Published in final edited form as:

Lancet Neurol. 2014 May ; 13(5): 490–502. doi:10.1016/S1474-4422(14)70004-3.

Neurologic Complications of Cardiac Surgery

David L. McDonagh, MD^{1,2}, Miles Berger, MD, PhD¹, Joseph P. Mathew, MD¹, Carmelo Graffagnino, MD², Carmelo A. Milano, MD³, and Mark F. Newman, MD¹

¹Department of Anesthesiology, Duke University Medical Center; Durham, North Carolina, USA

²Department of Neurology, Duke University Medical Center; Durham, North Carolina, USA

³Department of Surgery (Cardiovascular & Thoracic Surgery), Duke University Medical Center; Durham, North Carolina, USA

Abstract

The consultant neurologist is frequently called upon to assess patients with neurologic complications from cardiac surgery. Some complications mandate acute intervention while others require longer term observation and management. The body of literature pertaining to these complications is massive and ever-changing. Similarly, technological advancements in surgical intervention and modifications in surgical technique create new avenues for neurologic injury. Rapid precise neurologic assessment is paramount and rests on a solid understanding of the evidence base and procedural variables. This clinically focused review is intended to describe the current state of the field for the consultant neurologist.

Keywords

Cardiac surgery; Cardiovascular surgery; Cardiopulmonary bypass; Neurologic Complications; Neurocognitive disorders; Postoperative delirium; Postoperative stroke; Postoperative cognitive decline; Acute Ischemic Stroke; Therapeutic Hypothermia

Corresponding Author: Dr. David McDonagh, M.D., Corresponding Author's Institution: Duke University Medical Center.

Authors Contribution:

David L. McDonagh, MD- provided written content, images, & table creation
Miles Berger, MD, PhD- provided written content & manuscript review
Joseph P. Mathew, MD- provided written content, images, & manuscript review
Carmelo Graffagnino, MD- provided manuscript review
Carmelo A. Milano, MD- provided manuscript review
Mark F. Newman, MD- provided manuscript review

Conflict of Interest Statement:

Dr. McDonagh is a consultant for Cephalogics Corporation, LLC.
Dr. Berger has no conflicts of interest.
Dr. Mathew has no conflicts of interest.
Dr. Milano has no conflicts of interest.
Dr. Graffagnino has research funding from Edge Therapeutics, Astra Zeneca, Ornim, and Zoll Corporation.
Dr. Newman has no conflicts of interest.

Introduction

Neurologic complications have been a major concern throughout the history of cardiac surgery.¹ Advancements in technology and technique have produced open, minimally invasive, and endovascular therapeutics to repair vascular, valvular, and myocardial pathology. Coronary artery bypass grafting (CABG) and percutaneous coronary interventions (PCI) are now conducted more safely than ever before.^{2–4} Despite these advancements, neurologic complications after cardiovascular surgery including ischemic stroke,⁵ delirium and cognitive decline occur frequently.

In this manuscript we review ischemic stroke including: risk assessment, comparative risk of cardiac interventions, approaches to minimizing perioperative thromboembolic events, and acute stroke therapeutics. Ischemic stroke is amongst the most feared complications and carries great morbidity and mortality. Therefore, much of the review focuses on this topic. We also cover hypoxic ischemic cerebral injury and acute therapy. Finally, we discuss neurocognitive complications and future directions in the field.

I. Managing perioperative risk for ischemic stroke

a. Assessing risk for perioperative stroke—Ischemic stroke related to perioperative cerebral thromboembolic or hypoperfusion injury is a well-recognized complication of cardiovascular surgery. However, advances in perioperative medical and surgical care have progressively reduced stroke rates following primary CABG.⁶ Recent studies report post-CABG stroke rates of 1% – 5%.^{7–9} Diabetic patients have higher post-CABG stroke risk (5.2% at 5 years).⁸ Valvular surgery carries an even higher risk for perioperative stroke, potentially due to particulate and air embolization.¹⁰ In a prospective series of > 16,000 cardiac surgery patients, stroke risk was 4.8% after isolated aortic valve replacement, 8.8% after mitral valve replacement, and 9.7% after multi-valve surgery.¹⁰ In this study, CABG was associated with a 3.8% stroke risk, and CABG + valve had a 7.4% stroke risk.¹⁰ The lack of standardized care across surgeons or institutions may explain the differential neurologic complication rates and risk factors.

Perioperative strokes can be divided into 2 categories: *early*, present at extubation (intraoperative), and *late*, occurring post-extubation (postoperative). Tarakji et al studied > 45,000 cardiac surgical patients treated over a period of 28 years at the Cleveland Clinic³ and found that some risk factors were associated with both early and late stroke, while others were associated with only early or late stroke (Table 1). On-pump procedures with hypothermic circulatory arrest carried the highest early stroke risk. Off-pump CABG and On-pump beating heart CABG were associated with the lowest risk of stroke. Interestingly, new onset postoperative AF was *not* associated with postoperative stroke in this study.³ Hedberg and colleagues also found unique risk factors associated with intraoperative vs postoperative strokes (Table 1).¹¹ Although they found different risk factors associated with early and late stroke, these studies suggest that early and late perioperative strokes may arise from different pathophysiologic processes.

The Society of Thoracic Surgeons (STS) has created an ‘on-line risk calculator’ for post-surgical complications (<http://riskcalc.sts.org/STSTWebRiskCalc273/>; accessed July 28,

2013). This tool uses 3 risk models for CABG, valve, and CABG + valve surgery. Based on demographics, comorbidities, laboratory and cardiac diagnostic data, and procedural variables, risk for 9 clinical endpoints can be calculated. The **European System for Cardiac Operative Risk Evaluation (EUROSCORE)** is also a commonly used tool for determining a patient's mortality risk after cardiac surgery but it does not specifically assess the risk for neurologic injury (<http://www.euroscore.org/calc.html>; accessed July 28, 2013).

b. Planning interventions for coronary artery disease: CABG vs PCI—Recent studies have compared the effectiveness of CABG vs PCI for treating coronary disease, and the neurologic complication rates after each procedure type. The SYNTAX trial^{12, 13} randomized patients with 3-vessel or left main disease to CABG or PCI with drug-eluting stents. Patients in the CABG group had more strokes, but had fewer combined major adverse cardiac and cerebrovascular events (the primary composite endpoint).¹³ The FREEDOM trial randomized diabetic patients with multi-vessel coronary disease to CABG or PCI.⁸ This study also showed higher stroke rates in the CABG group (5.2% vs 2.4%; $P = 0.03$) although the composite primary 5-year endpoint of death, stroke or myocardial infarction occurred less frequently in the CABG group. Finally, the ASCERT study retrospectively compared CABG with PCI,¹⁴ and found lower 4 year mortality in the CABG group (stroke data not yet published).

These 3 studies are consistent with a previous meta-analysis that showed a trend toward survival benefit from CABG.¹⁵ As highlighted in a recent systematic review,¹⁶ these studies consistently show that CABG is superior to PCI in terms of mortality and overall composite endpoints, even though CABG is associated with increased perioperative stroke risk. Nonetheless, the decision to perform CABG vs PCI should be made collaboratively (the 'Heart Team' approach) by cardiac surgeons and cardiologists^{16, 17} based on an assessment of an individual patient's coronary disease pattern, comorbidities, and perioperative stroke risk.

c. Off-pump surgery vs cardiopulmonary bypass—Neurocognitive complications of cardiac surgery were historically attributed to embolic events and inflammatory responses related to cardiopulmonary bypass (CPB).² However, a systematic review published in 2005 suggested that there was no difference in stroke or death at 30 days following on-pump vs. off-pump CABG.¹⁸ This analysis was limited by the evidence available at the time. Several studies have since randomized CABG patients to undergo CPB or off-pump surgery, and have consistently found no difference in stroke rates, neurocognitive outcomes, or composite outcomes including mortality.^{9, 19, 20} In fact, the increased cerebral emboli detected during CPB have largely not correlated with neurocognitive injury.^{2, 21} While undesirable, their clinical significance is unclear.

These studies suggest that CPB alone does not contribute to perioperative stroke. Since neurological outcomes are similar after on-pump and off-pump CABG, procedure choice is determined by surgical expertise, vascular anatomy, and patient-related variables as there are technical limitations to the use of off-pump surgery. As an example, off-pump surgery is associated with an increased risk of early coronary revascularization.¹⁹

d. Pharmacologic therapies to reduce risk—Aspirin initiated preoperatively or within 6 hours postoperatively is standard of care in cardiac surgery.² The Multicenter Study of Perioperative Ischemia found a 50% reduction in perioperative stroke (1.3% vs 2.6%, $P = 0.01$) if aspirin was administered within 48 hours of revascularization.²² Recent meta-analysis²³ of preoperative statin therapy trials found that statin use in CABG (or CABG plus Valve) surgery reduces post-operative atrial fibrillation (AF), shortens hospital stay, and contrary to a smaller 2012 meta-analysis,²⁴ reduces stroke and mortality. Furthermore, there is concern that statin withdrawal after cardiac surgery may be injurious.²⁵ Thus, statin therapy should be administered to reduce perioperative stroke as well as non-neurologic complications (Class 1, Level A Recommendation).²

e. Atrial fibrillation and stroke—AF occurs in up to half of patients after CABG, most commonly on post-operative day 2.² Preoperative AF is a risk factor for both early and late post-operative stroke.^{3, 26} Post-operative AF is associated with late post-operative stroke.^{11, 26} It is interesting that the recent analysis by Tarakji³ did not correlate post-operative AF with post-operative stroke, perhaps demonstrating the efficacy of aggressive anticoagulation and/or early cardioversion therapies in current practice.

Numerous trials in cardiac surgery have sought to reduce stroke due to *postoperative* AF with various interventions, such as posterior pericardiotomy, or pharmacotherapies.²⁷ n-3 polyunsaturated fatty acids (n-3 PUFAs) have been the focus of numerous cardiac surgery trials but neither the largest prospective trial²⁸ nor a meta-analysis of 8 randomized trials showed that PUFAs reduce postoperative AF or adverse outcomes.²⁹ Beta-blockers carry a Class I, Level B recommendation for reducing the incidence of AF; amiodarone is considered second tier therapy. Metoprolol, sotalol, magnesium, amiodarone, statins, atrial pacing and posterior pericardiotomy all reduce AF rates,^{24, 27} with a non-significant trend toward reduction in stroke rates.²⁷

Thrombus formation in the left atrial appendage (LAA) is presumed to be the etiology of stroke from AF.³⁰ LAA closure with a variety of percutaneous devices is under investigation to reduce stroke in non-cardiac surgical patients with AF.³⁰ In cardiac surgery, some surgeons ligate the LAA if a thrombus is visible on intraoperative transesophageal echo (TEE), or to reduce the stroke risk in patients with chronic (preoperative) AF. In patients with chronic AF, LAA ligation may also be combined with cryo- or radiofrequency atrial ablation.³¹ A prospective trial demonstrated a reduction in persistent postoperative AF but not stroke incidence, at 1 year, following LAA ligation and atrial ablation.³¹ At present, LAA closure remains experimental.³²

f. Occlusive cerebrovascular disease—Concomitant cerebrovascular atherosclerotic disease increases stroke risk for cardiac surgery patients and raises a number of questions. First, what is the value of screening for atherosclerotic disease? Extracranial carotid disease is a risk factor for stroke after cardiac surgery. A recent meta-analysis³³ concluded that patients with 50–99% carotid stenosis, or occlusion, had a 7.4% perioperative stroke risk. After excluding those with symptomatic disease and/or carotid occlusion, even asymptomatic patients with 50–99% stenosis had a 3.8% stroke risk. Ipsilateral stroke occurred in 2.0% of patients with an asymptomatic unilateral stenosis, while patients with

bilateral asymptomatic stenoses had a 6.5% stroke risk. Intracranial cerebral atherosclerosis has been difficult to assess and understudied in this arena. Interestingly, a recent magnetic resonance angiography study suggests that intracranial atherosclerosis independently increases post-CABG stroke risk.³⁴

Second, does this increased stroke risk justify carotid intervention? If so, should carotid atherosclerotic disease be treated in advance of cardiac surgery or as part of a combined operative procedure? The Carotid Revascularization Endarterectomy vs Stenting Trial (CREST)³⁵ randomized patients (not undergoing cardiac surgery) with carotid atherosclerosis to carotid artery stenting (CAS) or endarterectomy, and found no difference in the primary composite endpoint of stroke, myocardial infarction, or death. The endarterectomy group had fewer strokes, but more myocardial infarctions. Prospective data in cardiac surgical patients does not exist. Stenting requires dual antiplatelet therapy, and is typically not performed as a combined procedure with cardiac surgery. However, its feasibility as a combined procedure has been reported.³⁶ A retrospective study³⁷ examined 27,084 patients who underwent carotid stenting before CABG, or carotid endarterectomy (CEA) combined with CABG (CEA-CABG). Postoperative stroke occurred more often in the CEA-CABG group, although no significant difference in the composite risk for stroke and death was found between the 2 groups after adjusting for baseline co-morbidities.

CEA can be performed either before the carotid surgery or as combined CEA-CABG as just discussed. Shishehbor³⁸ recently analyzed 3 groups of patients who had undergone staged CEA-CABG, combined CEA-CABG, or staged CAS-CABG at one treatment center. Staged CEA-CABG patients fared worst due to myocardial infarction following the CEA. Staged CAS-CABG and combined CEA-CABG had similar early outcomes while the staged CAS-CABG patients had better outcomes after one year. A larger retrospective analysis³⁹ of the Nationwide Inpatient Sample database found no difference between staged and combined CEA-CABG in terms of neurologic complications or mortality.

For now, the longstanding approach that the *most symptomatic* atherosclerotic vascular bed should be treated first still holds true, but prospective trials are needed. Current guidelines recommend multidisciplinary assessment of patients with significant carotid disease before cardiac surgery (Class I, Level C), carotid duplex screening for high risk patients (Class IIa, Level C), and consideration of simultaneous or staged ‘combined’ carotid and coronary revascularization in patients with symptomatic carotid disease (Class IIa, Level C).² In asymptomatic patients (without previous stroke) with bilateral high-grade stenoses, or with unilateral high-grade stenosis and contralateral occlusion, carotid revascularization ‘may be considered’ (Class IIa, Level C).

f. Aortic valve surgery: transcatheter aortic valve implantation vs. open replacement—Aortic Valve Replacement (AVR) can be performed by an open, minimally invasive, or catheter-based procedure. For transcatheter aortic valve implantation (TAVI), the transcatheter device is inserted via a percutaneous endovascular approach, or via a cardiac transapical approach. This procedure is typically used in patients deemed too high risk for conventional open replacement.⁴⁰ The Placement of Aortic Transcatheter Valves (PARTNER) trial⁴¹ compared patients randomized to TAVI vs open AVR. The incidence of

all transient ischemic attacks (TIA) or stroke at 1 year was 8.7% for TAVI and 4.3% for open AVR ($P = 0.03$); 11.2% vs 6.5% ($P = 0.05$) at 2 years. Stroke alone was not statistically different between groups; 6.0% for TAVI and 3.2% for open AVR at 1 year ($P = 0.08$). Mortality was approximately 25% at 1 year and 35% at 2 years in this high risk patient population. Nonetheless, specific procedural strategies such as implantation without valvuloplasty and cerebral embolic protection devices have been proposed to decrease TAVI-associated stroke risk.⁴² Patients are also typically treated with dual antiplatelet therapy following TAVI, but comparative effectiveness data regarding various antithrombotic strategies are limited at present.⁴⁰

For valvular surgeries performed using minimally invasive or robotic techniques, outcomes are considered acceptable when compared with traditional techniques; however, comparative data are limited.⁴³

II. INTRAOPERATIVE MANAGEMENT TO MINIMIZE STROKE

a. Optimizing blood pressure during cardiac surgery—Several studies have attempted to define the optimal blood pressure which would result in the fewest neurologic complications after cardiac surgery. Cardiac surgery patients randomized to a higher mean arterial pressure (MAP) (80–100 mmHg vs. 50–60 mmHg) had decreased neurologic complications in one trial.⁴⁴ Indeed, a subsequent trial⁴⁵ found an association between intraoperative hypotension and the incidence of neurologic complications. In these trials, patients with severe aortic atherosclerotic disease had reduced stroke rates with a MAP target of 80 mmHg. Aronson and colleagues⁴⁶ conducted a post hoc analysis of perioperative blood pressure variability in >1500 patients from the ECLIPSE cardiac surgery trials, a combination of 3 prospective randomized parenteral antihypertensive drug treatment trials. They found that systolic blood pressure variability correlated with 30-day mortality in proportion to the time spent outside a 75–135 mmHg range intraoperatively, and outside 85–145 mmHg postoperatively, but it is unclear whether these hemodynamic derangements actually contributed to increased mortality or whether they were simply surrogate markers for sicker patients. Another recent study found less early cognitive dysfunction in cardiac surgery patients randomized to high (vs low) pressure CPB,⁴⁷ but the small sample size limits definitive conclusions.⁴⁸ Taken together, these studies suggest that maintaining an intraoperative MAP >80 mmHg may decrease neurologic complications in cardiac surgery patients. Larger randomized trials will be necessary to confirm this finding, and to assess the incidence of other complications associated with higher pressure CPB. More sophisticated approaches to individualizing cerebral perfusion pressure targets are discussed below.

b. Intraoperative cerebral monitoring to prevent neurologic complications—

Continuous global cerebral blood flow monitoring is not routinely available in the operating room; therefore, various surrogates for cerebral blood flow have been utilized in cardiac surgery. Continuous electroencephalographic (cEEG) monitoring, used to detect ischemia-induced changes in brain electrical activity, can monitor large areas of cortex but cannot detect focal cerebral ischemia and is confounded by temperature effects during intraoperative hypothermia.⁴⁹ However, cEEG use in critical care is expanding and may

prove to be a beneficial tool for ongoing monitoring of cerebral perfusion or subclinical seizures after cardiac surgery.

Near-infrared spectroscopy (NIRS), based on the differential absorption of light by oxygenated vs deoxygenated hemoglobin, is an attractive option for intraoperative cerebral perfusion monitoring.^{50, 51} Cerebral desaturation events measured by NIRS have correlated with cognitive decline after cardiac surgery.⁵² Another study randomized CABG patients to receive cerebral oximetry monitoring with an active treatment protocol for desaturation events, or a control group with blinded monitors.⁵³ A decreased incidence in the composite endpoint of major morbidity or mortality was seen in the active treatment arm. A non-significant trend toward stroke reduction was also noted.

Ono and colleagues found impaired cerebral autoregulation in 20% of cardiac surgery patients using combined monitoring with transcranial Doppler (TCD) and NIRS.⁵⁴ These patients had increased perioperative stroke rates vs those with intact autoregulation. The same group subsequently reported the validation of a stand-alone NIRS monitor in measuring autoregulation,⁵⁵ and correlated time below the lower limit of autoregulation with perioperative morbidity following cardiac surgery.⁵⁶ Larger studies will be necessary to determine whether NIRS perfusion and/or autoregulation monitoring, with individualized treatment protocols, decreases stroke or neurocognitive outcomes in cardiac surgery.

c. Hypothermic vs. normothermic CPB—Despite its common use, there is no proven benefit for cooling below 32°C – 34°C (mild hypothermia) during CPB.^{57–59} Multiple trials have shown that moderate hypothermia (28°C – 32°C) during CPB does not alter the rate of intraoperative cerebral emboli⁵⁸ (as measured by TCD) nor the rate of stroke or cognitive decline.⁵⁹ On the other hand, rewarming may be a source of cerebral injury, and recommendations are to rewarm slowly with avoidance of overshoot hyperthermia intraoperatively or postoperatively.⁶⁰

d. Transesophageal echocardiography and epiaortic ultrasound—The degree of aortic atherosclerosis is strongly associated with perioperative stroke in cardiac surgery patients.² Epiaortic ultrasound (EAU) evaluation of the aorta is superior to manual palpation or TEE assessment for detecting aortic atherosclerosis.⁶¹ EAU is an intuitive approach to detect and avoid embolizing aortic atheroma, and it has a Class IIa, Level B recommendation from the American Heart Association.² However, it is unclear whether EAU use improves neurologic outcomes as randomized trials are lacking.⁶¹ It should be noted that randomized trials will be difficult to conduct in this area due to a lack of equipoise; EAU evaluation is believed to decrease stroke risk, and there are few risks associated with its use.

e. Neuraxial analgesia and neurologic outcome—Epidural analgesia has been shown to decrease thromboembolism and improve outcomes following non-cardiac surgery.⁶² These findings have led to additional studies to determine whether epidural analgesia also improves outcomes in cardiac surgery. A meta-analysis indicated that thoracic epidural analgesia (TEA) reduced supraventricular arrhythmias and respiratory complications in cardiac surgery patients, but did not reduce neurocognitive complications.⁶³ However, the largest randomized trial to date showed no clinically relevant benefit of TEA in 654 cardiac

surgery patients.⁶⁴ Overall, TEA is rarely used in cardiac surgery due to risk of epidural hematoma formation in the setting of high-dose heparinization for CPB, and because of a lack of evidence for benefit over routine care.

f. Hemodilution and transfusion—Extreme intraoperative hemodilution (hematocrit <18%) during CPB has been practiced to minimize transfusion-related complications. However, it is associated with increased stroke⁶⁵ and postoperative cognitive decline (POCD),⁶⁶ and is no longer standard care. The Transfusion Requirement After Cardiac Surgery (TRACS) trial found that a restrictive transfusion strategy targeting a hematocrit 24% was non-inferior to a liberal strategy targeting 30%; a 6% incidence of neurologic complications was observed in both groups.⁶⁷ Current STS guidelines⁶⁸ recommend maintaining a hemoglobin level >6mg/dL on CPB and 7mg/dl postoperatively (Class IIa, Level C) with individual tailoring as clinically indicated.

g. Glycemic control—Preoperative optimization of glycemic control has correlated with small improvements in neurologic outcome in some cardiac surgery trials.² Tight glycemic control in ICU patients (many of whom underwent cardiac surgery) demonstrated a reduction in morbidity and mortality.⁶⁹ Intraoperative hyperglycemia has been associated with increased risk for neurocognitive injury in non-diabetic patients,⁷⁰ although a subsequent study showed that tight glycemic control yields no demonstrable benefit and actually increases morbidity.⁷¹ Two other studies also found that tight glycemic control during cardiac surgery does not improve neurologic outcomes,^{72, 73} and the >6000 patient NICE-SUGAR critical care trial found an association between hypoglycemic episodes (due to tight glycemic control) and mortality.⁷⁴ Current recommendations thus suggest maintaining blood glucose at < 180 mg/dL during and after cardiac surgery (Class I, Level B).²

III. TREATING ACUTE ISCHEMIC STROKE IN THE PERIOPERATIVE SETTING

Current stroke guidelines recommend avoiding systemic thrombolysis within 14 days of major surgery,⁷⁵ thus precluding the use of *intravenous* alteplase (t-PA) in most cases of stroke after cardiovascular surgery. Localized intra-arterial thrombolysis has been described with acceptable safety in this setting in one small case series.⁷⁶

a. Clot/embolus extraction—Clot retrieval devices hold promise for acute ischemic stroke (AIS) therapy after cardiac surgery. Currently, 4 clot extraction devices are FDA-approved for use in the United States: the Merci Retriever, Penumbra System, Trevo Pro, and the Solitaire Device (<http://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm>; accessed July 1, 2013). Neurointerventionalists also use aspiration and microcatheter disruption techniques⁷⁷ to treat AIS, although any of these therapies must be performed within 8 hours of stroke ictus. Patients with AIS (verified by absence of hemorrhage on brain CT imaging) can undergo CT or MR angiography to identify large vessel occlusion, or may go directly to catheter angiography, depending on institutional protocols.

The randomized SWIFT trial showed that the Solitaire stent-retriever was superior to the helical Merci device for clot/embolus retrieval.⁷⁷ Indeed, a higher number of patients in the

Solitaire group were recanalized (Thrombolysis In Myocardial Ischemia [TIMI] grade 2 or 3 flow), and had good neurologic outcomes at 3 months. Similarly, the TREVO2 study showed higher reperfusion rates in patients randomized to undergo clot retrieval with the Trevo Pro stent retriever vs the Merci retriever.⁷⁸ Extrapolation of these data to the perioperative setting is speculative, but these data clearly show that stent retriever devices are superior to the helical devices, and anecdotal reports support their use perioperatively.⁷⁹ Looking ahead, cardiovascular surgery performed in ‘hybrid’ operating rooms with endovascular equipment could facilitate immediate cerebral angiography and subsequent clot extraction in the setting of a unilateral change in cerebral oximetry, cEEG, or TCD velocities.

It should be noted that there is controversy regarding the use of general anesthesia for acute stroke interventions. Many neurointerventionalists prefer general anesthesia for these clot extraction procedures, but retrospective data suggests an association between the use of general anesthesia for AIS interventions and worsened outcomes.⁸⁰ This association may actually reflect cerebral hypoperfusion (SBP < 140mmHg).⁸⁰ Prospective randomized trials with equal blood pressure targets in patients under general anesthesia vs controls should clarify this issue. Until then, it is unclear whether general anesthesia is detrimental in these cases, although clear blood pressure targets may be helpful.

IV. THERAPEUTIC HYPOTHERMIA FOR GLOBAL HYPOXIC-ISCHEMIC CEREBRAL INJURY

Hypoxic cerebral injury from dysrhythmias, mechanical injury to the heart, or other complications leading to cardiac arrest can occur during cardiac surgery. While therapeutic hypothermia (TH) remains unproven in CPB and AIS, strong evidence supports its use after out-of-hospital cardiac arrest.⁸¹ Comatose survivors of out-of-hospital cardiac arrest with return of spontaneous circulation, benefit from rapid induction of TH.⁸² Target temperature is 32°C–34°C, and duration of TH is 24 hours in most centers. Furthermore, an increasing number of in-hospital cardiac arrest survivors are undergoing TH,⁸³ although outcome data are limited.

Determining whether a patient is comatose after the return of spontaneous circulation is often challenging in the perioperative setting due to the presence of anesthetic agents. In these situations, an empiric decision must be made regarding whether to induce TH. The goal is rapid induction of hypothermia, although there is no evidence to suggest a set therapeutic time window beyond which cooling is futile.⁸¹ Cooling can be facilitated by CPB in the operating room, or most efficiently by bolus infusion of cold intravenous fluids in other settings.⁸⁴ Hypothermia can be maintained with surface or endovascular cooling devices.⁸⁵ These devices allow automated temperature control and controlled rewarming (typically 0.1°C–0.3°C/hr over 12–24 hours) to avoid overshoot hyperthermia. Anti-epileptic seizure prophylaxis may also be considered, but in our practice we administer this only to patients with epileptiform EEG activity or clinical seizures.

In general, TH is well tolerated and the only viable treatment option after cardiac arrest, but there is only evidence regarding feasibility,⁸⁶ not safety or efficacy, after cardiac surgery. Coagulopathy and immunosuppression are both risks of TH, although these risks may be small compared to a potentially devastating neurologic injury.⁸¹

V. NEUROCOGNITIVE COMPLICATIONS: DELIRIUM AND COGNITIVE DECLINE

Ever since Bedford's seminal case series in 1955,⁸⁷ we have known that some patients experience neurocognitive difficulties after anesthesia and surgery. Although perioperative outcomes have clearly improved since that time, neurocognitive sequelae of cardiac surgery, including delirium and POCD, remain common and may affect over half of patients,^{88, 89} although spontaneously resolving in as many as 50% of those affected.^{89, 90} Whether delirium and POCD are on a pathophysiologic continuum or represent distinct cerebral injuries is unclear; however, immediate post-operative delirium (POD) has been associated with longer term decreases in cognition.⁸⁹ It is difficult to understand the relationship between delirium and POCD in part because we do not fully understand the pathophysiology of either condition.

a. Post-operative delirium—Delirium is an acute change in mental status marked by confusion and inattention, with a poorly defined pathophysiology.⁹¹ It is a psychiatric diagnosis, subtyped into hyper- and hypoactive forms and requires formal assessment, such as the confusion assessment method (CAM; 82% sensitivity, 99% specificity on recent meta-analysis),⁹² to avoid underdiagnosis. Saczynski and colleagues prospectively studied cardiac surgery patients to investigate the correlation between POD and POCD.⁸⁹ Patients who developed POD (46%) were older, more often female, had lower educational level and baseline cognitive scores, higher Charleson Comorbidity Indices, and more prior strokes or TIAs. Mini-mental state examination (MMSE) scores declined significantly at post-operative day 2, and then increased on days 3–5. Improvement slowed through 6 months, and stabilized from 6–12 months. Patients without POD returned to their baseline cognitive status by 1 month postoperatively, while patients with POD did not return to baseline by 1 year. Functional impairment (compared to baseline) was also seen in a higher proportion of patients with POD (vs those without POD) at 6 months. Other studies have also linked delirium to higher mortality, cognitive decline, and decreased quality of life.^{93, 94} Most recently, Arensen et al⁹⁵ retrospectively analyzed over 1000 cardiac surgery patients in two distinct ICU environments. Delirium rates were similar in both groups at approximately 15%. Factors associated with delirium included: age >65yrs, postoperative stroke, mechanical ventilation >24hrs, post-operative renal insufficiency, post-operative blood product administration, concomitant CABG-valve surgery, and pre-operative benzodiazepine use.⁹⁵

As highlighted above, traditional risk factors for POD in cardiac surgery patients include depression, stroke or TIA history, decreased baseline MMSE score, increased baseline serum creatinine, and abnormal serum albumin.^{94, 96} Despite the identification of these risk factors, the pathophysiology of POD remains unclear. Numerous biomarkers have been correlated with delirium,⁹⁷ including inflammatory markers,⁹⁸ markers of brain injury,⁹⁹ and serum creatinine.⁹⁴ Neuroimaging findings can also correlate with delirium.¹⁰⁰ The challenge will be determining whether these correlations can lead us to mechanisms underlying the pathophysiology of POD.

Although our understanding of POD is incomplete, interventions to prevent or treat POD have been studied in cardiac surgery patients. The centrally acting acetylcholinesterase

inhibitor rivastigmine did not prevent delirium in one trial.¹⁰¹ A rivastigmine trial in critically ill patients found no decrease in delirium duration and was stopped early due to increased mortality in the rivastigmine group.¹⁰²

Neuroleptic prophylaxis for delirium has been more successful. Cardiac surgery patients randomized to receive risperidone after developing ‘subsyndromal delirium’ showed a significant reduction in frank delirium when compared to placebo-treated patients,¹⁰³ consistent with results of a prior study.¹⁰⁴ Finally, dexmedetomidine is superior to lorazepam,¹⁰⁵ midazolam,^{106, 107} and propofol¹⁰⁷ in reducing delirium in mechanically ventilated patients. In the DEXmedetomidine COMpared to Morphine, DEXCOM study,¹⁰⁸ dexmedetomidine decreased the duration but not the incidence of delirium in cardiac surgery patients. These studies suggest that neuroleptics and dexmedetomidine reduce the incidence and duration of delirium, respectively. However, more trials are needed to define the management of POD in cardiac surgery patients.

b. Postoperative cognitive decline: definition and controversy—POCD is a somewhat controversial syndrome,^{109, 110} defined by a drop in neuropsychological test scores from before to after surgery. There are three main reasons for this controversy. First, different studies have used different test score thresholds and methodologies to define POCD.¹¹¹ Second, POCD is not a clinical diagnosis. It is not listed in the DSM-V, and patients cannot be described as having POCD unless they undergo a formal preoperative cognitive testing battery. Third, some studies of POCD have not included a non-surgical control group,⁸⁸ so it remains possible that patients who developed the cognitive deficits measured by POCD testing would have done so whether or not they undergone operative care.¹⁰⁹ This last question focuses on etiology, and the question of what causes these cognitive deficits should not misinterpreted to imply that these cognitive deficits do not exist. Importantly, POCD has been associated with decreased quality of life¹¹² and increased 1 year mortality in multiple studies,^{113, 114} strongly indicating that it is an important problem that affects some of our patients.

Patient factors such as baseline cognition and comorbidities correlate better with the development of POCD than do procedural variables.^{110, 115} Furthermore, conflicting data exists regarding the difference, if any, in post-operative cognitive trajectory among surgery patients vs non-surgery controls.^{110, 115–118} Nonsurgical control groups have included patients who had subsequently undergone PCI or other surgical procedures under general anesthesia, introducing additional confounders into the control group.¹¹⁰ Taken together, these studies raise the question of whether POCD reflects the natural course of age-related cognitive decline, ie, *patient* factors, or whether it is an effect of anesthesia and/or surgery on cognitive function, ie, *procedural* factors. The latter possibility is supported by data demonstrating that perioperative care is associated with unique pathophysiologic processes such as transcerebral platelet activation¹¹⁹ and inflammation¹²⁰ that may impact cognition. Unraveling the role of patient and procedural factors in POCD will remain an area of active investigation and debate.

A number of therapeutic trials have aimed to reduce POCD after cardiac surgery. Our group recently reported a trial of intravenous magnesium, an N-methyl-D-aspartate antagonist, vs

placebo and found no difference in neurocognitive outcome.¹²¹ Similarly, we found no effect of lidocaine on POCD.¹²² Other groups have investigated piracetam,¹²³ ischemic preconditioning,¹²⁴ mild intraoperative hypothermia,¹²⁵ and avoidance of CPB,¹²⁶ without finding an impact on postoperative cognition. These endeavors highlight the need for better mechanistic studies of pathophysiology moving forward.

c. Mechanisms of neurocognitive injury: genetic predisposition, biochemical markers, silent stroke, and hypoperfusion—Genetic¹²⁷ and proteomic¹²⁸ approaches have been used to study the pathophysiology of POCD. Single nucleotide polymorphisms for C-reactive protein and P-selectin were associated with reduced cognitive decline in a cardiac surgery cohort,¹²⁷ whereas the apolipoprotein E4 polymorphism, which is associated with the development of Alzheimer's disease, did not predict the development of POCD.¹²⁹ Plasma protein biomarkers of inflammation and brain injury also did not correlate with POCD,¹³⁰ although cerebrospinal fluid (CSF) biomarkers including S100 β , tau, and beta-amyloid, did correlate with cognitive decline.¹³¹ These findings suggest that CSF markers may better reflect the cerebral milieu of patients with POCD than plasma markers.

Several studies have also attempted to correlate POCD with microembolic cerebral injury seen on diffusion weighted MRI. These 'silent strokes' are seen in up to 70% of patients after cardiac surgery, but the small studies to date have not correlated these radiographic lesions with clinical stroke or cognitive decline.^{132–135} Blood-brain barrier dysfunction after cardiac surgery has also been reported,¹³⁶ which could facilitate an influx of inflammatory mediators¹²⁰ that may contribute to POCD (reviewed in¹³⁷).

Finally, POCD may also be related to cerebral hypoperfusion. Mounting evidence suggests a connection between decreased cerebral perfusion and neurocognitive impairment outside of cardiac surgery.^{138, 139} Similarly, decreased preoperative blood flow in the dominant hemisphere, ie, decreased MCA velocity as measured by TCD, has been associated with both early POCD¹⁴⁰ and late POCD.¹⁴¹

New MRI technologies, such as diffusion-weighted imaging and functional imaging, may help us to better identify patients at risk for or suffering from cognitive deficits after surgery.¹⁴² Future studies that couple neuroimaging and neuromonitoring technologies with biochemical studies and cognitive testing will likely shift current paradigms regarding POCD.

CONCLUSION

As increasing numbers of elderly patients undergo cardiovascular surgery, neurologic complications remain a significant source of morbidity. This overview highlights current interventions to minimize stroke risk, treat perioperative stroke, and manage perioperative hypoxic-ischemic injury. We also summarize current approaches to perioperative neurocognitive disorders with an outlook toward future developments in the field.

Neurologists should be prepared to manage a spectrum of complications in the perioperative cardiac surgical patient, including acute cerebral thromboembolic events, anoxic brain injury, and cognitive deficits such as delirium and POCD. Protocols to deliver therapeutic

hypothermia emergently following hypoxic brain injury, and endovascular therapy following acute ischemic stroke, should be created at all cardiovascular surgery centers. New neuroimaging and investigative neuroscience technologies are being used to probe the pathophysiology of perioperative neurocognitive dysfunction, which at present remains unknown.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Kathy Gage (Duke University, Department of Anesthesiology) for editorial assistance.

Support: This work was funded by the Duke University Department of Anesthesiology and supported in part by grants #HL096978, HL108280 and HL109971 (JPM) from the National Institutes of Health, Washington, DC.

References

1. Gilman S. Cerebral Disorders after Open-Heart Operations. *The New England journal of medicine*. 1965; 272:489–98. [PubMed: 14250198]
2. Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, et al. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011; 124(23):e652–735. [PubMed: 22064599]
3. Tarakji KG, Sabik JF 3rd, Bhudia SK, Batizy LH, Blackstone EH. Temporal onset, risk factors, and outcomes associated with stroke after coronary artery bypass grafting. *JAMA : the journal of the American Medical Association*. 2011; 305(4):381–90. [PubMed: 21266685]
4. Barreto-Filho JA, Wang Y, Dodson JA, Desai MM, Sugeng L, Geirsson A, et al. Trends in aortic valve replacement for elderly patients in the United States, 1999–2011. *JAMA : the journal of the American Medical Association*. 2013; 310(19):2078–85. [PubMed: 24240935]
5. Alam M, Virani SS, Shahzad SA, Siddiqui S, Siddiqui KH, Mumtaz SA, et al. Comparison by Meta-Analysis of Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting in Patients With a Mean Age of ≥ 70 Years. *The American journal of cardiology*. 2013
6. ElBardissi AW, Aranki SF, Sheng S, O'Brien SM, Greenberg CC, Gammie JS. Trends in isolated coronary artery bypass grafting: an analysis of the Society of Thoracic Surgeons adult cardiac surgery database. *The Journal of thoracic and cardiovascular surgery*. 2012; 143(2):273–81. [PubMed: 22248680]
7. Newman MF, Ferguson TB, White JA, Ambrosio G, Koglin J, Nussmeier NA, et al. Effect of adenosine-regulating agent acadesine on morbidity and mortality associated with coronary artery bypass grafting: the RED-CABG randomized controlled trial. *JAMA : the journal of the American Medical Association*. 2012; 308(2):157–64. [PubMed: 22782417]
8. Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, et al. Strategies for multivessel revascularization in patients with diabetes. *The New England journal of medicine*. 2012; 367(25):2375–84. [PubMed: 23121323]
9. Houlind K, Kjeldsen BJ, Madsen SN, Rasmussen BS, Holme SJ, Nielsen PH, et al. On-pump versus off-pump coronary artery bypass surgery in elderly patients: results from the Danish on-pump versus off-pump randomization study. *Circulation*. 2012; 125(20):2431–9. [PubMed: 22523305]
10. Bucerius J, Gummert JF, Borger MA, Walther T, Doll N, Onnasch JF, et al. Stroke after cardiac surgery: a risk factor analysis of 16,184 consecutive adult patients. *The Annals of thoracic surgery*. 2003; 75(2):472–8. [PubMed: 12607656]
11. Hedberg M, Boivie P, Engstrom KG. Early and delayed stroke after coronary surgery - an analysis of risk factors and the impact on short- and long-term survival. *European journal of cardio-thoracic*

- surgery : official journal of the European Association for Cardio-thoracic Surgery. 2011; 40(2): 379–87. [PubMed: 21333545]
12. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *The New England journal of medicine*. 2009; 360(10):961–72. [PubMed: 19228612]
 13. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Stahle E, Colombo A, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet*. 2013; 381(9867):629–38. [PubMed: 23439102]
 14. Weintraub WS, Grau-Sepulveda MV, Weiss JM, O'Brien SM, Peterson ED, Kolm P, et al. Comparative effectiveness of revascularization strategies. *The New England journal of medicine*. 2012; 366(16):1467–76. [PubMed: 22452338]
 15. Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet*. 2009; 373(9670):1190–7. [PubMed: 19303634]
 16. Deb S, Wijeyesundera HC, Ko DT, Tsubota H, Hill S, Fremes SE. Coronary artery bypass graft surgery vs percutaneous interventions in coronary revascularization: a systematic review. *JAMA : the journal of the American Medical Association*. 2013; 310(19):2086–95. [PubMed: 24240936]
 17. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*. 2011; 124(23):e574–651. [PubMed: 22064601]
 18. Bainbridge D, Martin J, Cheng D. Off pump coronary artery bypass graft surgery versus conventional coronary artery bypass graft surgery: a systematic review of the literature. *Seminars in cardiothoracic and vascular anesthesia*. 2005; 9(1):105–11. [PubMed: 15735848]
 19. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, et al. Off-pump or on-pump coronary-artery bypass grafting at 30 days. *The New England journal of medicine*. 2012; 366(16): 1489–97. [PubMed: 22449296]
 20. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, et al. Effects of Off-Pump and On-Pump Coronary-Artery Bypass Grafting at 1 Year. *New England Journal of Medicine*. 2013; 368(13):1179–88. [PubMed: 23477676]
 21. Liu YH, Wang DX, Li LH, Wu XM, Shan GJ, Su Y, et al. The effects of cardiopulmonary bypass on the number of cerebral microemboli and the incidence of cognitive dysfunction after coronary artery bypass graft surgery. *Anesthesia and analgesia*. 2009; 109(4):1013–22. [PubMed: 19762724]
 22. Mangano DT. Aspirin and mortality from coronary bypass surgery. *The New England journal of medicine*. 2002; 347(17):1309–17. [PubMed: 12397188]
 23. Kuhn EW, Liakopoulos OJ, Stange S, Deppe AC, Slottosch I, Choi YH, et al. Preoperative statin therapy in cardiac surgery: a meta-analysis of 90 000 patients. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 2013
 24. Liakopoulos OJ, Kuhn EW, Slottosch I, Wassmer G, Wahlers T. Preoperative statin therapy for patients undergoing cardiac surgery. *Cochrane Database Syst Rev*. 2012; 4 CD008493.
 25. Collard CD, Body SC, Shernan SK, Wang S, Mangano DT. Preoperative statin therapy is associated with reduced cardiac mortality after coronary artery bypass graft surgery. *The Journal of thoracic and cardiovascular surgery*. 2006; 132(2):392–400. [PubMed: 16872968]
 26. Likosky DS, Leavitt BJ, Marrin CA, Malenka DJ, Reeves AG, Weintraub RM, et al. Intra- and postoperative predictors of stroke after coronary artery bypass grafting. *The Annals of thoracic surgery*. 2003; 76(2):428–34. discussion 35. [PubMed: 12902078]
 27. Arsenault KA, Yusuf AM, Crystal E, Healey JS, Morillo CA, Nair GM, et al. Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery. *Cochrane Database Syst Rev*. 2013; 1 CD003611.

28. Mozaffarian D, Marchioli R, Macchia A, Sillelta MG, Ferrazzi P, Gardner TJ, et al. Fish oil and postoperative atrial fibrillation: the Omega-3 Fatty Acids for Prevention of Post-operative Atrial Fibrillation (OPERA) randomized trial. *JAMA : the journal of the American Medical Association*. 2012; 308(19):2001–11. [PubMed: 23128104]
29. Mariani J, Doval HC, Nul D, Varini S, Grancelli H, Ferrante D, et al. N-3 polyunsaturated fatty acids to prevent atrial fibrillation: updated systematic review and meta-analysis of randomized controlled trials. *Journal of the American Heart Association*. 2013; 2(1):e005033. [PubMed: 23525440]
30. Reddy VY, Doshi SK, Sievert H, Buchbinder M, Neuzil P, Huber K, et al. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-Year Follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) Trial. *Circulation*. 2013; 127(6):720–9. [PubMed: 23325525]
31. Budera P, Straka Z, Osmancik P, Vanek T, Jelinek S, Hlavicka J, et al. Comparison of cardiac surgery with left atrial surgical ablation vs. cardiac surgery without atrial ablation in patients with coronary and/or valvular heart disease plus atrial fibrillation: final results of the PRAGUE-12 randomized multicentre study. *European heart journal*. 2012; 33(21):2644–52. [PubMed: 22930458]
32. Cox JL. Mechanical closure of the left atrial appendage: Is it time to be more aggressive? *The Journal of thoracic and cardiovascular surgery*. 2013; 146(5):1018–27. e2. [PubMed: 23993272]
33. Naylor AR, Bown MJ. Stroke after cardiac surgery and its association with asymptomatic carotid disease: an updated systematic review and meta-analysis. *European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery*. 2011; 41(5):607–24.
34. Lee EJ, Choi KH, Ryu JS, Jeon SB, Lee SW, Park SW, et al. Stroke risk after coronary artery bypass graft surgery and extent of cerebral artery atherosclerosis. *Journal of the American College of Cardiology*. 2011; 57(18):1811–8. [PubMed: 21527154]
35. Brott TG, Hobson RW 2nd, Howard G, Roubin GS, Clark WM, Brooks W, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *The New England journal of medicine*. 2010; 363(1):11–23. [PubMed: 20505173]
36. Barrera JG, Rojas KE, Balestrini C, Espinel C, Figueredo A, Saaibi JF, et al. Early results after synchronous carotid stent placement and coronary artery bypass graft in patients with asymptomatic carotid stenosis. *Journal of vascular surgery : official publication, the Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, North American Chapter*. 2013; 57(2 Suppl):58S–63S.
37. Timaran CH, Rosero EB, Smith ST, Valentine RJ, Modrall JG, Clagett GP. Trends and outcomes of concurrent carotid revascularization and coronary bypass. *Journal of vascular surgery : official publication, the Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, North American Chapter*. 2008; 48(2):355–60. discussion 60–1.
38. Shishehbor MH, Venkatachalam S, Sun Z, Rajeswaran J, Kapadia SR, Bajzer C, et al. A Direct Comparison of Early and Late Outcomes with Three Approaches to Carotid Revascularization and Open Heart Surgery. *Journal of the American College of Cardiology*. 2013
39. Gopaldas RR, Chu D, Dao TK, Huh J, LeMaire SA, Lin P, et al. Staged versus synchronous carotid endarterectomy and coronary artery bypass grafting: analysis of 10-year nationwide outcomes. *The Annals of thoracic surgery*. 2011; 91(5):1323–9. discussion 9. [PubMed: 21457941]
40. Desai CS, Bonow RO. Transcatheter valve replacement for aortic stenosis: balancing benefits, risks, and expectations. *JAMA : the journal of the American Medical Association*. 2012; 308(6):573–4. [PubMed: 22871866]
41. Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *The New England journal of medicine*. 2012; 366(18):1686–95. [PubMed: 22443479]
42. Webb JG, Barbanti M. Cerebral embolization during transcatheter aortic valve implantation. *Circulation*. 2012; 126(13):1567–9. [PubMed: 23008467]
43. Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, et al. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart

Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2008; 118(15):e523–661. [PubMed: 18820172]

44. Gold JP, Charlson ME, Williams-Russo P, Szatrowski TP, Peterson JC, Pirraglia PA, et al. Improvement of outcomes after coronary artery bypass. A randomized trial comparing intraoperative high versus low mean arterial pressure. *The Journal of thoracic and cardiovascular surgery*. 1995; 110(5):1302–11. discussion 11–4. [PubMed: 7475182]
45. Charlson ME, Peterson JC, Krieger KH, Hartman GS, Hollenberg JP, Briggs WM, et al. Improvement of outcomes after coronary artery bypass II: a randomized trial comparing intraoperative high versus customized mean arterial pressure. *Journal of cardiac surgery*. 2007; 22(6):465–72. [PubMed: 18039205]
46. Aronson S, Dyke CM, Levy JH, Cheung AT, Lumb PD, Avery EG, et al. Does perioperative systolic blood pressure variability predict mortality after cardiac surgery? An exploratory analysis of the ECLIPSE trials. *Anesthesia and analgesia*. 2011; 113(1):19–30. [PubMed: 21346163]
47. Siepe M, Pfeiffer T, Gieringer A, Zemmann S, Benk C, Schlensak C, et al. Increased systemic perfusion pressure during cardiopulmonary bypass is associated with less early postoperative cognitive dysfunction and delirium. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 2011; 40(1):200–7. [PubMed: 21168339]
48. Alhan CH, Toraman F, Karabulut H. Is increased perfusion pressure really necessary during cardiopulmonary bypass? *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 2012; 41(5):1213–4. author reply 4. [PubMed: 22219454]
49. Kertai MD, Whitlock EL, Avidan MS. Brain monitoring with electroencephalography and the electroencephalogram-derived bispectral index during cardiac surgery. *Anesthesia and analgesia*. 2012; 114(3):533–46. [PubMed: 22253267]
50. Ghosh A, Elwell C, Smith M. Review article: cerebral near-infrared spectroscopy in adults: a work in progress. *Anesthesia and analgesia*. 2012; 115(6):1373–83. [PubMed: 23144435]
51. Zheng F, Sheinberg R, Yee MS, Ono M, Zheng Y, Hogue CW. Cerebral near-infrared spectroscopy monitoring and neurologic outcomes in adult cardiac surgery patients: a systematic review. *Anesthesia and analgesia*. 2013; 116(3):663–76. [PubMed: 23267000]
52. Slater JP, Guarino T, Stack J, Vinod K, Bustami RT, Brown JM 3rd. Cerebral oxygen desaturation predicts cognitive decline and longer hospital stay after cardiac surgery. *The Annals of thoracic surgery*. 2009; 87(1):36–44. discussion -5. [PubMed: 19101265]
53. Murkin JM, Adams SJ, Novick RJ, Quantz M, Bainbridge D, Iglesias I, et al. Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study. *Anesthesia and analgesia*. 2007; 104(1):51–8. [PubMed: 17179242]
54. Ono M, Joshi B, Brady K, Easley RB, Zheng Y, Brown C, et al. Risks for impaired cerebral autoregulation during cardiopulmonary bypass and postoperative stroke. *British journal of anaesthesia*. 2012; 109(3):391–8. [PubMed: 22661748]
55. Ono M, Zheng Y, Joshi B, Sigl JC, Hogue CW. Validation of a stand-alone near-infrared spectroscopy system for monitoring cerebral autoregulation during cardiac surgery. *Anesthesia and analgesia*. 2013; 116(1):198–204. [PubMed: 23223100]
56. Ono M, Brady K, Easley RB, Brown C, Kraut M, Gottesman RF, et al. Duration and magnitude of blood pressure below cerebral autoregulation threshold during cardiopulmonary bypass is associated with major morbidity and operative mortality. *The Journal of thoracic and cardiovascular surgery*. 2013
57. Ho KM, Tan JA. Benefits and risks of maintaining normothermia during cardiopulmonary bypass in adult cardiac surgery: a systematic review. *Cardiovascular therapeutics*. 2011; 29(4):260–79. [PubMed: 20041882]
58. Boodhwani M, Rubens F, Wozny D, Rodriguez R, Nathan HJ. Effects of sustained mild hypothermia on neurocognitive function after coronary artery bypass surgery: a randomized, double-blind study. *The Journal of thoracic and cardiovascular surgery*. 2007; 134(6):1443–50. discussion 51–2. [PubMed: 18023662]

59. Grigore AM, Mathew J, Grocott HP, Reves JG, Blumenthal JA, White WD, et al. Prospective randomized trial of normothermic versus hypothermic cardiopulmonary bypass on cognitive function after coronary artery bypass graft surgery. *Anesthesiology*. 2001; 95(5):1110–9. [PubMed: 11684979]
60. Grigore AM, Murray CF, Ramakrishna H, Djaiani G. A core review of temperature regimens and neuroprotection during cardiopulmonary bypass: does rewarming rate matter? *Anesthesia and analgesia*. 2009; 109(6):1741–51. [PubMed: 19923500]
61. Glas KE, Swaminathan M, Reeves ST, Shanewise JS, Rubenson D, Smith PK, et al. Guidelines for the performance of a comprehensive intraoperative epiaortic ultrasonographic examination: recommendations of the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists; endorsed by the Society of Thoracic Surgeons. *Anesthesia and analgesia*. 2008; 106(5):1376–84. [PubMed: 18420847]
62. Mauermann WJ, Shilling AM, Zuo Z. A comparison of neuraxial block versus general anesthesia for elective total hip replacement: a meta-analysis. *Anesthesia and analgesia*. 2006; 103(4):1018–25. [PubMed: 17000823]
63. Svircevic V, van Dijk D, Nierich AP, Passier MP, Kalkman CJ, van der Heijden GJ, et al. Meta-analysis of thoracic epidural anesthesia versus general anesthesia for cardiac surgery. *Anesthesiology*. 2011; 114(2):271–82. [PubMed: 21239975]
64. Svircevic V, Nierich AP, Moons KG, Diephuis JC, Ennema JJ, Brandon Bravo Bruinsma GJ, et al. Thoracic epidural anesthesia for cardiac surgery: a randomized trial. *Anesthesiology*. 2011; 114(2):262–70. [PubMed: 21239976]
65. Karkouti K, Djaiani G, Borger MA, Beattie WS, Fedorko L, Wijeyesundera D, et al. Low hematocrit during cardiopulmonary bypass is associated with increased risk of perioperative stroke in cardiac surgery. *The Annals of thoracic surgery*. 2005; 80(4):1381–7. [PubMed: 16181875]
66. Mathew JP, Mackensen GB, Phillips-Bute B, Stafford-Smith M, Podgoreanu MV, Grocott HP, et al. Effects of extreme hemodilution during cardiac surgery on cognitive function in the elderly. *Anesthesiology*. 2007; 107(4):577–84. [PubMed: 17893453]
67. Hajjar LA, Vincent JL, Galas FR, Nakamura RE, Silva CM, Santos MH, et al. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. *JAMA : the journal of the American Medical Association*. 2010; 304(14):1559–67. [PubMed: 20940381]
68. Ferraris VA, Brown JR, Despotis GJ, Hammon JW, Reece TB, Saha SP, et al. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. *The Annals of thoracic surgery*. 2011; 91(3):944–82. [PubMed: 21353044]
69. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. *The New England journal of medicine*. 2001; 345(19):1359–67. [PubMed: 11794168]
70. Puskas F, Grocott HP, White WD, Mathew JP, Newman MF, Bar-Yosef S. Intraoperative hyperglycemia and cognitive decline after CABG. *The Annals of thoracic surgery*. 2007; 84(5):1467–73. [PubMed: 17954047]
71. Lazar HL, McDonnell MM, Chipkin S, Fitzgerald C, Bliss C, Cabral H. Effects of aggressive versus moderate glycemic control on clinical outcomes in diabetic coronary artery bypass graft patients. *Annals of surgery*. 2011; 254(3):458–63. discussion 63–4. [PubMed: 21865944]
72. Butterworth J, Wagenknecht LE, Legault C, Zaccaro DJ, Kon ND, Hammon JW Jr, et al. Attempted control of hyperglycemia during cardiopulmonary bypass fails to improve neurologic or neurobehavioral outcomes in patients without diabetes mellitus undergoing coronary artery bypass grafting. *The Journal of thoracic and cardiovascular surgery*. 2005; 130(5):1319. [PubMed: 16256784]
73. Gandhi GY, Nuttall GA, Abel MD, Mullany CJ, Schaff HV, O'Brien PC, et al. Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: a randomized trial. *Ann Intern Med*. 2007; 146(4):233–43. [PubMed: 17310047]
74. Finfer S, Liu B, Chittock DR, Norton R, Myburgh JA, McArthur C, et al. Hypoglycemia and risk of death in critically ill patients. *The New England journal of medicine*. 2012; 367(12):1108–18. [PubMed: 22992074]

75. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke; a journal of cerebral circulation*. 2013; 44(3):870–947.
76. Moazami N, Smedira NG, McCarthy PM, Katzan I, Sila CA, Lytle BW, et al. Safety and efficacy of intraarterial thrombolysis for perioperative stroke after cardiac operation. *The Annals of thoracic surgery*. 2001; 72(6):1933–7. discussion 7–9. [PubMed: 11789774]
77. Saver JL, Jahan R, Levy EI, Jovin TG, Baxter B, Nogueira RG, et al. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. *Lancet*. 2012; 380(9849):1241–9. [PubMed: 22932715]
78. Nogueira RG, Lutsep HL, Gupta R, Jovin TG, Albers GW, Walker GA, et al. Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial. *Lancet*. 2012; 380(9849):1231–40. [PubMed: 22932714]
79. Duraes AR, Brito JC. Images in clinical medicine. Selective intraarterial thrombolysis for cardioembolic stroke. *The New England journal of medicine*. 2012; 367(17):e24. [PubMed: 23094751]
80. Davis MJ, Menon BK, Baghirzada LB, Campos-Herrera CR, Goyal M, Hill MD, et al. Anesthetic management and outcome in patients during endovascular therapy for acute stroke. *Anesthesiology*. 2012; 116(2):396–405. [PubMed: 22222475]
81. Mackensen GB, McDonagh DL, Warner DS. Perioperative hypothermia: use and therapeutic implications. *Journal of neurotrauma*. 2009; 26(3):342–58. [PubMed: 19231924]
82. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *The New England journal of medicine*. 2002; 346(8):549–56. [PubMed: 11856793]
83. Mikkelsen ME, Christie JD, Abella BS, Kerlin MP, Fuchs BD, Schweickert WD, et al. Use of Therapeutic Hypothermia After In-Hospital Cardiac Arrest*. *Critical care medicine*. 2013; 41(6):1385–95. [PubMed: 23518870]
84. Polderman KH, Rijnsburger ER, Peerdeeman SM, Girbes AR. Induction of hypothermia in patients with various types of neurologic injury with use of large volumes of ice-cold intravenous fluid. *Critical care medicine*. 2005; 33(12):2744–51. [PubMed: 16352954]
85. Song SS, Lyden PD. Overview of therapeutic hypothermia. *Current treatment options in neurology*. 2012; 14(6):541–8. [PubMed: 23007950]
86. Vollroth M, Roehrich K, Correia C, Seeburger J, Noack T, Kiefer P, et al. Cooling after successful resuscitation in cardiac surgery patients. *Journal of cardiothoracic surgery*. 2013; 8(1):190. [PubMed: 24053475]
87. Bedford PD. Adverse cerebral effects of anaesthesia on old people. *Lancet*. 1955; 269(6884):259–63. [PubMed: 13243706]
88. Newman MF, Kirchner JL, Phillips-Bute B, Gaver V, Grocott H, Jones RH, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. *The New England journal of medicine*. 2001; 344(6):395–402. [PubMed: 11172175]
89. Saczynski JS, Marcantonio ER, Quach L, Fong TG, Gross A, Inouye SK, et al. Cognitive trajectories after postoperative delirium. *The New England journal of medicine*. 2012; 367(1):30–9. [PubMed: 22762316]
90. Fontes MT, Swift RC, Phillips-Bute B, Podgoreanu MV, Stafford-Smith M, Newman MF, et al. Predictors of cognitive recovery after cardiac surgery. *Anesthesia and analgesia*. 2013; 116(2):435–42. [PubMed: 23302978]
91. Hipp DM, Ely EW. Pharmacological and nonpharmacological management of delirium in critically ill patients. *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics*. 2012; 9(1):158–75. [PubMed: 22270810]
92. Shi Q, Warren L, Saposnik G, Macdermid JC. Confusion assessment method: a systematic review and meta-analysis of diagnostic accuracy. *Neuropsychiatric disease and treatment*. 2013; 9:1359–70. [PubMed: 24092976]
93. Koster S, Hensens AG, Schuurmans MJ, van der Palen J. Consequences of delirium after cardiac operations. *The Annals of thoracic surgery*. 2012; 93(3):705–11. [PubMed: 21992939]

94. Bakker RC, Osse RJ, Tulen JH, Kappetein AP, Bogers AJ. Preoperative and operative predictors of delirium after cardiac surgery in elderly patients. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 2012; 41(3):544–9. [PubMed: 22345177]
95. Arenson BG, MacDonald LA, Grocott HP, Hiebert BM, Arora RC. Effect of intensive care unit environment on in-hospital delirium after cardiac surgery. *The Journal of thoracic and cardiovascular surgery*. 2013; 146(1):172–8. [PubMed: 23317943]
96. Rudolph JL, Jones RN, Levkoff SE, Rockett C, Inouye SK, Sellke FW, et al. Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. *Circulation*. 2009; 119(2):229–36. [PubMed: 19118253]
97. Osse RJ, Fekkes D, Tulen JH, Wierdsma AI, Bogers AJ, van der Mast RC, et al. High preoperative plasma neopterin predicts delirium after cardiac surgery in older adults. *Journal of the American Geriatrics Society*. 2012; 60(4):661–8. [PubMed: 22316274]
98. Rudolph JL, Ramlawi B, Kuchel GA, McElhaney JE, Xie D, Sellke FW, et al. Chemokines are associated with delirium after cardiac surgery. *The journals of gerontology Series A, Biological sciences and medical sciences*. 2008; 63(2):184–9.
99. Georgiadis D, Berger A, Kowatschev E, Lautenschlager C, Borner A, Lindner A, et al. Predictive value of S-100beta and neuron-specific enolase serum levels for adverse neurologic outcome after cardiac surgery. *The Journal of thoracic and cardiovascular surgery*. 2000; 119(1):138–47. [PubMed: 10612773]
100. Hatano Y, Narumoto J, Shibata K, Matsuoka T, Taniguchi S, Hata Y, et al. White-Matter Hyperintensities Predict Delirium After Cardiac Surgery. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry*. 2012
101. Gamberini M, Bolliger D, Lurati Buse GA, Burkhart CS, Grapow M, Gagneux A, et al. Rivastigmine for the prevention of postoperative delirium in elderly patients undergoing elective cardiac surgery--a randomized controlled trial. *Critical care medicine*. 2009; 37(5):1762–8. [PubMed: 19325490]
102. van Eijk MM, Roes KC, Honing ML, Kuiper MA, Karakus A, van der Jagt M, et al. Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. *Lancet*. 2010; 376(9755):1829–37. [PubMed: 21056464]
103. Hakim SM, Othman AI, Naoum DO. Early treatment with risperidone for subsyndromal delirium after on-pump cardiac surgery in the elderly: a randomized trial. *Anesthesiology*. 2012; 116(5):987–97. [PubMed: 22436797]
104. Prakanrattana U, Prapaitrakool S. Efficacy of risperidone for prevention of postoperative delirium in cardiac surgery. *Anaesthesia and intensive care*. 2007; 35(5):714–9. [PubMed: 17933157]
105. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA : the journal of the American Medical Association*. 2007; 298(22):2644–53. [PubMed: 18073360]
106. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA : the journal of the American Medical Association*. 2009; 301(5):489–99. [PubMed: 19188334]
107. Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA : the journal of the American Medical Association*. 2012; 307(11):1151–60. [PubMed: 22436955]
108. Shehabi Y, Grant P, Wolfenden H, Hammond N, Bass F, Campbell M, et al. Prevalence of delirium with dexmedetomidine compared with morphine based therapy after cardiac surgery: a randomized controlled trial (DEXmedetomidine COrnpared to Morphine-DEXCOM Study). *Anesthesiology*. 2009; 111(5):1075–84. [PubMed: 19786862]
109. Avidan MS, Evers AS. Review of clinical evidence for persistent cognitive decline or incident dementia attributable to surgery or general anesthesia. *Journal of Alzheimer's disease : JAD*. 2011; 24(2):201–16. [PubMed: 21447878]

110. Selnes OA, Gottesman RF, Grega MA, Baumgartner WA, Zeger SL, McKhann GM. Cognitive and neurologic outcomes after coronary-artery bypass surgery. *The New England journal of medicine*. 2012; 366(3):250–7. [PubMed: 22256807]
111. Rudolph JL, Schreiber KA, Culley DJ, McGlinchey RE, Crosby G, Levitsky S, et al. Measurement of post-operative cognitive dysfunction after cardiac surgery: a systematic review. *Acta anaesthesiologica Scandinavica*. 2010; 54(6):663–77. [PubMed: 20397979]
112. Phillips-Bute B, Mathew JP, Blumenthal JA, Grocott HP, Laskowitz DT, Jones RH, et al. Association of neurocognitive function and quality of life 1 year after coronary artery bypass graft (CABG) surgery. *Psychosomatic medicine*. 2006; 68(3):369–75. [PubMed: 16738066]
113. Steinmetz J, Christensen KB, Lund T, Lohse N, Rasmussen LS. Long-term consequences of postoperative cognitive dysfunction. *Anesthesiology*. 2009; 110(3):548–55. [PubMed: 19225398]
114. Monk TG, Weldon BC, Garvan CW, Dede DE, van der Aa MT, Heilman KM, et al. Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology*. 2008; 108(1):18–30. [PubMed: 18156878]
115. Evered L, Scott DA, Silbert B, Maruff P. Postoperative cognitive dysfunction is independent of type of surgery and anesthetic. *Anesthesia and analgesia*. 2011; 112(5):1179–85. [PubMed: 21474666]
116. Wahrborg P, Booth JE, Clayton T, Nugara F, Pepper J, Weintraub WS, et al. Neuropsychological outcome after percutaneous coronary intervention or coronary artery bypass grafting: results from the Stent or Surgery (SoS) Trial. *Circulation*. 2004; 110(22):3411–7. [PubMed: 15557380]
117. Sweet JJ, Finnin E, Wolfe PL, Beaumont JL, Hahn E, Marymont J, et al. Absence of cognitive decline one year after coronary bypass surgery: comparison to nonsurgical and healthy controls. *The Annals of thoracic surgery*. 2008; 85(5):1571–8. [PubMed: 18442540]
118. Medi C, Evered L, Silbert B, Teh A, Halloran K, Morton J, et al. Subtle post-procedural cognitive dysfunction after atrial fibrillation ablation. *Journal of the American College of Cardiology*. 2013; 62(6):531–9. [PubMed: 23684686]
119. Mathew JP, Rinder HM, Smith BR, Newman MF, Rinder CS. Transcerebral platelet activation after aortic cross-clamp release is linked to neurocognitive decline. *The Annals of thoracic surgery*. 2006; 81(5):1644–9. [PubMed: 16631650]
120. Reinsfelt B, Ricksten SE, Zetterberg H, Blennow K, Freden-Lindqvist J, Westerlind A. Cerebrospinal fluid markers of brain injury, inflammation, and blood-brain barrier dysfunction in cardiac surgery. *The Annals of thoracic surgery*. 2012; 94(2):549–55. [PubMed: 22698770]
121. Mathew JP, White WD, Schinderle DB, Podgoreanu MV, Berger M, Milano CA, et al. Intraoperative Magnesium Administration Does Not Improve Neurocognitive Function After Cardiac Surgery. *Stroke; a journal of cerebral circulation*. 2013
122. Mathew JP, Mackensen GB, Phillips-Bute B, Grocott HP, Glower DD, Laskowitz DT, et al. Randomized, double-blinded, placebo controlled study of neuroprotection with lidocaine in cardiac surgery. *Stroke; a journal of cerebral circulation*. 2009; 40(3):880–7.
123. Holinski S, Claus B, Alaraj N, Dohmen PM, Neumann K, Uebelhack R, et al. Cerebroprotective effect of piracetam in patients undergoing open heart surgery. *Annals of thoracic and cardiovascular surgery : official journal of the Association of Thoracic and Cardiovascular Surgeons of Asia*. 2011; 17(2):137–42.
124. Meybohm P, Renner J, Broch O, Caliebe D, Albrecht M, Cremer J, et al. Postoperative neurocognitive dysfunction in patients undergoing cardiac surgery after remote ischemic preconditioning: a double-blind randomized controlled pilot study. *PloS one*. 2013; 8(5):e64743. [PubMed: 23741380]
125. Nathan HJ, Rodriguez R, Wozny D, Dupuis JY, Rubens FD, Bryson GL, et al. Neuroprotective effect of mild hypothermia in patients undergoing coronary artery surgery with cardiopulmonary bypass: five-year follow-up of a randomized trial. *The Journal of thoracic and cardiovascular surgery*. 2007; 133(5):1206–11. [PubMed: 17467430]
126. Kennedy ED, Choy KC, Alston RP, Chen S, Farhan-Alanie MM, Anderson J, et al. Cognitive outcome after on- and off-pump coronary artery bypass grafting surgery: a systematic review and meta-analysis. *Journal of cardiothoracic and vascular anesthesia*. 2013; 27(2):253–65. [PubMed: 23507014]

127. Mathew JP, Podgoreanu MV, Grocott HP, White WD, Morris RW, Stafford-Smith M, et al. Genetic variants in P-selectin and C-reactive protein influence susceptibility to cognitive decline after cardiac surgery. *Journal of the American College of Cardiology*. 2007; 49(19):1934–42. [PubMed: 17498578]
128. Reis HJ, Wang L, Verano-Braga T, Pimenta AM, Kalman J, Bogats G, et al. Evaluation of post-surgical cognitive function and protein fingerprints in the cerebro-spinal fluid utilizing surface-enhanced laser Desorption/Ionization time-of-flight mass-spectrometry (SELDI-TOF MS) after coronary artery bypass grafting: review of proteomic analytic tools and introducing a new syndrome. *Current medicinal chemistry*. 2011; 18(7):1019–37. [PubMed: 21254974]
129. Silbert BS, Evered LA, Scott DA, Cowie TF. The apolipoprotein E epsilon4 allele is not associated with cognitive dysfunction in cardiac surgery. *The Annals of thoracic surgery*. 2008; 86(3):841–7. [PubMed: 18721571]
130. Gerriets T, Schwarz N, Bachmann G, Kaps M, Kloeve Korn WP, Sammer G, et al. Evaluation of methods to predict early long-term neurobehavioral outcome after coronary artery bypass grafting. *The American journal of cardiology*. 2010; 105(8):1095–101. [PubMed: 20381659]
131. Palotas A, Reis HJ, Bogats G, Babik B, Racsmany M, Engvau L, et al. Coronary artery bypass surgery provokes Alzheimer's disease-like changes in the cerebrospinal fluid. *Journal of Alzheimer's disease : JAD*. 2010; 21(4):1153–64. [PubMed: 21504113]
132. Cook DJ, Huston J 3rd, Trenerry MR, Brown RD Jr, Zehr KJ, Sundt TM 3rd. Postcardiac surgical cognitive impairment in the aged using diffusion-weighted magnetic resonance imaging. *The Annals of thoracic surgery*. 2007; 83(4):1389–95. [PubMed: 17383345]
133. Mirow N, Zittermann A, Korperich H, Borgermann J, Koertke H, Knobl H, et al. Diffusion-weighted magnetic resonance imaging for the detection of ischemic brain lesions in coronary artery bypass graft surgery: relation to extracorporeal circulation and heparinization. *The Journal of cardiovascular surgery*. 2011; 52(1):117–26. [PubMed: 21224820]
134. Knipp SC, Matatko N, Wilhelm H, Schlamann M, Massoudy P, Forsting M, et al. Evaluation of brain injury after coronary artery bypass grafting. A prospective study using neuropsychological assessment and diffusion-weighted magnetic resonance imaging. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 2004; 25(5):791–800. [PubMed: 15082284]
135. Fairbairn TA, Mather AN, Bijsterveld P, Worthy G, Currie S, Goddard AJ, et al. Diffusion-weighted MRI determined cerebral embolic infarction following transcatheter aortic valve implantation: assessment of predictive risk factors and the relationship to subsequent health status. *Heart*. 2012; 98(1):18–23. [PubMed: 21737581]
136. Merino JG, Latour LL, Tso A, Lee KY, Kang DW, Davis LA, et al. Blood-brain barrier disruption after cardiac surgery. *AJNR American journal of neuroradiology*. 2013; 34(3):518–23. [PubMed: 22918429]
137. Vacas S, Degos V, Feng X, Maze M. The neuroinflammatory response of postoperative cognitive decline. *British medical bulletin*. 2013; 106:161–78. [PubMed: 23558082]
138. Marshall RS. Effects of altered cerebral hemodynamics on cognitive function. *Journal of Alzheimer's disease : JAD*. 2012; 32(3):633–42.
139. de la Torre JC. Cerebral hemodynamics and vascular risk factors: setting the stage for Alzheimer's disease. *Journal of Alzheimer's disease : JAD*. 2012; 32(3):553–67. [PubMed: 22842871]
140. Messerotti Benvenuti S, Zanatta P, Longo C, Mazzarolo AP, Palomba D. Preoperative cerebral hypoperfusion in the left, not in the right, hemisphere is associated with cognitive decline after cardiac surgery. *Psychosomatic medicine*. 2012; 74(1):73–80. [PubMed: 22155944]
141. Messerotti Benvenuti S, Zanatta P, Valfre C, Polesel E, Palomba D. Preliminary evidence for reduced preoperative cerebral blood flow velocity as a risk factor for cognitive decline three months after cardiac surgery: an extension study. *Perfusion*. 2012; 27(6):486–92. [PubMed: 22798170]

Search Strategy

This article is intended to provide a clinically focused review for the consultant neurologist. PubMed databases were searched for articles using primarily the following search terms: cardiac surgery, cardiopulmonary bypass, neurologic complications, postoperative stroke, ischemic stroke, therapeutic hypothermia, neurocognitive disorders, delirium, cognitive decline, postoperative cognitive dysfunction. Preference was given to articles published since 2005.