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Cerebrovascular Disease and Stroke (D Greer, Section Editor)

Perioperative Stroke: Risk Assessment, Prevention and Treatment

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Opinion statement

Numerous risk factors for perioperative stroke have been identified and many are modifiable. Surgical patients with a history of cerebrovascular disease should be evaluated by a neurologist. Cardiac and cerebrovascular testing is critical in identifying patients at high risk for perioperative stroke. The identification and treatment of carotid disease in the context of upcoming surgery has been a source of controversy. Routine carotid revascularization performed with coronary artery bypass graft (CABG) surgery for incidentally discovered carotid stenosis is not recommended. Prior to aortic manipulation during CABG, epiaortic ultrasound should be performed to identify aortic atheromatous plaques. If possible, preoperative aspirin, beta blocker, statin, and angiotensin converting-enzyme (ACE) inhibitor therapy should be continued in the perioperative period. Patients who are prescribed anticoagulation at high risk of thromboembolism should receive bridging anticoagulation during the perioperative period. The identification and prevention of postoperative atrial fibrillation (AF) is central to stroke prevention. CABG patients should be initiated on beta blockade +/– amiodarone to prevent postoperative AF. Many practitioners have been traditionally nihilistic towards acute perioperative stroke treatment. Given the narrow therapeutic window of treatment options, candidacy is dependent on timely recognition. Intravenous and endovascular thrombolysis/therapies are viable options in selected patients under the guidance and expertise of a neurologist. This article will present the epidemiology of perioperative stroke, the pathophysiology, risk assessment and stratification for common surgeries. The article will additionally focus on treatment options including modifiable risk factor reduction and the perioperative management of medications.

Introduction

Despite improved surgical techniques and medical management of surgical patients, the incidence of perioperative stroke has not decreased [1, 2]. Perioperative stroke can have devastating consequences. In several studies focusing on cardiac surgery, the mortality rate ranged from 19–32.8 % compared to 2.6-4.9 % for patients without a stroke, a 6–7 fold increase [1, 3–5]. Stroke after general surgery can be similarly lethal [6]. Morbidity is also much worse, as perioperative stroke is associated with doubling of the length of ICU stay, length of hospital stay, and cost of care [1].

Epidemiology

Surgery-associated stroke risk varies. As Table 1 below demonstrates, uncomplicated general surgery is associated with the lowest incidence of perioperative stroke, but the risk increases substantially in the setting of cerebrovascular disease. Isolated coronary artery bypass graft surgery (CABG) is associated with a much higher incidence of perioperative stroke than uncomplicated general surgery, and this risk is significantly higher as the complexity of the surgery increases. The risk of perioperative stroke for these procedures increases with a history of stroke or transient ischemic attack (TIA) or as the degree of cerebrovascular disease worsens.

Pathophysiology

Inflammation and hypercoagulability, age and associated risk factors

While surgery is anatomically focused, there is ample evidence that it leads to a systemic hypercoagulable state [24] by increasing systemic inflammation [25, 26]. Inflammation increases risk of atherosclerotic plaque rupture and thrombosis [27], and leads to platelet activation and platelet-leukocyte interaction [24], all of which may contribute to perioperative stroke. Furthermore, cerebral inflammatory markers seem to be heightened in older surgical patients [28]. Surgical patients also have several more risk factors for perioperative stroke, including increased susceptibility to infection [29] and diminished mobility, which can exacerbate their predisposed hypercoagulable state. Compounding these factors is that stroke leads to an inflammatory cascade that appears to be associated with both infarct volume [30] and increased mortality [31].

Surgical patients tend to be of advanced age. In a large review of over 25,000 consecutive isolated CABG surgeries from 1997 to 2006, the mean age was 64.7 years [18•]. A third of the patients were older than 70. Normal pathophysiology of an aging brain involves cerebral volume reduction [32]. Surgical patients often have medical comorbidities that further diminish cerebral volume and impair physiologic capacity. In 2004, among 290 patients undergoing isolated CABG at one institution, 80 % had hypertension and 37 % had diabetes [1]. First, chronic hypertension is an important risk factor for age-related white matter changes in the brain (leukoaraiosis) [33], and these white matter changes seem to correlate with risk of perioperative stroke during some procedures [34]. Second, chronic hypertension also leads

Table 1. Surgery-specific risk of perioperative stroke. The left column indicates the type of surgery. The numbers in the right column indicate the percentage risk of perioperative stroke with literature citations in brackets

Uncomplicated general surgery	0.2-0.7 [7, 8]
General surgery after prior stroke	2.9 [9]
General surgery with carotid stenosis and bruit or prior cerebrovascular symptoms	3.6 [9]
Uncomplicated peripheral vascular surgery	1.0 [10]
CEA with asymptomatic carotid stenosis	< 1.0-2.5 [11–13]
CEA with symptomatic carotid stenosis	3.9-6.6 [12, 14, 15]
CEA with contralateral carotid stenosis 0-69 %	1.7 [12]
CEA with contralateral carotid stenosis 70-99 %	3.9 [12]
CEA with contralateral carotid occlusion	5.6 [12]
CAS with embolic/cerebral protection device	2.0-3.1 [16, 17]
Isolated CABG	1.6-4.1 [1, 3–5, 18•]
Off-pump CABG	1.4 [19••]
CABG after prior stroke or TIA	8.5 [2]
CABG+unilateral>50 % carotid stenosis	3.0 [2]
CABG+bilateral>50 % carotid stenosis	5.0 [2]
CABG+carotid occlusion	7.0-15.6 [9, 20]
CABG+valve surgery	7.4-7.9 [1, 4]
Aortic valve surgery	4.8-6.5 [4, 21]
Mitral valve surgery	8.8 [4]
Thoracic aorta surgery	4.6-8.7 [1, 5, 22]
Head and neck surgery	0.2-5.0 [23]

CEA = carotid endarterectomy; CAS = carotid artery stenting; CABG = coronary artery bypass graft surgery; TIA = transient ischemic attack

to impaired cerebral autoregulation, possibly rendering the brain more susceptible to injury during certain surgeries in which blood pressure fluctuates [35].

In sum, a rather typical surgical patient is at increased risk of perioperative stroke for several common reasons: advanced age is associated with increased cerebral inflammation, hypertension leads to diminished cerebral reserve and impaired autoregulation, and surgery leads to hypercoagulability via elevated inflammatory markers, postoperative hypomobility and increased susceptibility to infection.

Stroke subtypes

The vast majority of perioperative strokes are ischemic, not hemorrhagic [36, 37]. Cardiac surgery [37, 38] and carotid revascularization [39, 40] are strongly associated with embolism; however, general surgery [23, 36] may be associated with a mix of embolism, thrombosis and hypoperfusion. There are multiple important causes of embolic stroke in the perioperative period. Postoperative atrial fibrillation (AF) has been shown to complicate over 30 % of isolated CABG surgeries and up to 60 % of CABG plus valve surgeries [41]. Aortic manipulation can lead to thrombosis and embolism, especially with cannulation and clamping of the aorta during on-pump CABG [42]. Carotid thromboembolism can occur during both carotid endarterectomy (CEA) [43] and carotid artery stenting (CAS) [16]. The pathophysiology includes microemboli released during CEA [39, 40] and CAS [16], non-

occlusive thrombosis with subsequent embolization [43], occlusive thrombosis [43], and in-stent thrombosis during CAS [44]. Cardiopulmonary bypass during on-pump CABG may be a primary source of microemboli leading to stroke [45], while off-pump CABG has recently been shown in a large meta-analysis to be significantly associated with fewer perioperative strokes than on-pump CABG [19••]. Perioperative vascular borderzone (watershed) infarcts do occur, but their incidence has been difficult to determine as the literature is not consistent. Furthermore, the mechanism behind watershed strokes has also been debated—it is possible the mechanism involves some mixture of relative hypotension [46], uncleared emboli [47], and possibly cerebrovascular stenosis [47]. Other, less common causes of perioperative stroke, include paradoxical venous thromboembolism via venous-to-arterial shunt, vascular catheter tip thrombosis and embolism during endovascular procedures, air emboli during vascular catheter insertion, paradoxical fibrocartilaginous and fat emboli during orthopedic procedures, lacunar (small vessel) infarction, and hemorrhagic stroke.

Risk assessment and stratification models

Perioperative stroke associated with cardiac surgery has been scrutinized extensively, leading to the development of several models that estimate the likelihood of perioperative stroke based on preoperative risk factors. Charlesworth et al., studied over 33,000 consecutive patients in northern New England undergoing isolated CABG, and were able to develop a perioperative stroke risk assessment model incorporating seven preoperative variables, including age, diabetes, ejection fraction<40 %, female gender, priority of surgery, renal failure, and vascular disease, which were assigned different points based on their proportional contribution to stroke risk [48]. A simpler model to predict the risk of perioperative stroke in isolated CABG was developed at Johns Hopkins and requires only three variables: age, history of hypertension, and history of stroke [1]. Other investigators have also developed models estimating CABG-associated perioperative stroke risk [38, 49–51].

A recent model was developed to predict the risk of perioperative stroke associated with carotid endarterectomy (CEA). Goodney et al., prospectively studied nearly 3,000 CEAs in northern New England between 2003–2007, and identified five independent risk factors for perioperative stroke: emergency procedure, age≥70, congestive heart failure, ipsilateral cortical symptoms (both TIA and stroke), and contralateral ICA occlusion [11]. Zero or one risk factor predicted the risk of stroke or death to be<1 %, but with three or more risk factors the incidence of perioperative stroke was nearly 5 % [11]. Several other independent risk factors for perioperative stroke associated with CEA have been identified, including contralateral carotid stenosis>50 % [52] or>70 % [12] and active coronary artery disease [52].

Perioperative stroke risk reduction

History of stroke or TIA

Is consistently identified as a major independent risk factor for perioperative stroke, for nearly all procedures—CABG [4, 18•], other cardiac

and aortic surgery [4], CEA [12, 52], peripheral vascular surgery [23], and general surgery [23]. The perioperative evaluation is a multidisciplinary one, involving neurologists to evaluate the mechanisms underlying a previous history of cerebrovascular disease. Work-up should include: (1) evaluation of cardiac function and rhythm, including transthoracic echocardiogram (TTE) with agitated saline contrast to assess for a PFO, electrocardiogram (EKG), and perioperative cardiac monitoring; (2) imaging of the intracranial and extracranial vasculature; and (3) brain imaging. A combination of studies can be used and is often dependent on institution and patient factors. Magnetic resonance imaging with angiography (MRI and MRA, respectively) of the neck and head with and without gadolinium offers a single test that allows excellent visualization of the extracranial and intracranial vessels and the brain. Many reasons may arise to prevent this study, including institutional unavailability and patient factors such as a pacemaker or other retained metallic objects, renal failure, inability to lie flat or be less monitored for a prolonged time, or simple agitation and claustrophobia. If MRI and MRA cannot be performed, carotid duplex ultrasonography or computed tomography (CT) angiography and head CT parenchymal imaging can be done.

Atrial fibrillation

(AF) is commonly encountered in the perioperative period, either known preoperative AF or new AF arising de novo postoperatively. In the setting of known preoperative AF, the primary driver of increased perioperative stroke risk is stopping antithrombotic therapy, as withdrawal of both warfarin [53] and aspirin [54] may lead to rebound hypercoagulability. Fortunately, medically-managed preoperative AF is not felt to be a significant cause of perioperative stroke. One large study found that patients with preoperative AF undergoing cardiac surgery who discontinued aspirin or warfarin two to three days prior to surgery, then restarted quickly postoperatively, did not have increased incidence of perioperative stroke compared to patients with preoperative sinus rhythm [55]. It is generally recommended that preoperative antithrombotic therapy be continued throughout the perioperative period. For patients with AF at high risk of thromboembolism, the American College of Chest Physicians (ACCP) recommends bridging with anticoagulation therapy rather than stopping anticoagulation in the perioperative period [56••].

AF arising de novo postoperatively is prevalent in over 30 % of CABG surgeries [41, 57, 58], 50 % of valve surgeries [41], and 60 % of combined CABG-valve surgeries [41]. Postoperative AF increases morbidity in that it doubles the risk of perioperative stroke [41, 59]. Risk factors for new-onset postoperative AF include advanced age, decreased left ventricular ejection fraction, left atrial enlargement, diabetes, chronic kidney disease, chronic obstructive pulmonary disease, and withdrawal of beta-blocker therapy or angiotensin converting-enzyme (ACE) inhibitor therapy [57, 60]. Risk reduction is associated with beta-blocker and ACE inhibitor therapy [57]. The pathophysiology of postoperative AF appears to be related to age-related atrial inflammation [60], electrolyte changes [60] and net fluid balance [58].

A 2013 Cochrane Database meta-analysis reviewed 118 randomized trials with over 17,000 patients and determined that beta blockers (odds ratio (OR) 0.33), sotalol (OR 0.34), amiodarone (OR 0.43), atrial pacing

(OR 0.47) and magnesium (OR 0.55) all significantly reduce the incidence of postoperative AF [61••]. Prophylactic therapy was associated with a nonsignificant reduction in the odds of postoperative stroke (OR 0.69). Another large meta-analysis determined that off-pump CABG significantly reduced the incidence of postoperative AF (OR 0.59) and was associated with a nonsignificant trend toward perioperative stroke reduction [62].

Because of the morbidity associated with postoperative AF and the trend toward stroke reduction with prevention, it is recommended that preoperative beta blocker therapy be continued through the perioperative period [60]. In addition, the American College of Cardiology (ACC) and American Heart Association (AHA) jointly released a new summary of guidelines in 2013 recommending initiation of beta blocker therapy to prevent postoperative AF in all cardiac surgery patients and adding preoperative amiodarone in patients at high risk for postoperative AF [63••]. If postoperative AF is identified, the 2013 ACC/AHA guidelines strongly endorse initiation of an atrioventricular nodal blocking agent and consideration of both cardioversion and anticoagulation therapy [63••].

Carotid disease

Atherosclerosis is a diffuse process, and surgical patients commonly have significant disease in several vascular beds, including the coronary arteries [64] and aorta [65]. Approximately 8 % of patients evaluated for CABG have carotid stenosis>70 % [66], while about 17 % of patients undergoing CABG have carotid stenosis>50 % and about 6 % have stenosis>80 % [67]. Carotid disease is a significant independent predictor of CABG-associated perioperative stroke or TIA, with an incidence of 7.5-9.2 % with carotid disease versus 1.7-1.9 % without carotid disease [20, 68–70]. The risk of perioperative stroke also increases as the degree of carotid stenosis increases [20, 71, 72]. One study demonstrated the incidence of perioperative stroke or TIA to be 7.4 % in patients with carotid stenosis but 15.6 % with carotid occlusion [20]. In effect, carotid stenosis is common among CABG patients, the stenosis is often critical, and the degree of stenosis seems to correlate with risk of perioperative stroke. Despite the presence of carotid disease, most perioperative strokes are not thought to be caused by carotid disease [2, 70]. Interestingly, the degree of carotid stenosis still predicts the risk of perioperative stroke [2, 70]. A retrospective study by Li et al., in 2009 of over 4,000 patients undergoing CABG or CABG plus aortic valve replacement found that carotid stenosis≥50 % did not increase the risk of perioperative ipsilateral stroke [70]. In fact, in nearly 78 % of the strokes in this study, the stroke occurred outside the territory supplied by the diseased vessel. Most of the strokes were actually thought to be cardioembolic in origin caused by atrial fibrillation. This led to further investigation of whether intervention is indicated if carotid stenosis is discovered in preoperative screening prior to CABG. In this same study, 53 patients with≥70 % stenosis underwent combined CEA and cardiac surgery while 51 patients with similar carotid stenosis and risk factors underwent cardiac surgery only. The perioperative stroke rate was about 15 % in the CABG plus CEA group, and zero in the CABG-only group. This emphasizes that routine carotid revascularization for incidentally discovered carotid stenosis should not be performed with CABG.

Significant risk factors for carotid disease include advancing age, diabetes, left main coronary artery disease, previous stroke or TIA, peripheral vascular disease (PVD), and smoking [68, 73]. These risk factors inform current guidelines on preoperative carotid screening. The American Society of Neuroimaging issued guidelines in 2007 concerning preoperative screening for extracranial carotid disease (typically using carotid duplex ultrasonography as the initial study) prior to open heart surgery [74]. First, screening of all patients can be considered, but this is generally not recommended. Second, screening is strongly recommended for patients who are≥65 years of age and have a history of stroke or TIA. Screening is also strongly recommended if the patient has any of the following characteristics: left main coronary artery stenosis; PVD; history of cigarette smoking; carotid bruit; previous carotid surgery; or diabetes [74]. The 2011 guidelines issued by the American College of Cardiology Foundation and American Heart Association (ACCF/AHA) do not differ greatly from these recommendations, except that chronically hypertensive patients may also warrant preoperative carotid screening [75•].

Patients who have ongoing neurological symptoms attributable to a moderate or high-grade carotid stenosis warrant revascularization. In 1991, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) demonstrated that patients with symptomatic carotid stenosis 70–99 % greatly benefited from CEA compared to medical management alone, with a two-year ipsilateral stroke rate (failure rate) of 9 % compared to 26 % ($p<$ 0.001) [14]. The benefit of surgery in asymptomatic carotid stenosis is being contested. In 2004, Halliday et al., demonstrated that asymptomatic patients with at least 70 % carotid stenosis who underwent expedited CEA had half the five-year stroke rate of medically-managed patients [13]. However, more recent longitudinal studies evaluating risk of asymptomatic carotid disease in the context of current medical management calculate annual stroke risk to be less than 0.5 % [76•].

Several important findings have emerged concerning carotid stenosis and endarterectomy: symptomatic patients undergoing CEA are at significantly higher risk of perioperative stroke than asymptomatic patients [11, 12]; increasing stenosis of the contralateral carotid independently predicts increasing risk of perioperative stroke [12, 52]; contralateral carotid occlusion is associated with higher risk of perioperative stroke than is contralateral stenosis [11, 12]; and increasing stenosis of the ipsilateral (operated-upon) carotid does not significantly affect perioperative stroke rate [12]. Measures to decrease risk of perioperative stroke in CEA include preoperative antiplatelet therapy [11] and local rather than general anesthesia [52, 77].

Previous studies found that carotid artery stenting (CAS) is associated with a higher risk of perioperative stroke than CEA. Proponents of stenting point out that in a recent trial, CAS and CEA were equivalent with respect to primary outcome measures which included perioperative myocardial infarction in addition to perioperative stroke [78•]. However, CAS was again associated with greater risk of perioperative stroke, which resulted in much greater long-term morbidity than did perioperative myocardial infarction [76•].

This leads to current recommendations concerning intervention. The 2011 ACCF/AHA guidelines on CABG state that in the setting of a previous TIA or stroke and 50–99 % stenosis, it is reasonable to consider carotid revascularization in conjunction with CABG, with simultaneous or staged interventions determined by the relative severity of the carotid and coronary disease (class IIa, level of evidence C) [75•]. In the setting of no history of TIA or stroke, carotid revascularization may be considered in the presence of bilateral severe (70–99 %) carotid stenosis or a unilateral severe carotid stenosis with a contralateral occlusion (class IIb, level of evidence C) [75•]. However, it is the opinion of the authors of this review, that caution be exercised when considering combined CABG and carotid intervention given the high risk of perioperative stroke detailed in prior studies [70].

Aortic disease

Disruption of aortic atherosclerotic plaques leads to perioperative stroke [42, 65], while intraoperative measures during CABG to identify and avoid plaques, such as epiaortic ultrasound [79], reduce atheroembolic stroke risk during cross-clamping and cannulation. The ACCF/AHA 2011 guidelines recommend epiaortic ultrasound prior to aortic manipulation during CABG (class IIa, level of evidence B) [75•]. Furthermore, a recent meta-analysis demonstrated that off-pump CABG was associated with a significant 30 % reduction in the incidence of perioperative stroke (1.4 versus 2.1 %) compared to on-pump CABG [19••]. Off-pump CABG is recommended in place of traditional CABG in the setting of significant aortic atherosclerosis.

Blood pressure and other medical management

Prevention of venous thromboembolism (VTE) and blood glucose, fluid, and electrolyte management are other important modifiable risk factors for perioperative stroke. Postoperative patients should be mobilized as quickly as possible, and mechanical or pharmacological prophylaxis to prevent VTE should be employed throughout the perioperative period except in low risk patients [56••]. In patients at high risk of VTE with no contraindications, both mechanical and pharmacological prophylaxis should be employed [56••]. Achievement of euglycemia without inducing hypoglycemia is recommended, as hyperglycemia appears to be associated with increased clinical severity of stroke, stroke volume, and likelihood of hemorrhagic conversion [80]. Finally, maintenance of adequate fluid volume and avoidance of large fluid and electrolyte shifts contribute to prevention of postoperative atrial fibrillation [58, 60]. Most studies indicate that hypotension is not independently predictive of stroke during or after CABG [2, 42, 81]. In the setting of embolic events, hypotension may decrease clearance of emboli and lead to greater risk of stroke [47], but in isolation it does not appear to be responsible for perioperative stroke. One study did find that relative intraoperative hypotension compared to preoperative baseline was associated with increased risk of watershed strokes, but this association did not reach statistical significance [46]. Studies of CEA also implicate emboli rather than hypotension as the primary cause of perioperative stroke [11, 39, 40]. Perioperative hypertension and hypotension commonly complicate

CEA, likely due to manipulation of the carotid baroreceptor during dissection, clamping, or shunt placement, but most perioperative strokes even in this setting are thought to be thromboembolic [40, 82, 83].

Perioperative management of medications

Aspirin

Preoperative aspirin therapy for CABG patients is associated with a significant decrease in mortality [84, 85] and a nonsignificant trend toward fewer perioperative strokes [84]. A review of the available literature concluded that the benefits of continuing preoperative aspirin outweigh the potential risks of increased bleeding [86]. In the setting of CEA, a large prospective study of over 3,000 CEAs found that preoperative aspirin was independently associated with reduced risk of perioperative stroke (OR 0.4) [11]. In addition, there is evidence that stopping aspirin causes a rebound hypercoagulable state [54]. The 2012 ACCP guidelines recommend continuing aspirin in nearly all perioperative situations except patients at low risk of cardiovascular events undergoing noncardiac surgeries [56••]. Specifically for CABG, the ACCF/AHA recommends preoperative aspirin [75•].

Clopidogrel and Prasugrel

Preoperative clopidogrel has also been shown to reduce the risk of perioperative stroke with CEA [11]. Patients undergoing CABG who received clopidogrel within seven days prior to surgery were much more likely to require reoperation for hemorrhage [87, 88]. One study found clopidogrel to be significantly associated with reduced risk of perioperative stroke [18•], while another found this trend to be nonsignificant [87]. The 2012 ACCP guidelines recommend that CABG patients receiving dual antiplatelet therapy with aspirin and one of these agents stop clopidogrel or prasugrel five days prior to surgery and continue aspirin in the perioperative period [56••]. However, in the setting of recent stent placement and no option of CABG deferral, dual antiplatelet therapy should be continued [56••].

Anticoagulants

For patients who require withholding of vitamin K antagonist (VKA) therapy, such as warfarin, prior to surgery, the ACCP recommends stopping VKAs five days prior to surgery and resuming VKA therapy 12 to 24 hours after surgery [56••]. Patients at high risk of venous thromboembolism (VTE) should receive bridging anticoagulation in the perioperative period rather than no anticoagulation, while patients at moderate risk require careful assessment prior to initiating bridging anticoagulation [56••]. Patients undergoing procedures with low risk of hemorrhage, such as minor dental, ophthalmological, and dermatologic procedures, should continue VKA therapy throughout the perioperative period and take measures to prevent local hemorrhage.

Beta blockers

Stopping beta blocker therapy prior to cardiac surgery is a risk factor for postoperative AF [57], while treatment with beta blockade significantly reduces the incidence of postoperative AF [57, 61••] and nonsignificantly reduces the risk of perioperative stroke [61••, 89]. When preoperative beta blockade is combined with preoperative statin therapy, however, CABG patients have been shown to have a significant reduction in the incidence of perioperative stroke [90••]. Chronic beta blocker therapy should be continued through the perioperative period [60], and patients undergoing cardiac surgery who had not received a beta blocker should be initiated on beta blocker therapy as prophylaxis against postoperative AF [63••]. While the benefits of preoperative beta blockade in cardiac surgery are clear, this has not been substantiated in non-cardiac surgical patients [91].

Angiotensin converting-enzyme (ACE) inhibitors

Stopping ACE inhibitor therapy prior to cardiac surgery is a significant risk factor for postoperative AF [57]. Due to concerns regarding perioperative hypotension with ACE inhibitor therapy [92], firm preoperative recommendations regarding initiation of ACE inhibitors cannot be made at this time.

Statins

A meta-analysis of randomized and observational trials of over 30,000 cardiac surgery patients found that preoperative statin therapy was associated with significant reductions in perioperative mortality, stroke, and AF [93]. A study of cardiac surgery patients with no history of statin therapy or AF were randomized to statin or placebo seven days prior to surgery, and the statin group had a significant 61 % reduction in the incidence of postoperative AF [94]. This study also demonstrated that elevated C-reactive protein was a predictor of postoperative AF [94], and previous studies have shown that statins appear to diminish the likelihood of ischemic stroke in the face of increased inflammation [27]. It is recommended that all surgical patients be initiated on preoperative statin therapy unless contraindicated. This is summarized in Table 2 below.

Treatment of perioperative stroke

Early recognition of stroke symptoms is critical in achieving positive outcomes. Staff vigilance [95], minimizing sedation, and local rather than general anesthesia [52, 77] may aid timely diagnosis and treatment. While patients under general anesthesia are unlikely to manifest clear symptoms, most perioperative strokes actually do not occur intraoperatively but rather postoperatively after uneventful recovery from sedation [96]. This reinforces the need for staff awareness and a low threshold for the stroke team or neurology consultation.

As soon as stroke is suspected, rapid assessment by the primary team and a neurologist is an optimum. An expedited noncontrast head CT is standard of care. CT is sensitive for acute intracranial hemorrhage and guides the direction of further management; however, perioperative strokes are usually ischemic, not hemorrhagic [36, 37].

Table 2. Risk factors and modification/prevention of perioperative stroke

History of stroke or TIA	Expedited evaluation for mechanism underlying previous stroke or TIA. This should at least include brain imaging, extracranial and intracranial vascular imaging, and assessment of cardiac rhythm and function.
Atrial fibrillation (AF)	For preoperative AF, continue antithrombotic therapy unless specifically contraindicated. To prevent postoperative AF, continue preoperative beta blocker and ACE inhibitor and correct electrolyte and volume changes. Initiate beta blocker treatment in all cardiac surgery patients and add amiodarone in high-risk cardiac surgery patients.
Carotid stenosis	Screen patients 65 or older *and* history of stroke or TIA; left main coronary disease; hypertension; PVD; smoking; carotid bruit; diabetes; or history of carotid surgery. Routine carotid revascularization for incidentally discovered carotid stenosis should not be performed with CABG, but combined or staged CABG and CEA can be considered with severe carotid disease but is not strongly recommended. Symptomatic stenosis 70-99 % warrants revascularization, but asymptomatic stenosis may not. Preoperative antiplatelet therapy and local anesthesia reduce risk of CEA-related stroke.
Aortic atherosclerosis	Epiaortic ultrasound during CABG. Off-pump CABG is indicated if severe aortic atherosclerosis.
Medications	Continue preoperative aspirin, statin, beta blocker, and likely ACE inhibitor. Employ bridging anticoagulation for patients at high risk of thromboembolism if anticoagulation is stopped preoperatively.

The treatment of stroke after major surgery is limited. Intravenous tissue plasminogen activator (IV tPA) is a proven effective therapy for acute ischemic stroke, but it is relatively contraindicated within 14 days of major surgery due to risk of hemorrhagic complications [97•]. The 2013 guidelines recommend that post-surgical patients be evaluated on a case-by-case basis and not be excluded outright from IV tPA therapy [97•]. Intra-arterial (IA) thrombolysis given within six hours of stroke onset and catheter-based mechanical interventions are possible alternatives in this situation [97•]. IA thrombolysis has also been found to be effective after CEA [98]. IV tPA for acute stroke after endovascular procedures is appropriate and can be efficacious. A retrospective study of both IV and IA thrombolysis following cardiac catheterization demonstrated that therapy led to improved outcomes without an increased risk of symptomatic intracranial hemorrhage [99].

Conclusions

The incidence of perioperative stroke has not decreased despite improved medical care and understanding of surgical patients. Cardiac and aortic manipulations carry the greatest risk, especially with concomitant extracranial and intracranial cerebrovascular disease. The occurrence of perioperative stroke is influenced by general factors such as advanced age, chronic hypertension, surgery-associated inflammation and hypercoagulability, and hypomobility. Other factors increasing the risk of perioperative stroke in-

clude previous stroke or TIA, AF, aortic and carotid disease, and inappropriate discontinuation of preoperative medications. Embolism is the predominant mechanism underlying perioperative stroke in cardiac, aortic and carotid procedures, but general surgery-associated strokes seem to have a more mixed etiology. Emphasis is placed on risk factor recognition and preventive measures. A history of past stroke or TIA should be thoroughly evaluated with brain imaging, neurovascular imaging and evaluation and monitoring of cardiac rhythms and function. Preoperative aspirin, beta blocker, statin, and ACE inhibitor should be continued in the perioperative period. Patients prescribed anticoagulation at high risk of thromboembolism should receive bridging anticoagulation in the perioperative period. Interventions to decrease risk include initiating beta blockade +/− amiodarone to prevent postoperative AF in high risk CABG patients, epiaortic ultrasound to avoid atheromatous plaque disruption during CABG, and appropriate screening for carotid disease. Routine carotid revascularization for incidentally discovered carotid stenosis should not be performed with CABG, however, due to a high risk of associated stroke. Treatment of acute perioperative stroke is dependent on timely recognition and early involvement of a consultant neurologist. IV tPA is an option in select cases, but is relatively contraindicated for 14 days following major surgery. IA tPA with or without mechanical clot retrieval may be reasonable in carefully chosen patients.

Compliance with Ethics Guidelines

Conflict of Interest
Dr. Daniel C. Brooks and Dr. Joseph L. Schindler each declare no potential conflicts of interest relevant to this article.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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