specific study characteristics that may affect applicability will be noted on evidence tables by study abstractors/evaluators. These characteristics may include, but are not limited to, non-U.S. settings, narrow eligibility criteria, participant age or other comorbid characteristics, and cognitive assessments not typically used in current practice.²⁰

V. References


VI. Definition of Terms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVR</td>
<td>aortic valve replacement</td>
</tr>
<tr>
<td>CABG</td>
<td>coronary artery bypass grafting</td>
</tr>
<tr>
<td>CAS</td>
<td>coronary artery stenting</td>
</tr>
<tr>
<td>CEA</td>
<td>carotid endarterectomy</td>
</tr>
<tr>
<td>CV</td>
<td>cardiovascular</td>
</tr>
<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
</tr>
<tr>
<td>FDA</td>
<td>U.S. Food &amp; Drug Administration</td>
</tr>
<tr>
<td>MCI</td>
<td>mild cognitive impairment</td>
</tr>
<tr>
<td>MVR</td>
<td>mitral valve replacement</td>
</tr>
<tr>
<td>PCI</td>
<td>percutaneous coronary intervention</td>
</tr>
<tr>
<td>PFO</td>
<td>patent foramen ovale</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>RFTO</td>
<td>request for task order</td>
</tr>
<tr>
<td>SOE</td>
<td>strength of evidence</td>
</tr>
<tr>
<td>TAVR</td>
<td>transcatheter aortic valve replacement</td>
</tr>
<tr>
<td>TIA</td>
<td>transient ischemic attack</td>
</tr>
</tbody>
</table>

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

VIII. Review of Key Questions
Key questions were reviewed and refined as needed by the EPC with input from AHRQ staff and the topic nominator to assure that the questions were specific and explicit about what information is being reviewed. This project will not involve Key Informants or a Technical Expert Panel (TEP), and the key questions will not be posted for public comment.

**IX. Key Informants**

This project will not involve Key Informants.

**X. Technical Experts**

This project will not involve a Technical Expert Panel.

**XI. Peer Reviewers**

Peer reviewers will be invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual peer reviewers. The dispositions of the peer review comments will be documented and will be published three months after the publication of the Evidence report.

Individuals under consideration to serve as peer reviewers will be required to disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Individuals will not be eligible to serve as a peer reviewer if they have any financial conflict of interest greater than $10,000. However, individuals who disclose potential business or professional conflicts of interest still may submit comments on draft reports through the separate public comment mechanism.

**XII. EPC Team Disclosures**
EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest which cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. 290-2007-10064 EPCIII from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer will review contract deliverables for adherence to contract requirements and quality. The authors of this report will be responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.