Circulation

AHA/ASA SCIENTIFIC STATEMENT

Perioperative Neurological Evaluation and Management to Lower the Risk of Acute Stroke in Patients Undergoing Noncardiac, Nonneurological Surgery

A Scientific Statement From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.

The American Association of Neurological Surgeons/Congress of Neurological Surgeons Cerebrovascular Section affirms the educational benefit of this document.

ABSTRACT: Perioperative stroke is a potentially devastating complication in patients undergoing noncardiac, nonneurological surgery. This scientific statement summarizes established risk factors for perioperative stroke, preoperative and intraoperative strategies to mitigate the risk of stroke, suggestions for postoperative assessments, and treatment approaches for minimizing permanent neurological dysfunction in patients who experience a perioperative stroke. The first section focuses on preoperative optimization, including the role of preoperative carotid revascularization in patients with high-grade carotid stenosis and delaying surgery in patients with recent strokes. The second section reviews intraoperative strategies to reduce the risk of stroke, focusing on blood pressure control, perioperative goal-directed therapy, blood transfusion, and anesthetic technique. Finally, this statement presents strategies for the evaluation and treatment of patients with suspected postoperative strokes and, in particular, highlights the value of rapid recognition of strokes and the early use of intravenous thrombolysis and mechanical embolectomy in appropriate patients.

Curtis Benesch, MD, MPH, Chair
Laurent G. Glance, MD, Vice Chair
Colin P. Derdeyn, MD, FAHA
Lee A. Fleisher, MD, FAHA
Robert G. Holloway, MD, MPH
Steven R. Messé, MD
Christina Mijalski, MD, MPH
M. Timothy Nelson, MD
Martha Power, MSN, ANP, FAHA
Babu G. Welch, MD
On behalf of the American Heart Association Stroke Council; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Council on Epidemiology and Prevention

Previously published guidelines have provided recommendations for the cardiovascular evaluation and management of patients undergoing noncardiac surgery.[1,2] This scientific statement focuses on the cerebrovascular complications of noncardiac surgery and summarizes the current literature concerning the preoperative neurological risk stratification and management of patients before undergoing noncardiac, nonneurological surgery; intraoperative strategies to mitigate the risk of stroke; and the identification and treatment of patients who experience a perioperative stroke.

Each member of the writing group contributed to the initial outline for this article and to all drafts and revisions. The initial literature review used the following search terms: *perioperative stroke*, *stroke*, *ischemic stroke*, *noncardiac surgery*, *neurological complications*, *acute stroke treatment*, *endovascular treatment*, and *thrombectomy*, all limited to publications within the previous 10 years. Additional citations were generated in an iterative process from the original list of references, with contributions from the writing group focusing on each member's area of expertise and familiarity with the published literature. Priority for inclusion in the article emphasized publications based on randomized, controlled trials, followed by those describing meta-analyses, very large administrative databases and quality registries, and relevant, smaller observational studies. When possible,

Key Words: AHA Scientific Statements ■ complications ■ embolectomy ■ ischemic stroke ■ stroke ■ surgical procedures, operative ■ therapeutics ■ thrombectomy

https://www.ahajournals.org/journal/circ

we sought to clearly inform the reader on the content source of the suggestions and observations included in this summary statement. For many of the clinical situations addressed in this statement, high-quality evidence is lacking. Therefore, many of the recommendations in this statement reflect the consensus of experts and our desire to provide pragmatic guidance to practitioners who, despite a lack of definitive evidence, must make real-world decisions every day in clinical practice.

PREOPERATIVE EVALUATION AND MANAGEMENT TO REDUCE RISK OF STROKE

Definition and Risk of Perioperative Stroke

Perioperative stroke can be defined as any embolic, thrombotic, or hemorrhagic cerebrovascular event with motor, sensory, or cognitive dysfunction lasting at least 24 hours, occurring intraoperatively or within 30 days after surgery. As with nonperioperative cerebrovascular events, most perioperative strokes are ischemic rather than hemorrhagic.[3]

The incidence of perioperative stroke in patients undergoing noncardiac, nonneurological surgery is between 0.1% and 1.0% according to retrospective studies of 2 large databases[4–6] (Table 1).

In a recent large, prospective international study of >40 000 patients undergoing noncardiac surgery, the rate of perioperative stroke was 0.3% overall, with higher risk associated with vascular and neurosurgical operations.[7] Other studies have demonstrated a lower perioperative stroke risk (0.028%–0.075%), but these analyses were limited to experiences at single institutions.[8,9]

Using the National Inpatient Sample from 2004 to 2013 in the United States, Smilowitz et al[10] reported that despite an overall decrease in the composite of major adverse cardiovascular and cerebrovascular events after noncardiac surgery between 2004 and 2013, the rate of perioperative stroke increased from 0.52% in 2004 to 0.77% in 2013 (Figure 1). Although patients undergoing vascular surgery were at the highest risk of major adverse cardiovascular and cerebrovascular events, some of these patients may have undergone surgery as a result of an ischemic stroke. After the exclusion of those patients undergoing vascular surgery, the increase in perioperative stroke risk persisted. The upward trend in stroke risk was also evident in both men and women and across races and ethnic groups.[10] It is important to note that for all of these studies, investigators did not perform independent clinical assessments of patients or account for potential temporal changes in the use of magnetic resonance imaging (MRI) to evaluate for stroke; the true incidence of clinical stroke may be higher or lower than these estimates.

Table 1. Incidence of Stroke for Noncardiac, Nonvascular, Nonneurological Surgeries

	Stroke, all ages, % (n)	Stroke, age ≥65 y, % (n)
Bateman et al,[4] 2009; Nationwide Inpatient Sample		
Hip arthroplasty (n=1568)	0.4 (6)	0.5 (5)
Lung resection (n=1484)	0.3 (5)	0.7 (5)
Colectomy (n=33 426)	0.4 (130)	0.7 (100)
Mashour et al,[5] 2011; American College of Surgeons–National Surgical Quality Improvement Program		
Hepatobiliary–biliary tree (n=43 289)	0.1 (36)	0.2 (23)
Excisional breast (n=36 793)	0.0 (16)	0.1 (11)
Hernia–ventral/umbilical/incisional/other (n=32 638)	0.1 (28)	0.3 (21)
Hernia–inguinal/femoral incisional mesh (n=26 448)	0.1 (17)	0.1 (10)
Colorectal–appendectomy (n= 26 046)	0.0 (6)	0.2 (4)
Esophagogastric–bariatric (n=23 766)	0.0 (5)	0.0 (0)
Head and neck–tumor (n=20 057)	0.0 (7)	0.1 (3)
Minor vascular–chest/extremity (n=5883)	0.0 (2)	0.1 (1)
Small intestine–resection/ostomy (n=5860)	0.5 (27)	0.6 (14)
Small intestine–lysis of adhesions, other (n=5683)	0.3 (17)	0.7 (14)
Abdominal–exploration (n=5760)	0.5 (26)	0.9 (18)
Hepatobiliary–pancreas (n=4832)	0.3 (15)	0.5 (10)
Musculoskeletal–amputation (n=4800)	0.8 (37)	1.1 (29)
Esophagogastric–gastric (n=4749)	0.3 (16)	0.7 (12)
Esophagogastric (n=4635)	0.0 (1)	0.1 (1)
Hysterectomy (n=4454)	0.1 (3)	0.2 (2)
Musculoskeletal–arthroscopic (n=4255)	0.0 (0)	0.0 (0)
Musculoskeletal–spine (n=3480)	0.1 (4)	0.3 (3)
Colorectal–abdominoperineal resection (n=3169)	0.0 (0)	0.5 (5)
Musculoskeletal–knee (n=2970)	0.1 (4)	0.2 (4)
Anorectal–abscess (n=2508)	0.0 (0)	0.0 (0)
Simple skin and soft tissue (n=2383)	0.3 (6)	0.6 (4)
Colorectal–low anastomosis (n=2293)	0.2 (4)	0.2 (2)
Hepatobiliary–liver (n=2144)	0.3 (6)	0.8 (6)
Anorectal–resection (n=2103)	0.0 (1)	0.0 (0)
Musculoskeletal–fracture repair (n=2065)	0.1 (3)	0.3 (3)
Biopsy skin and soft tissue (n=2014)	0.1 (2)	0.2 (1)

Adapted from Mashour et al[6] with permission from Wolters Kluwer Health Inc. Copyright © 2014, Lippincott Williams & Wilkins.

Numerous studies have consistently identified advancing age, renal disease, and prior transient ischemic attack/stroke as key risk factors for perioperative stroke.[4,5,8,9,11,12] Other risk factors have been identified as independent predictors,[4,5,8,9] such as myocardial infarction within 6 months, atrial fibrillation, hypertension, chronic obstructive pulmonary disease, current smoking, female sex, and diabetes mellitus, with the presence

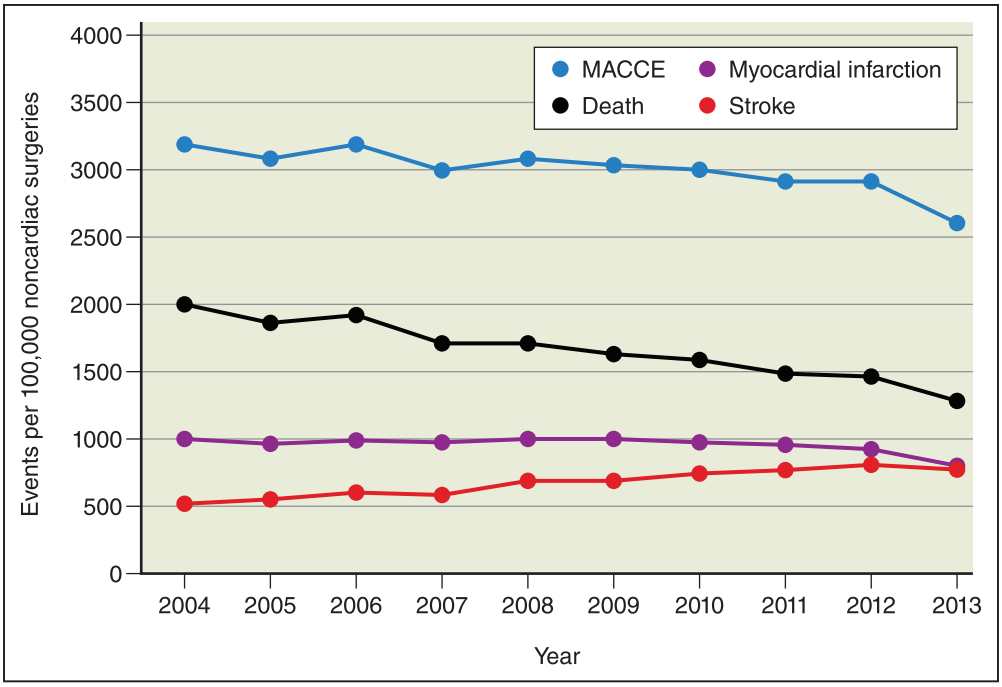

Figure 1. Rates of perioperative major adverse cardiovascular and cerebrovascular events (MACCEs) over time.
Reprinted from Smilowitz et al[10] with permission. Copyright © 2017, American Medical Association. All rights reserved.

of multiple risk factors further increasing the risk of perioperative stroke.[5] In addition, patients undergoing emergency surgery or certain types of surgical procedures (thoracic, head and neck, intra-abdominal, vascular, transplant, orthopedic) were at higher risk.[8–10,13]

Silent Cerebral Ischemia

Silent brain infarctions, sometimes known as covert strokes, are acute ischemic events that are not clinically apparent. These infarcts are typically identified by brain imaging and have been associated with cognitive decline, dementia, increased risk of stroke, and increased mortality in population-based studies.[14–17] The incidence of perioperative silent brain infarctions is variable according to the type of operation and is likely higher in patients undergoing vascular or cardiac surgery. Silent cerebral ischemia after carotid endarterectomy (CEA) occurs in up to 17% of patients, and rates may be as high as 30% to 50% in patients undergoing carotid artery stenting (CAS) or cardiac surgery.[18–20] Silent cerebral infarcts seen after CAS have been associated with increased risk of recurrent stroke or transient ischemic attack, and this risk increases with a larger number of lesions.[20] Studies of patients undergoing cardiac surgery have reported rates of new infarcts on MRI ranging from 25% to 55%, with the highest risk for patients undergoing open surgical valve replacement, and rates as high as 90% in those undergoing transcatheter aortic valve replacement.[21,22] Although the data are mixed overall, some studies have reported that silent cerebral ischemia after cardiac surgery is associated with cognitive decline and that the risk correlates with a larger number and volume of lesions.[19,21]

The incidence of silent cerebral infarcts after noncardiac surgery, however, may be as high as 10% according to postoperative MRI findings in a prospective, multicenter pilot study of 100 patients >65 years of age.[23] In a larger, multicenter prospective study of 1114 patients undergoing elective, noncardiac surgery, 7% had a silent cerebral infarction based on MRI findings obtained between day 2 and 9 after surgery.[24] Furthermore, the risk of cognitive decline at the 1-year follow-up was nearly 2-fold higher in patients with a silent perioperative stroke compared with those without a silent perioperative stroke. Overt stroke and perioperative delirium were also higher in the perioperative silent cerebral infarct group.[24] These findings underscore the need for additional studies to determine which factors lead to silent cerebral ischemia and how to mitigate that risk to decrease potential cognitive impairment.

Impact of Perioperative Stroke

Despite its relatively low incidence, perioperative stroke represents a significant public health burden. With >5 million patients >45 years of age undergoing noncardiac surgery each year in the United States, >25 000 people annually may have a stroke attributable to perioperative causes.[25] Furthermore, the individual impact of a perioperative stroke can be devastating. The 30-day mortality rates in patients who experience

a perioperative stroke are up to 8-fold higher than in controls, with absolute rates ranging between 21% and 26%.[5,12,26] Length of stay and the likelihood of discharge to a long-term care facility are also increased in patients with a perioperative stroke.[11,13,26]

Pathophysiology of Perioperative Stroke

Although it is well established that the vast majority of perioperative strokes are ischemic rather than hemorrhagic, the cause of ischemic stroke is variable and likely attributable to a number of factors. In patients undergoing cardiac surgery, nearly two-thirds of ischemic strokes are the result of proximal sources of embolism, either from direct cardiac/arterial manipulation or the bypass pump at the time of the procedure, or from delayed complications such as atrial fibrillation or myocardial infarction (MI).[27–29] In patients undergoing noncardiac, nonvascular surgery, however, the cause of stroke is less clear; stroke subtypes have not been ascertained in most studies because many of the earlier studies did not include advanced diagnostic testing such as MRI or vessel imaging.[3–5,30]

Recent studies of single-institution experiences in patients undergoing either noncardiac or nonvascular surgery indicate that ≈50% of strokes in the perioperative setting occur within the first 24 hours and up to 93% occur within the first 72 hours.[9,12] A large, multicenter analysis of patients undergoing noncarotid, major vascular surgery, however, found that only up to 15% of strokes occurred on postoperative day 0 to 1, with another 50% occurring between postoperative day 2 and 8.[11] These observations suggest that factors contributing to stroke risk in patients undergoing noncardiac, nonvascular surgery are distinct from other types of surgery and appear to be temporally related to the intraoperative and immediate postoperative periods.

Putative mechanisms of perioperative stroke in patients undergoing noncardiac, nonneurological surgery may include hypotension/low-flow states, previously undisclosed large-artery stenosis, anemia-associated tissue hypoxia, thromboembolism (including cardiac and transcardiac), fat embolism, and enhanced coagulability/thrombosis in the setting of systemic inflammation, endothelial dysfunction, and recent stoppage of antithrombotic medications.[31,32] Subsequent sections in this document address potential approaches to each of these mechanisms.

Hemorrhagic stroke in the perioperative period is rare and may represent only up to 5% of cases.[3,29] Uncontrolled hypertension and the use of antithrombotic medications, along with reperfusion injury and hyperperfusion syndrome observed after CEA, are potential contributors to the risk of perioperative hemorrhagic stroke.[30,33,34] The presence of an unruptured cerebral aneurysm did not result in an increase of perioperative hemorrhage in patients undergoing cardiovascular surgery,[35] which is almost certainly true for noncardiac, nonneurological surgery given the high prevalence of unruptured aneurysms in the population, although data are limited.[35]

Preoperative Risk Stratification

Numerous cardiovascular risk stratification tools have been used to predict perioperative complications in patients undergoing surgery, including the Revised Cardiac Risk Index,[36] the MI or cardiac arrest calculator,[37] and the American College of Surgeons (ACS) surgical risk calculator,[38] but these tools were not designed to specifically predict perioperative stroke risk. Two other scales, the $CHADS_2$ and CHA_2DS_2-VASc risk scores,[39,40] were initially developed and validated to predict annualized stroke risk in patients with nonvalvular atrial fibrillation but have also been shown to predict perioperative stroke risk in patients undergoing cardiac procedures, even in the absence of atrial fibrillation.[41,42]

All of these risk stratification tools were compared in a large retrospective cohort of patients (n=540 717) undergoing noncardiac surgery using the ACS National Surgical Quality Improvement Program registry.[26] The overall stroke risk incidence was 0.27%, with the highest incidence in patients undergoing vascular or neurosurgical procedures. The ACS surgical risk calculator and the MI or cardiac arrest risk calculator exhibited significantly better predictive accuracy compared with the other risk prediction models, despite not having been developed to predict stroke risk.[26] Because predictions are different for some patients depending on which risk calculator is used, we believe that it is important to recommend a single best risk score to use for risk stratification.[43] We suggest that risk stratification be performed with the web-based ACS surgical risk calculator to identify patients with elevated stroke risk who may benefit from targeted approaches that minimize the risk of perioperative stroke.[44]

These predictions can be discussed with patients to inform shared decision making with the caveat that although the ACS surgical risk calculator does not directly predict the risk of stroke, patients predicted to be at high risk of serious complications are more likely to experience a stroke perioperatively.

Preoperative Stroke Prevention Strategies

Timing of Surgery After Stroke

Patients with a history of stroke are at increased risk of perioperative stroke, and the timing of surgery relative to the most recent event modulates this risk. Jørgensen et al[45] analyzed data from a large Danish national health care database and reported that the risks of ischemic

Table 2. Adjusted Odds Ratios of 30-Day Ischemic Stroke Events Stratified by Stroke Before Surgery and Time Elapsed Between Stroke and Surgery

Source	Crude events, n	Sample size, n	Event rate, %	Odds ratio (95% CI)
No prior stroke	368	474 046	0.078	1 (Reference)
Prior stroke anytime	210	7137	2.94	16.24 (13.23–19.94)
Stroke <3 mo prior	103	862	11.95	67.60 (52.27–87.42)
Stroke 3–<6 mo prior	21	469	4.48	24.02 (15.03–38.39)
Stroke 6–<12 mo prior	16	898	1.78	10.39 (6.18–17.44)
Stroke ≥12 mo prior	70	4908	1.42	8.17 (6.19–10.80)

Adapted from Jørgensen et al[45] with permission. Copyright © 2014, American Medical Association. All rights reserved.

stroke and other major adverse cardiovascular events (MI and cardiovascular death) were significantly higher in patients undergoing noncardiac surgery after a prior stroke. Patients who underwent elective noncardiac surgery within 3 months of a prior stroke were at the highest risk of ischemic stroke (Table 2). Although the risk of major adverse cardiovascular and cerebrovascular events, 30-day mortality, and ischemic stroke was higher for patients undergoing noncardiac surgery within 12 months of prior stroke overall, the increased odds ratio for each of these end points leveled off at ≈9 months.[45] Using the same data, these authors also showed that the odds of stroke were >20-fold higher in patients undergoing emergency noncardiac surgery within 3 months of a prior stroke.[46] Similar temporal trends in stroke risk are seen after incident stroke in patients who do not undergo surgery, but the absolute rate of events in these studies of perioperative patients is higher than seen in observational studies or clinical trials of nonoperative patients with recent transient ischemic events or minor stroke.[47–49] Although the evidence between surgical timing and stroke risk is limited to only these 2 studies, we suggest that elective noncardiac surgery be deferred at least 6 months after a prior stroke, and possibly as long as 9 months to reduce the risk of perioperative stroke in patients undergoing noncardiac surgery. Alternatively, patients who stand to gain significant improvements in quality of life with elective surgery may consider waiting only 6 months after a prior stroke.

Extracranial Carotid Artery Stenosis

Current guidelines recommend that patients with high-grade extracranial carotid artery stenosis (>70%) and ipsilateral symptoms of ischemic stroke or transient ischemic attack within the past 6 months should be strongly considered for revascularization by CEA or CAS.[50] Symptomatic patients with moderate stenosis (50%–69%) should also be considered for revascularization provided that the surgical risk is <6%.[50] Some consideration of baseline risk factors is important because CAS is associated with a slightly higher risk of stroke and CEA with a slightly higher risk of MI.[51] The US Preventive Services Task Force does not recommend routine carotid screening in patients without symptoms, and this remains true for patients planning noncardiac surgery.[52] Recommendations for patients with known, asymptomatic, high-grade carotid stenosis undergoing noncardiac, nonneurological surgery are uncertain. However, for patients with known high-grade carotid stenosis in the general population who are asymptomatic, American Heart Association guidelines recommend that they be considered for CEA if the risk of perioperative stroke, MI, and death is <3% and may be considered for CAS if the stenosis is >70% by ultrasonography or >60% by catheter angiography.[53] However, these guidelines are based on older trials that did not incorporate current intensive medical management that has resulted in markedly lower stroke rates in contemporary medically treated cohorts.[54] CREST-2 (Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial) is currently underway to test whether carotid revascularization (either CEA or CAS) plus optimal medical therapy is superior to optimal medical therapy alone for patients with asymptomatic high-grade carotid stenosis (PMC5987521). Elective surgical procedures may be postponed if carotid artery revascularization treatment is planned (for either symptomatic or asymptomatic high-grade carotid stenosis), but the optimal duration of this delay is unknown and may be informed predominantly by timing of the most recent cerebrovascular event (see the Timing of Surgery After Stroke section). The optimal approach for patients with symptomatic, high-grade carotid stenosis who also require emergency surgery such as coronary artery bypass grafting (CABG) is unclear and may include a reversed-stage approach (CABG followed by CEA) or a combined approach (simultaneous CABG and CEA).[29,55] For patients with asymptomatic, high-grade stenosis who require CABG, it is unclear whether those patients should undergo carotid revascularization before cardiac surgery. A recent randomized trial comparing isolated CABG with synchronous CABG and CEA showed nearly a doubling of the perioperative stroke and death rate at 30 days in the combined treatment group (18.5% versus 9.7%), but these differences in rate were not statistically significant (P=0.12).[56]

Intracranial Stenosis

Symptomatic intracranial stenosis (50%–99% by catheter angiography) carries a stroke risk of 15% over the first year after symptom identification,[57] but the overall risk of perioperative stroke in this population is unknown. Intracranial stenosis is routinely managed medically, with antithrombotic therapy and assiduous risk factor modification[58]; stenting of intracranial stenosis is limited to select patients who fail maximal medical therapy, and no evidence supports its prophylactic use in the preoperative setting.[59] A small retrospective study of 38 patients with severe intracranial vertebral or basilar artery stenosis undergoing surgery (vascular, cardiac, or general) reported a perioperative stroke rate of 6%.[60]

Patent Foramen Ovale

A patent foramen ovale (PFO) is present in ≈25% of the population and in most patients is not associated with any morbidity.[61] Recent evidence from 3 clinical trials, however, now supports a potential association between a PFO and cryptogenic stroke in patients <60 years of age and the beneficial role of PFO closure in select patients.[62–64]

In a retrospective study of >150 000 patients undergoing noncardiac surgery with general anesthesia, Ng et al[65] found that the diagnosis of a PFO before surgery significantly increased the likelihood of a perioperative ischemic stroke. Perioperative strokes in patients with a PFO were also more severe and more likely to occur in a large vessel territory. In a large study of patients undergoing total hip arthroplasty in the Nationwide Inpatient Sample, perioperative stroke risk was 29 times greater (7.14% versus 0.26%; $P<0.001$) in patients with an atrial septal defect/PFO compared with control subjects.[66] These studies did not control for the possibility that the patients diagnosed with a PFO before surgery must have had a concern for cardiac disease or stroke, which in turn would lead to higher perioperative risk; that is, a workup bias. Further study is needed to better characterize this association between PFO and perioperative stroke risk to determine optimal diagnostic and treatment approaches in this population.[67] Patients already determined to need PFO closure may consider undergoing this procedure before elective surgery, although urgent and emergency surgery should not be delayed to address a PFO.

Perioperative Medication Management

β-Blockers

The use of β-blockers in the perioperative setting has been shown to reduce adverse cardiac events, but in 2008, a large randomized controlled trial showed increased mortality and higher stroke rates in patients treated with preoperative metoprolol compared with placebo.[68] In this trial, subjects randomly assigned to receive metoprolol (extended release, 100-mg dose) 2 to 4 hours before surgery (and continued for next 30 days) were less likely to reach the composite end point of cardiovascular death, nonfatal MI, and nonfatal cardiac arrest compared with control subjects. Patients in the metoprolol group, however, had significantly higher overall mortality rates and were twice as likely to experience a perioperative stroke (1.0% versus 0.5%; hazard ratio, 2.17 [95% CI, 1.26–3.74]; $P=0.0053$).[68] In addition, patients in the metoprolol group were more likely to experience clinically significant hypotension and bradycardia. Post hoc multivariate analyses further suggested that hypotension may be a mechanism by which β-blockers increase the risk of stroke.[68]

Mashour et al[69] reported a significant increase in perioperative stroke rate in patients taking metoprolol over those taking atenolol preoperatively and in patients receiving intraoperative metoprolol over labetalol or esmolol. This study also demonstrated that intraoperative hypotension was associated with perioperative stroke risk, but these episodes of hypotension were not associated specifically with metoprolol.[69] A subsequent large cohort study, however, failed to show any difference in risk of all-cause mortality or major adverse cardiac events across β-blocker subtypes.[70]

The "2014 ACC/AHA [American College of Cardiology/American Heart Association] Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery" strongly supports continuing β-blockers in patients who are on β-blockers long term.[2] These guidelines also state that it may be reasonable to begin β-blockade in patients who are at high risk according to preoperative testing or who have ≥3 of the risk factors in the Revised Cardiac Risk Index but that β-blockers should not be initiated on the day of surgery.

Statins

For patients already taking a statin (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor) before undergoing noncardiac surgery, perioperative continuation is recommended to lower the risk of cardiovascular events.[1,2] Multiple cohort studies and results from a recent meta-analysis of patients undergoing noncardiac surgery (study populations included vascular and neurosurgical procedures) demonstrate that perioperative statin use is associated with a significant reduction in a variety of cardiovascular end points: postoperative MI,[71,72] all-cause mortality,[71,73] new-onset atrial fibrillation,[72] and the composite end points of all-cause mortality, myocardial injury, and stroke.[72,73] None of these studies, however, found a significant decrease in perioperative stroke risk associated with perioperative statin use.

Table 3. Risk Stratification for Perioperative Thromboembolism

Risk stratum	Indication for VKA therapy		
	Mechanical heart valve	Atrial fibrillation	VTE
High*	Any mitral valve prosthesis Any caged-ball or tilting disc aortic valve prosthesis Recent (within 6 mo) stroke or transient ischemic attack	$CHADS_2$ score of 5 or 6 Recent (within 3 mo) stroke or transient ischemic attack Rheumatic valvular heart disease	Recent (within 3 mo) VTE Severe thrombophilia (eg, deficiency of protein C, protein S, or antithrombin); anti-phospholipid antibodies; multiple abnormalities
Moderate	Bileaflet aortic valve prosthesis and ≥1 of the following risk factors: atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age >75 y	$CHADS_2$ score of 3 or 4	VTE within the past 3–12 mo Nonsevere thrombophilia (eg, heterozygous factor V Leiden or prothrombin gene mutation) Recurrent VTE Active cancer (treated within 6 mo or palliative)
Low	Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke	$CHADS_2$ score of 0–2 (assuming no prior stroke or transient ischemic attack)	VTE >12 mo previously and no other risk factors

VKA indicates vitamin K antagonist; and VTE, venous thromboembolism.

*High-risk patients may also include those with a prior stroke or transient ischemic attack occurring >3 months before the planned surgery and $CHADS_2$ score <5, those with prior thromboembolism during temporary interruption of VKAs, or those undergoing certain types of surgery associated with an increased risk for stroke or other thromboembolism (eg, cardiac valve replacement, carotid endarterectomy, major vascular surgery).

Reprinted from Douketis et al[75] with permission from the American College of Chest Physicians. Copyright © 2012, American College of Chest Physicians.

Antithrombotic Therapy

Patients with risk factors for cerebrovascular disease are often taking antithrombotic medications, and numerous guidelines have addressed the approach to managing these medications in patients requiring surgery. Clinicians face the challenge of potentially increasing thromboembolic risk by adjusting/holding antithrombotic medications in the perioperative period while trying to mitigate perioperative bleeding risk. Validated scales may help quantify risk of thromboembolism and bleeding in select circumstances.[40,74]

Several indications requiring anticoagulant therapy have been stratified across low-, moderate-, and high-risk categories for thromboembolism (Table 3).

Recently published guidelines from the ACS include strategies for anticoagulant management across these categories of thromboembolic risk according to perioperative bleeding risk[76,77] (Table 4). The ACS guidelines also provide the most recent summary of broader approaches to antithrombotic management in the perioperative setting (Table 5).

These guidelines also reflect more recent evidence that suggests limiting the use of perioperative

Table 4. Recommended Perioperative Anticoagulation Management Strategies

Category	High-bleeding-risk procedure	Low-bleeding-risk procedure
High thromboembolic risk		
Warfarin	Give last dose 6 d before operation, bridge with LMWH or UFH, resume 24 h postoperatively	Give last dose 6 d before operation, bridge with LMWH or UFH, resume 24 h postoperatively
DOAC	Give last dose 3 d before operation, resume 2–3 d postoperatively*	Give last dose 2 d before operation, resume 24 h postoperatively*
Intermediate thromboembolic risk		
Warfarin	Give last dose 6 d before operation, determine need for bridging by clinician judgment and current evidence, resume 24 h postoperatively	Give last dose 6 d before operation, determine need for bridging by clinician judgment and current evidence, resume 24 h postoperatively
DOAC	Give last dose 3 d before operation, resume 2–3 d postoperatively*	Give last dose 2 d before operation, resume 24 h postoperatively*
Low thromboembolic risk		
Warfarin	Give last dose 6 d before operation, bridging not recommended, resume 24 h postoperatively	Give last dose 6 d before operation, bridging not recommended, resume 24 h postoperatively
DOAC	Give last dose 3 d before operation, resume 2–3 d postoperatively*	Give last dose 2 d before operation, resume 24 h postoperatively*

DOAC indicates direct oral anticoagulant; LMWH, low-molecular-weight heparin; and UFH, unfractionated heparin.

*In patients with creatinine clearance <50 mL/min on dabigatran, the last dose should be given 3 days before the procedure for low-bleeding-risk surgery and 4 to 5 days before the procedure for high-bleeding-risk operation.

Reprinted from Hornor et al[76] with permission from the American College of Surgeons. Copyright © 2018, American College of Surgeons. Published by Elsevier Inc. All rights reserved.

Table 5. Summary of Guidelines for Perioperative Management of Antithrombotic Medications

Clinical area	Guideline
Preoperative thromboembolic risk stratification	
Nonvalvular atrial fibrillation thromboembolic risk	Stratify thromboembolic risk with the CHA_2DS_2-VASc score
Prosthetic heart valve thromboembolic risk	Stratify risk according to valve type, location, and individual thromboembolic risk factors (atrial fibrillation, history of thromboembolism)
VTE thromboembolic risk	Stratify according to time elapsed since VTE diagnosis and individual risk factors (cancer, thrombophilia); elective operation should be deferred for ≥3 mo after VTE diagnosis
Coronary artery disease coronary thromboembolism risk	Elective operation should be deferred for ≥14 d for balloon angioplasty, 30 d for bare metal stent placement, and 1 y for drug-eluting stent placement
Stroke thromboembolic risk	Elective operation should be deferred for ≥9 mo after an ischemic stroke
Peripheral arterial disease thromboembolic risk	Patients presenting for surgical evaluation who receive antithrombotic medication for symptomatic peripheral arterial disease should be managed in close consultation with a vascular specialist or vascular surgeon.
Procedural bleeding risk stratification	
Bleeding risk inherent to patient characteristic	Stratify risk with the HAS-BLED score
Bleeding risk inherent to procedure	Largely a subjective decision on behalf of the operating surgeon; most operations under the purview of the general surgeon will be classified as at least low risk
Perioperative bridging therapy	
Antiplatelet therapy	Currently, there is no evidence to suggest a benefit from the use of antiplatelet bridging therapy perioperatively.
DOAC therapy	Currently, there is no evidence to suggest a benefit from the use of heparin bridging in patients taking DOACs.
Warfarin therapy	Use for those classified as high VTE risk; discontinue warfarin 5 d before an elective procedure, and when the INR falls below the patient's therapeutic range, begin LMWH at a therapeutic dose until 24 h before the procedure; reinitiate warfarin 12–24 h after operation; reinitiate LMWH 48–72 h after the operation
Perioperative antithrombotic medication management strategy	
Unfractionated heparin	
Intravenous	Hold 4–6 h before elective operation
Subcutaneous	Hold 12–24 h before elective operation
LMWH	Hold 24 h before operation; resume 48–72 h after operation
Warfarin	Hold for 5 d before an elective operation; resume at previous dosing levels 12–24 h after operation
Dabigatran	
Normal renal function	Hold for 2 d before high-bleeding-risk operation and 1 d before low-bleeding-risk operation; resume 2–3 d after high-bleeding-risk operation and 1 d after low-bleeding-risk operation
Impaired renal function	Hold for 4 d before high-bleeding-risk operation and 2 d before low-bleeding-risk operation
Rivaroxaban, apixaban, edoxaban	Hold for 2 d before high-bleeding-risk operation and 1 d before low-bleeding-risk operation; resume 2–3 d after high-bleeding-risk operation and 1 d after low-bleeding-risk operation
Aspirin	Hold aspirin for 7–10 d before high-bleeding-risk operation in patients who have not had a PCI; resume when bleeding risk has diminished; in patients with recent PCI, consult with cardiologist
Clopidogrel, prasugrel, ticagrelor	Hold 5–7 d before low- and high-bleeding-risk operation; resume when bleeding risk has diminished
Consideration in the nonelective setting	
Vitamin K antagonist	Administer vitamin K and 4-factor PCC to patients with an elevated INR secondary to warfarin who are actively bleeding or require urgent operation
Dabigatran	Administer idarucizumab to patients with evidence of significant dabigatran levels (by history of ingestion or laboratory parameter) who are bleeding or require emergency operation
Other DOAC	Administer 4-factor PCC transfusion (50 U/kg) for partial reversal in patients with evidence of active factor Xa inhibitor as needed in emergency situation
Antiplatelet agent	Transfuse 1 pooled unit of platelets immediately before operation and redose as needed for ongoing bleeding

DOAC indicates direct oral anticoagulant; INR, international normalized ratio; LMWH, low-molecular-weight heparin; PCC, prothrombin complex concentrate; PCI, percutaneous coronary intervention; and VTE, venous thromboembolism.

bridging therapy primarily to patients at high risk of thromboembolism[77] and suggest that continuation of low-dose aspirin in patients without prior percutaneous coronary intervention leads to higher perioperative bleeding risk without a reduction in nonfatal MI or mortality.[78]

Table 6. Summary of Preoperative Strategies to Reduce Perioperative Stroke

All patients undergoing evaluation before surgery should be assessed for perioperative stroke risk in terms of key risk factors (age, renal disease, and history of transient ischemic attack/stroke) with additional emphasis on timing of surgery relative to prior stroke, overall cardiovascular risk, and type of surgery planned. The presence of a PFO may also be associated with higher perioperative stroke risk. We suggest that clinicians use the web-based ACS-SRC to identify patients with elevated risks of perioperative stroke.[44]
If history of stroke exists, consider delaying elective surgery at least 6 mo and preferably 9 mo from time of incident stroke.
Perform carotid revascularization (CEA vs CAS) in patients with symptomatic (stroke or transient ischemic attack within last 6 mo) carotid artery stenosis (>70%) before planned surgery. Perioperative management of patients with high-grade asymptomatic carotid stenosis is uncertain but should be informed by existing guidelines for carotid revascularization and contemporary medical treatment in this population.
Use or adjustment of medications such as statins, β-blockers, and antithrombotic agents should be based on existing guidelines but tailored to individual patient characteristics. In particular, aspirin should be held unless patients have had a prior PCI. Patients with a mechanical heart valve receiving a vitamin K antagonist should be bridged with LMWH or intravenous heparin. Patients at high risk for thromboembolism taking a vitamin K antagonist (eg, atrial fibrillation with high CHA_2DS_2-VASc score, recent venous thromboembolic disease) may be bridged with full-dose (therapeutic) LMWH or intravenous heparin.
Consider nonsurgical treatment in discussion with patient and caregivers as an alternative to surgery in patients with elevated risk of stroke.

ACS-SRC indicates American College of Surgeons surgical risk calculator; CAS, coronary artery stenting; CEA, carotid endarterectomy; LMWH, low-molecular-weight heparin; PCI, percutaneous coronary intervention; and PFO, patent foramen ovale.

Table 6 summarizes preoperative strategies to reduce perioperative stroke.

INTRAOPERATIVE MANAGEMENT TO REDUCE RISK OF STROKE

Blood Pressure Management

Maintaining adequate end-organ perfusion to the heart, brain, and other vital organs is the cornerstone of anesthetic management. Without the ability to directly measure blood flow to critical organs such as the brain, anesthesiologists monitor blood pressure as an indirect measure of end-organ perfusion. Drops in blood pressure are very common during surgery, with mean arterial pressures (MAPs) falling below 20% of baseline occurring in up to 90% of surgical cases.[79] Hypotension is caused by the direct effects of anesthetics on heart (myocardial depression) and vasculature (drop in systemic vascular resistance and vasodilatation), anesthesia-mediated decreases in sympathetic tone, and volume shifts. Hypotension is treated with volume administration, boluses of short-acting adrenergic agonists, and, less commonly, continuous infusions of vasoactive drugs. Although a review identified 140 different definitions of intraoperative hypotension, the most common definitions of hypotension are a systolic blood pressure <80 mm Hg and a decrease in systolic blood pressure >20% below baseline.[79]

Hypotension may be a modifiable risk factor for perioperative stroke. Orthostatic hypotension was associated with a 2-fold higher risk of ischemic strokes in a large cohort study of middle-aged adults without atherosclerotic disease.[80] Many anesthesiologists routinely use an MAP of 60 mm Hg and a systolic blood pressure of 100 mm Hg as target blood pressures because healthy normotensive patients without cerebrovascular disease will maintain a constant cerebral blood flow when the MAP is between 60 and 150 mm Hg.[81] An accumulating body of evidence links intraoperative hypotension with myocardial injury, kidney injury, and death.[82–87] However, most of the evidence supporting a causal link between intraoperative hypotension and perioperative strokes is not very strong with the exception of results from POISE (Perioperative Ischemic Evaluation Trial).[68] This study, which was designed to test whether perioperative β-blockade improves cardiovascular outcomes in patients with atherosclerotic disease, unexpectedly showed that patients receiving metoprolol were more likely to die and were twice as likely to have a stroke.[68] In particular, patients with clinically significant hypotension perioperatively (defined as a systolic blood pressure <90 mm Hg requiring treatment) had a 2-fold higher odds of stroke (hazard ratio, 2.17 [95% CI, 1.26–3.74]; P=0.0053),[68] suggesting that optimal blood pressure management may play an important role in stroke prevention.[68] However, 3 observational studies each showed at most only a weak association between intraoperative hypotension and stroke. Bijker et al[88] reported that the stroke risk increased by 1.14-fold for every 10 minutes of hypotension, defined as a mean blood pressure 30% less than baseline. Hsieh et al[89] reported no association between mild hypotension (MAP <70 mm Hg) and stroke. Finally, Sun et al[90] reported a 1.13-fold higher risk of stroke in patients undergoing cardiac surgery with MAPs <64 mm Hg for every 10 minutes during cardiopulmonary bypass. The inability to detect a strong association between stroke and hypotension may be attributable to a number of factors, including the low incidence of recognized strokes for patients undergoing noncardiac surgery, which is between 0.1% and 1%,[4,5,11] and the observation that many patients are discharged before the defined period of 30 days of perioperative stroke expires, which may lead to unrecognized strokes. In addition, the incidence of unrecognized cerebral ischemia may be much higher than the incidence of clinically recognized strokes, as discussed in the Silent Cerebral Ischemia section.[23,24]

Although we lack sufficient evidence to fully identify blood pressure targets to specifically prevent cerebral

ischemia, there are data addressing blood pressure thresholds associated with overall end-organ damage and death. A recent systematic review reported moderate increases in the risk of end-organ injury and mortality (odds ratio/relative risk/hazard ratio between 1.4 and 2.0) at MAPs <65 mm Hg lasting >10 minutes.[91] This review did not identify significant associations between MAP thresholds and stroke. In addition, recent data from a multicenter randomized controlled trial showed that a standardized approach to treating intraoperative hypotension leads to fewer complications in patients undergoing predominantly abdominal surgery.[92] This study found that maintaining the systolic blood pressure within 10% of baseline was associated with a 30% reduction in postoperative organ dysfunction compared with using a less aggressive approach that targeted systolic blood pressure <80 mm Hg or systolic blood pressure <40% of baseline.[92] However, this study has been criticized because the blood pressure targets in the control group are much lower than those used by most anesthesiologists.[93]

Using the best available evidence, a recent consensus statement from the Perioperative Quality Initiative concluded that systolic blood pressures <100 mm Hg and MAPs below 60 to 70 mm Hg may be associated with myocardial injury and kidney injury.[93] The results from POISE-III (URL: ClinicalTrials.gov. Unique identifier: NCT03505723), a multicenter trial with a planned enrollment of 10 000 patients that will compare the incidence of a composite of MI, nonhemorrhagic stroke, peripheral arterial thrombosis, and venous thromboembolism in patients randomized to a treatment strategy targeting an intraoperative MAP ≥80 mm Hg compared with 60 mm Hg, may help inform future guidelines on the management of intraoperative hypotension. The results from a planned substudy on cognitive decline, which is associated with silent cerebral infarctions, may be particularly useful in defining intraoperative MAP thresholds for avoiding brain injury. Recognizing that there are still insufficient data to establish firm parameters for intraoperative blood pressure targets, we suggest that clinicians consider maintaining the MAP above 70 mm Hg intraoperatively to reduce the risk of perioperative stroke. Although evidence to specify a safe upper limit of MAP during noncardiac surgery is lacking, care should be taken to avoid extremes of hypertension, which can provoke myocardial ischemia, cerebral edema, or other end-organ injury.

Finally, we support the recommendation from the Society for Neuroscience in Anesthesiology and Critical Care that the difference in blood pressure between the brachial artery and the brain in patients undergoing surgery in the sitting position (eg, shoulder surgery, cervical spine surgery) should be considered.[6] In cases in which the intra-arterial blood pressure is monitored, the blood pressure transducer should be zeroed at the level of the auditory meatus. For patients whose blood pressure is monitored with a noninvasive cuff, the MAP target should account for the 0.8–mm Hg gradient between the brain and the brachial artery for every 1-cm difference in height between the blood pressure cuff and the auditory meatus.

Perioperative Goal-Directed Therapy

Targeting blood pressure as a means to improve overall surgical outcomes and to reduce the risk of strokes may oversimplify the goal of perioperative hemodynamic management, which is to optimize end-organ perfusion and oxygen delivery, not just to achieve specific blood pressure targets. Thirty years after the seminal work by Shoemaker et al[94] first describing the use of goal-directed therapy to optimize global perfusion in high-risk surgical patients, and despite controversy surrounding its benefit, goal-directed therapy is widely used.[95] A Cochrane meta-analysis published in 2013, based on 31 randomized trials with 5092 participants, showed that administration of fluids and vasoactive drugs targeted to increase global blood flow did not significantly reduce mortality but did reduce the overall rate of complications by 32%, including a 29% reduction in the incidence of renal impairment and 49% reduction in the incidence of respiratory failure/acute respiratory distress syndrome.[96] Subsequently, OPTIMISE (Effect of a Perioperative, Cardiac Output–guided Hemodynamic Therapy Algorithm on Outcomes Following Major Gastrointestinal Surgery), a pragmatic multicenter randomized controlled trial of cardiac output–guided therapy during the postoperative period in 734 high-risk patients undergoing major gastrointestinal surgery, reported a 6.8% lower absolute risk of the composite outcome of complications and 30-day mortality (95% CI, –0.38% to 13.9%; *P*=0.07). Although the findings from this study were not statistically significant, the use of a hemodynamic intervention algorithm was found to be associated with improved outcomes when these results were included in an updated meta-analysis (risk ratio, 0.77 [95% CI, 0.71–0.83]).[97] More recently, FEDORA (Effect of Goal-directed Haemodynamic Therapy on Postoperative Complications in Low–moderate Risk Surgical Patients), a prospective multicenter randomized trial in 450 low- and moderate-risk patients undergoing noncardiac surgery, reported nearly 50% fewer moderate or severe postoperative complications in patients randomized to intraoperative goal-directed therapy.[98] There was no significant difference in mortality rates at 180 days between groups.[98] None of these trials described significant reductions in strokes, most likely because of the low incidence of strokes and insufficient statistical power. Moreover, there is insufficient literature to make any firm suggestions on the use of goal-directed therapy to prevent strokes. Although it is unlikely that randomized trials to examine the effect of goal-directed therapy on overt strokes are feasible because of the low incidence

of overt strokes in noncardiac surgery, it may be possible to perform such a trial using silent cerebral ischemia as the end point given the much higher incidence of silent cerebral infarcts compared with overt strokes.[24]

Perioperative Blood Transfusion Management

Oxygen delivery to the brain is a function of cerebral blood flow, arterial oxygen saturation, and hemoglobin levels. Decreases in hemoglobin levels lead to cerebral arterial vasodilation, increases in sympathetic outflow, and increases in venous return, contractility, and heart rate, which together compensate for reduction in oxygen content by increasing cardiac output and cerebral blood flow.[99] In addition, oxygen extraction fraction can increase from a baseline of 40% up to 80% in low-flow conditions.[100] Healthy volunteers will exhibit reversible cognitive dysfunction after isovolumic reductions of blood hemoglobin concentrations to 6 g/dL and will maintain adequate global perfusion at blood hemoglobin concentrations as low as 5 g/dL, suggesting that these adaptive responses start to fail at hemoglobin concentrations <6 g/dL.[101] However, patients with cerebrovascular disease[102] or a recent stroke do not have the same cerebrovascular reserve as healthy volunteers and may develop brain hypoxia at hemoglobin thresholds >6 g/dL.[102–104] Because patients with significant internal carotid artery disease or intracranial stenosis may have partially exhausted their vascular and oxygen extraction reserves, they may not be able to increase cerebral perfusion to vulnerable brain areas to compensate for decreases in arterial oxygen content.[102,103,105]

Although anemia would be expected to increase the risk of stroke during the perioperative period, 2 large observational trials of patients undergoing noncardiac surgery did not show increases in the incidence of adverse central nervous system outcomes in patient with preoperative anemia.[106,107] These negative findings may have resulted from targeted perioperative clinical interventions that mitigated the risk of anemia. However, this is not likely because patients with preoperative anemia were found to have a significantly higher risk of mortality, cardiac complications, and respiratory complications compared with patients without anemia.[106-109] Using data from >227 000 patients, Musallam et al[106] found that patients with moderate to severe anemia had a 44% higher odds of mortality, a 52% higher odds of cardiac complications, and a 41% higher odds of respiratory complications but no difference in central nervous system complications compared with patients without anemia. Saager et al[107] also reported similar findings using data on nearly 575 000 patients. Anemia, however, has been reported to increase the risk of stroke in nonsurgical patients.[110–114] Anemia is also associated with a higher risk of poor functional outcomes and mortality in patients presenting with an acute stroke.[115–120] Together, these studies paint a somewhat confusing picture that anemia is a risk factor for stroke in the general population but not in patients undergoing noncardiac surgery.

Although anemia is associated with higher rates of mortality and morbidity in patients undergoing noncardiac surgery, observational studies have consistently shown that patients who receive blood transfusions perioperatively have worse outcomes compared with those who do not.[121–125] Several randomized trials have been performed to determine whether blood transfusions can be safely avoided with the use of a restrictive transfusion strategy, in which patients with a hemoglobin level <7 or 8 g/dL are transfused, compared with a "liberal" transfusion strategy that uses 9 g/dL as a transfusion threshold in patients undergoing cardiac[126–129] and noncardiac surgery[130,131] and in critically ill patients.[132,133] These trials showed that prior observational studies overestimated the risk of blood transfusions.[134] A recent meta-analysis based on 37 randomized controlled trials with >19 000 patients showed that the risk of stroke, MI, congestive heart failure, renal failure, and 30-day mortality was not significantly different between restrictive and liberal transfusion strategies.[135] According to the study authors, the main limitation of this meta-analysis is that it did not include enough information on patients with brain injury, acute coronary syndromes, or congestive heart failure to make recommendations for these very high-risk groups.[135] To this group, we should add patients with an elevated risk of perioperative stroke. On the basis of the evidence from these large randomized controlled trials, the AABB (formerly known as the American Association of Blood Banks) recommends a 2-tiered approach: a transfusion threshold of 7 g/dL for hemodynamically stable hospitalized patient and 8 g/dL for patients undergoing cardiac or orthopedic surgery or for patients with preexisting cardiovascular disease or symptoms such as hemodynamic instability unresponsive to volume resuscitation.[136]

We suggest that clinicians use the same transfusion threshold for patients with recent strokes or preexisting cerebrovascular disease that the AABB recommends for patients with preexisting cardiovascular disease: a transfusion threshold of 8 g/dL. The AABB clinical practice guidelines make no recommendations for patients with acute coronary syndromes, citing lack of evidence.[136] In light of the uncertainty across existing guidelines, we suggest that clinicians should consider a transfusion threshold of 8 g/dL for most patients with elevated stroke risk and a threshold of 9 g/dL for patients with an acute perioperative stroke or known cerebrovascular insufficiency resulting from severe carotid stenosis or occlusion. In considering a higher transfusion threshold in the highest-risk patients, the risk of noninfectious hazards of transfusion such as transfusion-associated

circulatory overload (which can occur in up to 5% of transfusions) should be weighed against the unproven benefit of using a higher transfusion threshold.[137] Of note, a trial is being planned to evaluate whether a liberal transfusion strategy leads to fewer adverse ischemic outcomes, including strokes, in elderly patients ≥70 years of age undergoing intermediate and high-risk noncardiac surgery (LIBERAL trial [Liberal Transfusion Strategy in Elderly Patients]; URL: ClinicalTrials.gov. Unique identifier: NCT03369210).[138] Finally, to the best of our knowledge, no trials are currently planned to examine transfusion thresholds limited to patients presenting with acute ischemic strokes, although 2 trials are currently underway for patients with acute coronary syndromes (REALITY [Restrictive and Liberal Transfusion Strategies in Patients With Acute Myocardial Infarction], URL: ClinicalTrials.gov. Unique identifier: NCT02648113; and MINT [Myocardial Ischemia and Transfusion], URL: ClinicalTrials.gov. Unique identifier: NCT02981407).[137] Future randomized trials should be considered to compare restrictive and liberal transfusion thresholds in patients presenting with acute strokes.

Effects of the Choice of Anesthetic Technique

Although anesthetic neuroprotection has been studied intensively over the past 50 years, there is no evidence that anesthetics are neuroprotective in humans despite the finding that anesthetics reduce the cerebral metabolic rate and mimic the effects of ischemic preconditioning.[139,140] Instead of focusing on anesthetic neuroprotection, the question today has shifted to the potential neurotoxicity of anesthetic agents[141] in part because of early influential studies suggesting that general anesthesia may be associated with cognitive decline in elderly patients.[141,142] Because nitrous oxide causes endothelial dysfunction, its use could lead to increases in cardiovascular complications and strokes. However, the results of ENIGMA-II (Evaluation of Nitrous Oxide in the Gas Mixture for Anaesthesia), a large international randomized controlled trial in patients with known or suspected coronary artery disease, showed that nitrous oxide did not lead to increases in the composite outcome of death and cardiovascular complications, including stroke, within 30 days or 1 year after major noncardiac surgery.[143,144] The Balanced Anesthesia Study, based on a large international trial of 6644 older patients with significant comorbidity undergoing major surgery, reported no significant difference in 1-year mortality, composite of cardiovascular outcomes, and stroke in patients randomized to light compared with deep general anesthesia.[145] In 2018, the Perioperative Neurotoxicity Working Group, sponsored by the American Society of Anesthesiology Brain Health Initiative, published a set of recommendations on best practices for brain health and reported that there is little evidence that inhaled anesthetic agents increase the risk of perioperative neurocognitive disorder.[146] The evidence to date suggests that anesthetic agents are neither neuroprotective nor neurotoxic and that the choice of anesthetic agent is unlikely to influence the risk of stroke in the perioperative period.

Since the seminal study by Yeager et al[147] from >30 years ago showing that patients undergoing major vascular procedures were half as likely to have major complications if they received epidural analgesia, there has been remarkable interest in the use of regional anesthesia to improve outcomes, as well as controversy concerning whether regional anesthesia actually improves surgical outcomes.[148] A recent meta-analysis from the Cochrane Library of randomized controlled trials, which included 31 studies with 3231 participants, compared neuraxial anesthesia (spinal or epidural) with general anesthesia in patients undergoing surgery for hip fractures. This study reported no difference in either 30-day mortality or rates of strokes or MIs but concluded that the quality of evidence was too low and the sample size too small to make any definitive conclusion.[149] A second meta-analysis, also from the Cochrane Library, compared general anesthesia with neuraxial anesthesia for patients undergoing lower-limb revascularization. This study, based on 696 participants, also reported no difference in mortality or MIs and cited that the evidence was insufficient to draw conclusions for strokes or postoperative cognitive deficits.[150] With estimated stroke rates <1%, it may not be possible to design randomized controlled trials to arrive at conclusions on the superiority of regional anesthesia compared with general anesthesia.

Two large retrospective studies, one based on 528 495 patients and the other based on 182 307 patients, suggest that neuraxial anesthesia may be weakly associated with fewer strokes compared with general anesthesia in patients undergoing hip surgery.[151,152] Smith et al[153] recently published a meta-analysis comparing neuraxial anesthesia and combined neuraxial and general anesthesia with general anesthesia for major truncal and lower limb surgery using nearly 1.1 million patient records. Neuraxial anesthesia, either alone or in combination with general anesthesia, was not associated with differences in 30-day mortality compared with general anesthesia alone.[153] Neuraxial anesthesia was associated with 60% fewer pulmonary complications but no differences in cardiac complications compared with general anesthesia alone. Combined neuraxial and general anesthesia was not associated with differences in the rate of pulmonary or cardiac complications. This meta-analysis, however, did not examine the association between regional anesthesia and stroke. There is currently insufficient evidence to support the use of regional anesthesia or analgesia versus general anesthesia alone to lower the perioperative risk of stroke.

Table 7. Summary of Intraoperative Management to Prevent Perioperative Stroke

Consider maintaining a mean arterial pressure >70 mm Hg, especially in patients who are at moderate or high risk for perioperative stroke.
It is reasonable to consider a transfusion threshold of 8 g/dL for patients with a history of recent stroke or significant cerebrovascular disease (eg, carotid or intracranial stenosis >70%). Clinicians may consider a transfusion threshold of 8–9 g/dL in patients with an acute perioperative stroke, ongoing bleeding, hemodynamic instability, and known cerebrovascular insufficiency attributable to stenosis or occlusion.
There is insufficient evidence to make clear suggestions on the use of general anesthesia vs regional anesthesia.
It is reasonable to consider a lung-protective ventilation strategy as part of an overall strategy to reduce postoperative complications, although there are no data to support this approach for the reduction of perioperative stroke.
Hypocarbia should be generally avoided in patients at high risk for perioperative stroke.

Table 7 provides a summary of intraoperative management to prevent perioperative stroke.

Ventilation Strategies

Although there is little empirical evidence on the association between ventilation strategies and the risk of perioperative strokes, there is substantial evidence that hyperventilation and hypocapnia lead to significant reductions in cerebral blood flow.[154,155] Hypocapnia causes the cerebral autoregulatory curve to be shifted downward, leading to reductions in cerebral blood flow, throughout the range of cerebral perfusion pressures.[156] Because hypocapnia can worsen cerebral ischemia, the injured brain may be particularly susceptible to the effects of hypocapnia.[157] These data suggest that avoiding hypocarbia in high-risk patients is reasonable and that hypocapnia may be exceptionally harmful in those patients who experience cerebral ischemia perioperatively.

Since the landmark work showing that the prevention of ventilator-induced lung injury with the use of lower tidal volumes reduces mortality in patients with acute lung injury and the acute respiratory distress syndrome,[158,159] protective lung ventilation has become a best practice for the care of critically ill patients. These findings have been replicated in patients undergoing noncardiac surgery in which the use of lung-protective ventilation leads to a lower incidence of major pulmonary complications, sepsis, and death.[160] Although stroke was not one of the outcomes studied, preventing pulmonary complications may lead to fewer episodes of hypoxemia perioperatively and decrease the risk of stroke in high-risk surgical patients. Although there are no data to show that lung-protective ventilation reduces the risk of strokes, it is reasonable to use protective lung ventilation as part of an overall strategy to improve perioperative outcomes.

IDENTIFICATION AND TREATMENT OF PERIOPERATIVE STROKE

Stroke Recognition in the Perioperative Setting

Between 4% and 17% of all strokes occur in patients who are already hospitalized for either medical or surgical indications.[161,162] Even after adjustment for comorbidities, patients experiencing a stroke in the hospital are more likely to have longer hospitalizations, worse outcomes, including higher mortality, and a lower probability of discharge home compared with patients who have a stroke in the community.[161,163] In a prospective cohort study, patients with in-hospital strokes were also significantly less likely to receive thrombolytic therapy and more likely to have delays in time to brain imaging and time to treatment compared with patients presenting from outside the hospital.[163] More than 60% of these in-hospital strokes were likely perioperative or periprocedural, occurring on either a surgical service or in the angiography suite.[163]

With nearly half of all perioperative strokes occurring in the first 24 hours after surgery,[9,12] the identification of stroke symptoms in patients during the perioperative period is challenging if intubation is prolonged, if there are residual effects from anesthesia, or because of the use of opioids and other psychoactive medications postoperatively. The hallmark of acute stroke is typically the sudden onset of focal neurological deficits; in the postoperative period, the exact onset of symptoms often cannot be determined, and the clinical presentation may be nonfocal, such as mental status changes, including agitated delirium, autonomic instability, or delayed emergence from anesthesia.[12,30] Many medications used in the perioperative period affecting mental status can be reversed in order to facilitate neurological evaluation of patients with suspected stroke.

Postanesthesia care units should consider routinely performing neurological assessments for early identification of stroke in high-risk patients, including evaluation of level of arousal, speech/language, and motor function. Staff members in these units may require additional training in performing neurological assessments. Multiple prehospital and emergency department scales exist to aid in the identification of stroke symptoms, but none have been validated in the perioperative setting.[164,165] Abbreviated versions of the National Institutes of Health Stroke Scale have been validated for use in clinical research and prehospital evaluation and may be a reasonable and more expeditious option over the standard National Institutes of Health Stroke Scale in the perioperative setting[165-167] (Figure 2). Alternatively, the Cincinnati Prehospital Stroke Scale is a rapid and easily administered stroke assessment tool that has been validated in prehospital applications and may be considered for use in the perioperative setting[168] (Figure 3).

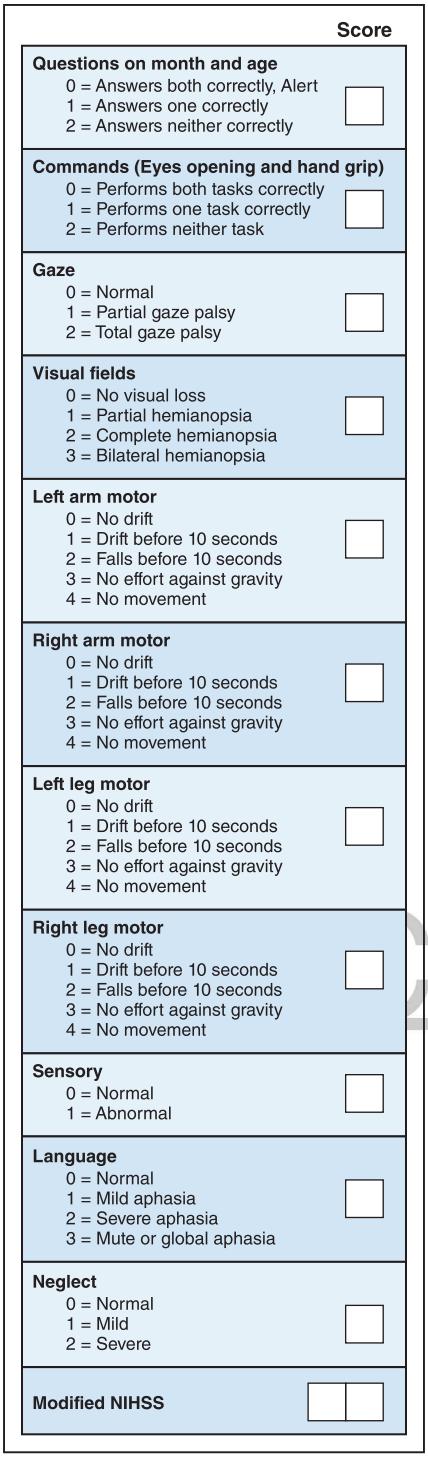

Figure 2. Modified National Institutes of Health Stroke Scale (NIHSS). Adapted from Sun et al[165] with permission. Copyright © 2016, The Author. Published by Oxford University Press on behalf of the *British Journal of Anaesthesia*. All rights reserved.

Emergent Evaluation: "Code Stroke"

Evidence-based guidelines exist for the identification and evaluation of patients presenting with acute stroke in the community or in the emergency room, emphasizing the use of an organized protocol and an acute stroke response team.[169] Similarly, if an acute stroke is suspected in the in-hospital perioperative setting, an institutional stroke code and a rapid response stroke team should be activated to ensure immediate neurological assessment, facilitate timely imaging, and initiate therapeutic medications and interventions.[170] All health care professionals need to be educated about the signs of stroke and should be empowered to initiate a stroke code.[171,172] Formal protocols should be used to guide practice, including immediate assessment of clinical parameters such as blood pressure, pulse, temperature, glucose level, and metabolic status, with special attention to pharmacological effects from anesthesia. A noncontrast head computed tomography (CT) scan should be obtained to rule out intracranial hemorrhage immediately, with additional CT angiography and perfusion studies in patients suspected of having a large vessel occlusion (LVO). An abbreviated MRI with diffusion-perfusion sequences may be indicated in select circumstances, but CT scanning is routinely faster, more available, and better tolerated by postoperative patients. Patients eligible for thrombolytic treatment, mechanical embolectomy, or both must be identified as early as possible, and optimal interventions should be determined by members of the surgical and perioperative teams, along with the vascular neurology and interventional teams.

Table 8 provides a suggested algorithm for the evaluation of a patient with suspected stroke in the perioperative setting, adapted from American Heart Association Phase III Target Stroke.[173]

Acute Stroke Treatment: Endovascular Therapy

Patients with LVO are likely to have the most devastating neurological outcomes if the LVO is not treated. The incidence of LVO stroke is >30% in patients presenting with acute ischemic strokes and 10.9% in patients with perioperative ischemic strokes after cardiac surgery.[174,175] Because mechanical embolectomy does not require anticoagulation and is superior to intravenous alteplase alone for the treatment of LVO strokes, patients who are suspected to have an LVO (eg, National Institutes of Health Stroke Scale score >6 and/or cortical deficits on examination) should undergo immediate CT angiography and possible CT perfusion studies to determine whether they are candidates for mechanical thrombectomy in addition to intravenous thrombolytic therapy. Patients with acute ischemic stroke can be considered for intravenous alteplase as long as treatment is initiated within 4.5 hours of symptom onset or time of last known well and there is no evidence of hemorrhage on the noncontrast CT.[169]

Patients experiencing a perioperative stroke are often ineligible for intravenous alteplase because of the risk of surgical bleeding but may otherwise be considered for mechanical thrombectomy provided that they meet existing criteria based on clinical characteristics and imaging findings. Decisions to pursue mechanical embolectomy in

Cincinnati Prehospital Stroke Scale (CPSS)

Facial Droop
Normal: Both sides of the face move equally
Abnormal: One side of the face does not move as well as the other

Arm Drift
Normal: Both arms move equally or not at all
Abnormal: One arm drifts compared to the other

Speech
Normal: Patient uses correct words with no slurring
Abnormal: Slurred or inappropriate words or mute

An abnormal finding in any one of the three components results in a positive CPSS and should trigger activation of the acute stroke team.

Figure 3. Modified Cincinnati Prehospital Stroke Scale (CPSS).
Reprinted from Kothari et al[168] with permission from the American College of Emergency Physicians. Copyright © 1999, American College of Emergency Physicians. Published by Elsevier Inc. All rights reserved.

the perioperative setting should be based on those clinical and imaging determinants, as well as an individualized risk/benefit assessment including current morbidities, type of surgery recently performed, and time from last known well. It is important to emphasize that mechanical thrombectomy for LVO can be performed without systemic anticoagulation. If a surgical procedure is to be performed at a center that is not thrombectomy capable, provisions for transfer to an advanced stroke center if a perioperative stroke is identified should be established beforehand. Procedures with a high risk of perioperative stroke should ideally be done only at thrombectomy-capable centers.[176]

Recent evidence has firmly established robust beneficial effects of mechanical thrombectomy in reducing disability in selected patients with LVO up to 24 hours after the onset of stroke symptoms.[169,177] Current guidelines for patients presenting within 6 hours of symptom onset are based on data from 6 randomized trials that demonstrated significantly improved functional outcomes in patients undergoing mechanical embolectomy (Table 9). Two recent trials of mechanical thrombectomy have further expanded the time window of eligibility up to 24 hours for patients with an LVO and favorable brain perfusion imaging.[178,179] In the DAWN trial (DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo), patients with symptom onset between 6 and 24 hours and a mismatch between clinical findings and infarct size based on advanced brain imaging who underwent mechanical thrombectomy had significantly improved outcomes at 90 days compared with those who had standard treatment.[178] In DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke), patients with an internal carotid artery or proximal middle cerebral artery occlusion and favorable brain imaging (mismatch between core infarct and ischemic penumbra) who were treated by mechanical thrombectomy had significantly less disability at 90 days compared with control subjects.[179] Current guidelines now support the use of mechanical thrombectomy in patients with symptom onset between 6 and 24 hours provided that they meet the eligibility criteria used in these 2 trials.[169]

Limited evidence exists describing mechanical embolectomy in the perioperative setting, including only small cases series in patients undergoing cardiac surgery[175,180,181] and 1 case-control study involving 25 patients with perioperative stroke after general surgery, neurosurgery, open heart procedures, or interventional vascular procedures.[182] In the study by Premat et al,[182] successful reperfusion was obtained in 76% of patients with a symptomatic hemorrhage rate of 8%, comparable to results seen in recent major trials. Mortality, however, was significantly higher in cases compared with matched controls (who did not have surgery before their stroke), which may be attributable to other surgical morbidities or differences in treatment. For instance, none of the 25 cases who underwent embolectomy were treated with intravenous alteplase compared with 64% of controls who received thrombolytic therapy.[182]

Although the benefits are unproven, patients with occlusion of other intracranial vessels (anterior cerebral, distal middle cerebral, vertebral, basilar, or posterior

Table 8. Perioperative In-Hospital Stroke Response Protocol

Time goals	Identification of acute stroke symptoms in hospitalized patients	Simultaneously perform
Stroke symptom discovery to stroke alert <5 min Stroke symptom discovery to neurological expertise <10 min	Initiate code stroke/telestroke consult Notify anesthesiologist and surgeon Perform screening assessment (CPSS, modified or full NIHSS) Fingerstick glucose (treat <60 mg/dL) Blood pressure (notify if >185/110 mm Hg, treat hypotension) Obtain pulse, temperature Continuous cardiac monitor and pulse oximetry (maintain O_2 saturation >94%) ECG, laboratory values (PT/INR, PTT, CBC, platelet count, troponin) Place second intravenous line to obtain laboratory values Do not delay CT to obtain ECG or laboratory values	Confirm LKW; may be anesthesia induction time Locate family for history and consent
Stroke symptom discovery to CT/MRI <25 min	Noncontrast CT of the brain CT phone number_____ If suspected LVO: additional CT angiography and perfusion studies or abbreviated MRI with perfusion/diffusion sequences if indicated. MRI phone number_____	
Stroke symptom discovery to CT/MRI result <45 min	Obtain radiological interpretation Contact number_____	
Stroke symptom discovery to initiation of treatment <60 min (alert to needle) <75 min (alert to puncture)	LKW <4.5 h, consider intravenous alteplase, along with mechanical embolectomy if LVO LKW <24 h, consider mechanical embolectomy if LVO Unknown time of onset of symptoms noted on awakening, with favorable advanced imaging and no LVO, consider intravenous alteplase Reversal of anticoagulation in patients with hemorrhagic stroke Transfer to ED/ICU/stroke unit or stroke center Contact number_____	Individualized risk/benefit discussion with all health care professionals and the patient/family American Heart Association.

CBC indicates complete blood count; CPSS, Cincinnati Prehospital Stroke Scale; CT, computed tomography; ED, emergency department; ICU, intensive care unit; INR, international normalized ratio; LKW, last known well; LVO, large vessel occlusion; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; PT, prothrombin time; and PTT, partial thromboplastin time.

Data derived from American Heart Association website.[173]

cerebral arteries) or who have greater premorbid disability may also be considered for mechanical thrombectomy if their National Institutes of Health Stroke Scale score is ≥6, their Alberta Stroke Program Early CT Score is ≥6, and they can be treated within 6 hours of symptom onset.[169] Additional evidence from meta-analyses supports a potential broadening of the indications for mechanical embolectomy to include patients with larger, more severe strokes (Alberta Stroke Program Early CT Score <6) or with distal middle cerebral artery occlusions.[183–185]

Acute Stroke Treatment: Thrombolytic Therapy

Patients presenting with a perioperative stroke after major surgery may be considered for treatment with intravenous alteplase within 4.5 hours from the time of last known well. Intracranial or intraspinal surgery within the past 3 months is an absolute contraindication to intravenous alteplase treatment.[169] Several retrospective studies have identified a small number of patients with recent surgery who underwent treatment with intravenous alteplase who had an increase in surgical site hemorrhages but had no major complications.[186–188] Voelkel et al[189] analyzed 134 patients treated with intravenous alteplase who had undergone surgery within the previous 90 days, including 49 patients who had surgery within 1 to 10 days. Surgical site hemorrhage occurred in only 9 patients (7%) and was identified as serious in 4 patients (3%). Two of these patients received red blood cell transfusions, and the other 2 were treated by surgical evacuation of the site hematoma or endoscopic clipping of a colonic adenoma.[189] Surgical site hemorrhage was significantly more likely to occur in more recent rather than later surgery.[189] From these observations, intravenous alteplase should be considered in patients with recent surgery after

Table 9. Guidelines for Treatment With Mechanical Thrombectomy With a Stent Retriever

Prestroke modified Rankin Scale score of disability 0–1 (able to carry out all usual activities)
Causative occlusion of distal internal carotid artery or proximal middle cerebral artery
Age ≥18 y
NIHSS score of ≥6
ASPECTS of ≥6
Treatment initiated (groin puncture) within 6 h of symptom onset

ASPECTS indicates Alberta Stroke Program Early CT Score; and NIHSS, National Institutes of Health Stroke Scale.

Adapted from Powers et al.[169] Copyright © 2019, American Heart Association, Inc.

a careful, individualized risk-benefit discussion between all health care professionals and the patient. In many cases, the adverse effects of a major stroke may be much greater than the risk of significant surgical bleeding.

Multiple recent trials have examined imaging-guided thrombolysis treatment beyond 4.5 hours. The WAKE-UP trial (Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke) randomized 503 patients with unknown time of onset and MRI findings of ischemia on diffusion-weighted imaging, but no changes on fluid-attenuated inversion recovery, to either intravenous alteplase or placebo.[190] A favorable outcome (modified Rankin Scale score, 0–1) was more likely in those given intravenous alteplase (adjusted odds ratio, 1.61 [95% CI, 1.09–2.36]; *P*=0.02), although 10 patients in the alteplase group died (4.1%) compared with 3 (1.2%) in the placebo group (odds ratio, 3.38 [95% CI, 0.92–12.52]; *P*=0.07), and symptomatic intracranial hemorrhage was more common in the intravenous alteplase group than in the placebo group (2% versus 0.4%; odds ratio, 4.95 [95% CI, 0.57–42.87]; *P*=0.15).[190] In addition, in a patient-level meta-analysis of 3 randomized placebo-controlled trials of intravenous alteplase (EPITHET [Echoplanar Imaging Thrombolytic Evaluation Trial], ECASS 4 [European Cooperative Acute Stroke Study 4–Extending the Time Window for Intravenous Thrombolysis in Acute Ischemic Stroke using Magnetic Resonance Imaging-based Patient Selection] and EXTEND [Extending the Time for Thrombolysis in Emergency Neurological Deficits]), patients >4.5 hours after onset of stroke or with wake-up stroke who were included on the basis of a diffusion-perfusion MRI or perfusion CT showed favorable outcomes for extended-window thrombolysis.[191] Among 414 included patients, patients given intravenous alteplase were more likely to have an excellent outcome (modified Rankin Scale score, 0–1) at 3 months (36% versus 29%; adjusted odds ratio, 1.86 [95% CI, 1.15–2.99]; *P*=0.011). However, symptomatic intracerebral hemorrhage was also more common in the intravenous alteplase group (5% versus <1%; adjusted odds ratio, 9.7 [95% CI, 1.23–76.55]; *P*=0.031), and there was a numerically higher mortality rate among those who received IV alteplase (14% versus 9%; adjusted odds ratio, 1.55 [95% confidence interval, 0.81–2.96]; *P*=0.66). Taken together, these data suggest that carefully selected patients beyond 4.5 hours from the time of last seen normal may have improved neurological recovery if treated with intravenous alteplase. Current guidelines now support the use of intravenous alteplase when administered within 4.5 hours of stroke symptom recognition in patients who awaken with stroke symptoms or have unclear time of onset >4.5 hours from last known well and have diffusion-weighted MRI lesion smaller than one-third of the middle cerebral artery territory and no visible signal change on fluid-attenuated inversion recovery.[169] However, there were numerically higher mortality rates in the patients who received thrombolysis, and it is likely that a recent surgery would also increase the risk for a serious adverse event. Therefore, the use of IV alteplase in this time window in surgical patients should be considered cautiously and undertaken only with selection criteria and high-level imaging similar to those used in these trials with well-documented informed consent. If mechanical thrombectomy is an option, that should take precedence (Table 9).

Table 10 provides a summary of the identification and treatment of perioperative stroke.

Table 10. Summary of Identification and Treatment of Perioperative Stroke

All centers performing surgery should consider establishing algorithms for the evaluation and treatment of patients with perioperative stroke by stroke code teams, with protocols in place for immediate treatment or transfer to hospitals capable of providing advanced care.
The risk of perioperative stroke (≤30 d) is higher within the first 72 h after surgery, with the first 24 h carrying the highest risk and offering the greatest challenge in identification of stroke symptoms because of lingering effects of the procedure and anesthetic medications.
Restoring blood flow to the injured brain is critically important. Patients with a perioperative stroke should be strongly considered for evaluation for mechanical embolectomy and intravenous thrombolysis because both interventions have been shown to be safe in select patients. Mechanical thrombectomy is preferable to intravenous thrombolysis alone in LVO strokes. Obtaining more advanced imaging initially, including CT angiography and perfusion studies, should be considered for patients with more severe stroke symptoms (NIHSS score >6 or cortical deficits) to determine eligibility for mechanical thrombectomy. The risk of bleeding at the surgical site must be considered in relation to intravenous thrombolytic treatment.

CT indicates computed tomography; LVO, large vessel occlusion; and NIHSS, National Institutes of Health Stroke Scale.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on December 15, 2020, and the American Heart Association Executive Committee on January 28, 2021. A copy of the document is available at https://professional.heart.org/statements by using either "Search for Guidelines & Statements" or the "Browse by Topic" area. To purchase additional reprints, call 215-356-2721 or email Meredith.Edelman@wolterskluwer.com.

The American Heart Association requests that this document be cited as follows: Benesch C, Glance LG, Derdeyn CP, Fleisher LA, Holloway RG, Messé SR, Mijalski C, Nelson MT, Power M, Welch BG; on behalf of the American Heart Association Stroke Council; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Council on Epidemiology and Prevention. Perioperative neurological evaluation and management to lower the risk of acute stroke in patients undergoing noncardiac, nonneurological surgery: a scientific statement from the American Heart Association/American Stroke Association. *Circulation.* 2021;143:e•••–e•••. doi: 10.1161/CIR.0000000000000968

The expert peer review of AHA-commissioned documents (eg, scientific statements, clinical practice guidelines, systematic reviews) is conducted by the AHA Office of Science Operations. For more on AHA statements and guidelines development, visit https://professional.heart.org/statements. Select the "Guidelines & Statements" drop-down menu, then click "Publication Development."

Disclosures

Writing Group Disclosures

Writing group member	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Curtis Benesch	University of Rochester School of Medicine and Dentistry	None	None	None	None	None	None	None
Laurent G. Glance	University of Rochester School of Medicine and Dentistry	None	None	None	None	None	None	None
Colin P. Derdeyn	University of Iowa	Siemens (investigator, CT Perfusion)*; Penumbra (MIND trial DSMB)*; NoNo (ESCAPE NA1 DSMB)*; Genae (Tigertriever trial DSMB)*	None	None	None	None	None	None
Lee A. Fleisher	University of Pennsylvania	None	None	None	None	None	None	None
Robert G. Holloway	University of Rochester School of Medicine and Dentistry	None	None	None	None	None	None	None
Steven R. Messé	University of Pennsylvania	None	None	None	None	Neuralert Technologies, LLC†	None	None
Christina Mijalski	Stanford University	None	None	None	None	None	None	None
M. Timothy Nelson‡	University of New Mexico	None	None	None	None	None	None	None
Martha Power	Retired (West Virginia University)	None	None	None	None	None	None	None
Babu G. Welch	UT Southwestern Medical Center	None	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

‡Dr. Nelson is now employed by the OU Health Tulsa Department of Surgery.

Reviewer Disclosures

Reviewer	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Seemant Chaturvedi	University of Maryland	NINDS (CREST 2 Executive Committee)*	None	None	None	None	None	None
DaiWai M. Olson	UT Southwestern Medical Center	Neuroptics†	None	None	Pfau Cochran Vertetis Amala PLLC*	None	None	None
Barney J. Stern	Johns Hopkins University	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

REFERENCES

1. Kristensen SD, Knuuti J, Saraste A, Anker S, Bøtker HE, Hert SD, Ford I, Gonzalez-Juanatey JR, Gorenek B, Heyndrickx GR, et al; Task Force Members. 2014 ESC/ESA guidelines on non-cardiac surgery: cardiovascular assessment and management: the Joint Task Force on Non-Cardiac Surgery: Cardiovascular Assessment and Management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). *Eur Heart J.* 2014;35:2383–2431. doi: 10.1093/eurheartj/ehu282
2. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, Davila-Roman VG, Gerhard-Herman MD, Holly TA, Kane GC, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;130:e278–e333. doi: 10.1161/CIR.0000000000000106
3. Ng JL, Chan MT, Gelb AW. Perioperative stroke in noncardiac, nonneurosurgical surgery. *Anesthesiology.* 2011;115:879–890. doi: 10.1097/ALN.0b013e31822e9499
4. Bateman BT, Schumacher HC, Wang S, Shaefi S, Berman MF. Perioperative acute ischemic stroke in noncardiac and nonvascular surgery: incidence, risk factors, and outcomes. *Anesthesiology.* 2009;110:231–238. doi: 10.1097/ALN.0b013e318194b5ff
5. Mashour GA, Shanks AM, Kheterpal S. Perioperative stroke and associated mortality after noncardiac, nonneurologic surgery. *Anesthesiology.* 2011;114:1289–1296. doi: 10.1097/ALN.0b013e318216e7f4
6. Mashour GA, Moore LE, Lele AV, Robicsek SA, Gelb AW. Perioperative care of patients at high risk for stroke during or after non-cardiac, non-neurologic surgery: consensus statement from the Society for Neuroscience in Anesthesiology and Critical Care. *J Neurosurg Anesthesiol.* 2014;26:273–285. doi: 10.1097/ANA.0000000000000087
7. Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators, Spence J, LeManach Y, Chan MTV, Wang CY, Sigamani A, Xavier D, Pearse R, Alonso-Coello P, Garutti I, Srinathan SK. Association between complications and death within 30 days after noncardiac surgery. *CMAJ.* 2019;191:E830–E837. doi: 10.1503/cmaj.190221
8. Wang L, Guo DJ, Feng Y, Jiang BL, Li YX, Zou SZ, Xue L. Risk factors for perioperative myocardial infarction in aged patients undergoing nonneurologic and noncardiac surgery. *J Am Geriatr Soc.* 2018;66:S448.
9. Vasivej T, Sathirapanya P, Kongkamol C. Incidence and risk factors of perioperative stroke in noncardiac, and nonaortic and its major branches surgery. *J Stroke Cerebrovasc Dis.* 2016;25:1172–1176. doi: 10.1016/j.jstrokecerebrovasdis.2016.01.051
10. Smilowitz NR, Gupta N, Ramakrishna H, Guo Y, Berger JS, Bangalore S. Perioperative major adverse cardiovascular and cerebrovascular events associated with noncardiac surgery. *JAMA Cardiol.* 2017;2:181–187. doi: 10.1001/jamacardio.2016.4792
11. Sharifpour M, Moore LE, Shanks AM, Didier TJ, Kheterpal S, Mashour GA. Incidence, predictors, and outcomes of perioperative stroke in noncarotid major vascular surgery. *Anesth Analg.* 2013;116:424–434. doi: 10.1213/ANE.0b013e31826a1a32
12. Wang H, Li SL, Bai J, Wang DX. Perioperative acute ischemic stroke increases mortality after noncardiac, nonvascular, and non-neurologic surgery: a retrospective case series. *J Cardiothorac Vasc Anesth.* 2019;33:2231–2236. doi: 10.1053/j.jvca.2019.02.009
13. Macellari F, Paciaroni M, Agnelli G, Caso V. Perioperative stroke risk in nonvascular surgery. *Cerebrovasc Dis.* 2012;34:175–181. doi: 10.1159/000339982
14. Longstreth WT Jr, Dulberg C, Manolio TA, Lewis MR, Beauchamp NJ Jr, O'Leary D, Carr J, Furberg CD. Incidence, manifestations, and predictors of brain infarcts defined by serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke.* 2002;33:2376–2382. doi: 10.1161/01.str.0000032241.58727.49
15. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med.* 2003;348:1215–1222. doi: 10.1056/NEJMoa022066
16. Bokura H, Kobayashi S, Yamaguchi S, Iijima K, Nagai A, Toyoda G, Oguro H, Takahashi K. Silent brain infarction and subcortical white matter lesions increase the risk of stroke and mortality: a prospective cohort study. *J Stroke Cerebrovasc Dis.* 2006;15:57–63. doi: 10.1016/j.jstrokecerebrovasdis.2005.11.001
17. Gupta A, Giambrone AE, Gialdini G, Finn C, Delgado D, Gutierrez J, Wright C, Beiser AS, Seshadri S, Pandya A, et al. Silent brain infarction and risk of future stroke: a systematic review and meta-analysis. *Stroke.* 2016;47:719–725. doi: 10.1161/STROKEAHA.115.011889
18. Schnaudigel S, Gröschel K, Pilgram SM, Kastrup A. New brain lesions after carotid stenting versus carotid endarterectomy: a systematic review of the literature. *Stroke.* 2008;39:1911–1919. doi: 10.1161/STROKEAHA.107.500603
19. Barber PA, Hach S, Tippett LJ, Ross L, Merry AF, Milsom P. Cerebral ischemic lesions on diffusion-weighted imaging are associated with neurocognitive decline after cardiac surgery. *Stroke.* 2008;39:1427–1433. doi: 10.1161/STROKEAHA.107.502989
20. Gensicke H, van der Worp HB, Nederkoorn PJ, Macdonald S, Gaines PA, van der Lugt A, Mali WP, Lyrer PA, Peters N, Featherstone RL, et al; ICSS-MRI Substudy Investigators. Ischemic brain lesions after carotid artery stenting increase future cerebrovascular risk. *J Am Coll Cardiol.* 2015;65:521–529. doi: 10.1016/j.jacc.2014.11.038
21. Indja B, Woldendorp K, Vallely MP, Grieve SM. Silent brain infarcts following cardiac procedures: a systematic review and meta-analysis. *J Am Heart Assoc.* 2019;8:e010920. doi: 10.1161/JAHA.118.010920
22. Giovannetti T, Price CC, Fanning M, Messé S, Ratcliffe SJ, Lyon A, Kasner SE, Seidel G, Bavaria JE, Szeto WY, et al; DENOVO Investigators. Cognition and cerebral infarction in older adults after surgical aortic valve replacement. *Ann Thorac Surg.* 2019;107:787–794. doi: 10.1016/j.athoracsur.2018.09.057
23. Mrkobrada M, Hill MD, Chan MT, Sigamani A, Cowan D, Kurz A, Sessler DI, Jacka M, Graham M, Dasgupta M, et al. Covert stroke after non-cardiac surgery: a prospective cohort study. *Br J Anaesth.* 2016;117:191–197. doi: 10.1093/bja/aew179
24. NeuroVISION Investigators. Perioperative covert stroke in patients undergoing non-cardiac surgery (NeuroVISION): a prospective cohort study. *Lancet.* 2019;394:1022–1029.
25. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, Gawande AA. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet.* 2008;372:139–144. doi: 10.1016/S0140-6736(08)60878-8
26. Wilcox T, Smilowitz NR, Xia Y, Berger JS. Cardiovascular risk scores to predict perioperative stroke in noncardiac surgery. *Stroke.* 2019;50:2002–2006. doi: 10.1161/STROKEAHA.119.024995
27. Likosky DS, Marrin CA, Caplan LR, Baribeau YR, Morton JR, Weintraub RM, Hartman GS, Hernandez F Jr, Braff SP, Charlesworth DC, et al; for the Northern New England Cardiovascular Disease Study Group. Determination of etiologic mechanisms of strokes secondary to coronary artery bypass graft surgery. *Stroke.* 2003;34:2830–2834. doi: 10.1161/01.STR.0000098650.12386.B3
28. Likosky DS, Caplan LR, Weintraub RM, Hartman GS, Malenka DJ, Ross CS, Landis ES, Applebaum B, Braff SP, O'Connor GT; Northern New England Cardiovascular Disease Study Group, Lebanon, New Hampshire. Intraoperative and postoperative variables associated with strokes following cardiac surgery. *Heart Surg Forum.* 2004;7:E271–E276. doi: 10.1532/HSF98.20041035
29. Selim M. Perioperative stroke. *N Engl J Med.* 2007;356:706–713. doi: 10.1056/NEJMra062668
30. Vlisides P, Mashour GA. Perioperative stroke. *Can J Anaesth.* 2016;63:193–204. doi: 10.1007/s12630-015-0494-9
31. Saito Y, Kitahara H, Matsumiya G, Kobayashi Y. Preoperative endothelial function and long-term cardiovascular events in patients undergoing cardiovascular surgery. *Heart Vessels.* 2019;34:318–323. doi: 10.1007/s00380-018-1248-8
32. Devereaux P, Chan M, Eikelboom J. Major vascular complications in patients undergoing non-cardiac surgery: magnitude of the problem, risk prediction, surveillance, and prevention. In: Yusuf S, Cairns J, Camm A, Fallen E, Gersh B, eds. *Evidence Based Cardiology*. 3rd ed. Wiley-Blackwell; 2010:47.
33. Ko SB. Perioperative stroke: pathophysiology and management. *Korean J Anesthesiol.* 2018;71:3–11. doi: 10.4097/kjae.2018.71.1.3
34. van Mook WN, Rennenberg RJ, Schurink GW, van Oostenbrugge RJ, Mess WH, Hofman PA, de Leeuw PW. Cerebral hyperperfusion syndrome. *Lancet Neurol.* 2005;4:877–888. doi: 10.1016/S1474-4422(05)70251-9
35. Nam JS, Jeon SB, Jo JY, Joung KW, Chin JH, Lee EH, Chung CH, Choi IC. Perioperative rupture risk of unruptured intracranial aneurysms in cardiovascular surgery. *Brain.* 2019;142:1408–1415. doi: 10.1093/brain/awz058
36. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, Sugarbaker DJ, Donaldson MC, Poss R, Ho KK, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation.* 1999;100:1043–1049. doi: 10.1161/01.cir.100.10.1043
37. Gupta PK, Gupta H, Sundaram A, Kaushik M, Fang X, Miller WJ, Esterbrooks DJ, Hunter CB, Pipinos II, Johanning JM, et al. Development and validation

of a risk calculator for prediction of cardiac risk after surgery. *Circulation.* 2011;124:381–387. doi: 10.1161/CIRCULATIONAHA.110.015701
38. Bilimoria KY, Liu Y, Paruch JL, Zhou L, Kmiecik TE, Ko CY, Cohen ME. Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons. *J Am Coll Surg.* 2013;217:833–842.e1. doi: 10.1016/j.jamcollsurg.2013.07.385
39. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA.* 2001;285:2864–2870. doi: 10.1001/jama.285.22.2864
40. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. *Chest.* 2010;137:263–272. doi: 10.1378/chest.09-1584
41. van Diepen S, Youngson E, Ezekowitz JA, McAlister FA. Which risk score best predicts perioperative outcomes in nonvalvular atrial fibrillation patients undergoing noncardiac surgery? *Am Heart J.* 2014;168:60–67.e5. doi: 10.1016/j.ahj.2014.03.015
42. Peguero JG, Issa O, Podesta C, Elmahdy HM, Santana O, Lamas GA. Usefulness of the CHA2DS2VASc score to predict postoperative stroke in patients having cardiac surgery independent of atrial fibrillation. *Am J Cardiol.* 2015;115:758–762. doi: 10.1016/j.amjcard.2014.12.037
43. Glance LG, Faden E, Dutton RP, Lustik SJ, Li Y, Eaton MP, Dick AW. Impact of the choice of risk model for identifying low-risk patients using the 2014 American College of Cardiology/American Heart Association perioperative guidelines. *Anesthesiology.* 2018;129:889–900. doi: 10.1097/ALN.0000000000002341
44. American College of Surgeons. Surgical risk calculator. Accessed March 12, 2021. https://riskcalculator.facs.org/riskcalculator/
45. Jørgensen ME, Torp-Pedersen C, Gislason GH, Jensen PF, Berger SM, Christiansen CB, Overgaard C, Schmiegelow MD, Andersson C. Time elapsed after ischemic stroke and risk of adverse cardiovascular events and mortality following elective noncardiac surgery. *JAMA.* 2014;312:269–277. doi: 10.1001/jama.2014.8165
46. Christiansen MN, Andersson C, Gislason GH, Torp-Pedersen C, Sanders RD, Føge Jensen P, Jørgensen ME. Risks of cardiovascular adverse events and death in patients with previous stroke undergoing emergency noncardiac, nonintracranial surgery: the importance of operative timing. *Anesthesiology.* 2017;127:9–19. doi: 10.1097/ALN.0000000000001685
47. Brown DL, Lisabeth LD, Roychoudhury C, Ye Y, Morgenstern LB. Recurrent stroke risk is higher than cardiac event risk after initial stroke/transient ischemic attack. *Stroke.* 2005;36:1285–1287. doi: 10.1161/01.STR.0000165926.74213.e3
48. Dhamoon MS, Sciacca RR, Rundek T, Sacco RL, Elkind MS. Recurrent stroke and cardiac risks after first ischemic stroke: the Northern Manhattan Study. *Neurology.* 2006;66:641–646. doi: 10.1212/01.wnl.0000201253.93811.f6
49. Johnston SC, Easton JD, Farrant M, Barsan W, Conwit RA, Elm JJ, Kim AS, Lindblad AS, Palesch YY; Clinical Research Collaboration, Neurological Emergencies Treatment Trials Network, and the POINT Investigators. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. *N Engl J Med.* 2018;379:215–225. doi: 10.1056/NEJMoa1800410
50. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, et al; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association [published correction appears in *Stroke*. 2015;46:e54]. *Stroke.* 2014;45:2160–2236. doi: 10.1161/STR.0000000000000024
51. Brott TG, Hobson RW 2nd, Howard G, Roubin GS, Clark WM, Brooks W, Mackey A, Hill MD, Leimgruber PP, Sheffet AJ, et al; CREST Investigators. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med.* 2010;363:11–23. doi: 10.1056/NEJMoa0912321
52. LeFevre ML; U.S. Preventive Services Task Force. Screening for asymptomatic carotid artery stenosis: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2014;161:356–362. doi: 10.7326/M14-1333
53. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, Creager MA, Eckel RH, Elkind MS, Fornage M, et al; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; Council on Hypertension. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2014;45:3754–3832. doi: 10.1161/STR.0000000000000046
54. Abbott AL. Medical (nonsurgical) intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis: results of a systematic review and analysis. *Stroke.* 2009;40:e573–e583. doi: 10.1161/STROKEAHA.109.556068
55. Chaturvedi S, Bruno A, Feasby T, Holloway R, Benavente O, Cohen SN, Cote R, Hess D, Saver J, Spence JD, et al; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Carotid endarterectomy: an evidence-based review: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology.* 2005;65:794–801. doi: 10.1212/01.wnl.0000176036.07558.82
56. Weimar C, Bilbilis K, Rekowski J, Holst T, Beyersdorf F, Breuer M, Dahm M, Diegeler A, Kowalski A, Martens S, et al; for the CABACS Trial Investigators. Safety of simultaneous coronary artery bypass grafting and carotid endarterectomy versus isolated coronary artery bypass grafting: a randomized clinical trial. *Stroke.* 2017;48:2769–2775. doi: 10.1161/STROKEAHA.117.017570
57. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, Levine SR, Chaturvedi S, Kasner SE, Benesch CG, et al; Warfarin-Aspirin Symptomatic Intracranial Disease Trial Investigators. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med.* 2005;352:1305–1316. doi: 10.1056/NEJMoa043033
58. Derdeyn CP, Chimowitz MI, Lynn MJ, Fiorella D, Turan TN, Janis LS, Montgomery J, Nizam A, Lane BF, Lutsep HL, et al; Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis Trial Investigators. Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. *Lancet.* 2014;383:333–341. doi: 10.1016/S0140-6736(13)62038-3
59. Banerjee C, Chimowitz MI. Stroke caused by atherosclerosis of the major intracranial arteries. *Circ Res.* 2017;120:502–513. doi: 10.1161/CIRCRESAHA.116.308441
60. Blacker DJ, Flemming KD, Wijdicks EF. Risk of ischemic stroke in patients with symptomatic vertebrobasilar stenosis undergoing surgical procedures. *Stroke.* 2003;34:2659–2663. doi: 10.1161/01.STR.0000092120.03676.D6
61. Meissner I, Khandheria BK, Heit JA, Petty GW, Sheps SG, Schwartz GL, Whisnant JP, Wiebers DO, Covalt JL, Petterson TM, et al. Patent foramen ovale: innocent or guilty? Evidence from a prospective population-based study. *J Am Coll Cardiol.* 2006;47:440–445. doi: 10.1016/j.jacc.2005.10.044
62. Søndergaard L, Kasner SE, Rhodes JF, Andersen G, Iversen HK, Nielsen-Kudsk JE, Settergren M, Sjöstrand C, Roine RO, Hildick-Smith D, et al; Gore REDUCE Clinical Study Investigators. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. *N Engl J Med.* 2017;377:1033–1042. doi: 10.1056/NEJMoa1707404
63. Mas JL, Derumeaux G, Amarenco P, Arquizan C, Aubry P, Barthelet M, Bertrand B, Brochet E, Cabanes L, Donal E, et al; CLOSE Investigators. CLOSE: Closure of Patent Foramen Ovale, Oral Anticoagulants or Antiplatelet Therapy to Prevent Stroke Recurrence: study design. *Int J Stroke.* 2016;11:724–732. doi: 10.1177/1747493016643551
64. Saver JL, Carroll JD, Thaler DE, Smalling RW, MacDonald LA, Marks DS, Tirschwell DL; RESPECT Investigators. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. *N Engl J Med.* 2017;377:1022–1032. doi: 10.1056/NEJMoa1610057
65. Ng PY, Ng AK, Subramaniam B, Burns SM, Herisson F, Timm FP, Med C, Rudolph MI, Med C, Scheffenbichler F, et al. Association of preoperatively diagnosed patent foramen ovale with perioperative ischemic stroke. *JAMA.* 2018;319:452–462. doi: 10.1001/jama.2017.21899
66. Perfetti DC, Chughtai M, Boylan MR, Naziri Q, Maheshwari AV, Mont MA. Atrial septal defect increases the risk for stroke after total hip arthroplasty. *J Arthroplasty.* 2017;32:3152–3156. doi: 10.1016/j.arth.2017.05.006
67. Kasner SE, Messe SR. Is patent foramen ovale a risk factor for perioperative stroke? *JAMA.* 2018;319:446–447. doi: 10.1001/jama.2017.21902
68. POISE Study Group; Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet.* 2008;371:1839–1847. doi: 10.1016/S0140-6736(08)60601-7
69. Mashour GA, Sharifpour M, Freundlich RE, Tremper KK, Shanks A, Nallamothu BK, Vlisides PE, Weightman A, Matlen L, Merte J, et al.

Perioperative metoprolol and risk of stroke after noncardiac surgery. *Anesthesiology.* 2013;119:1340–1346. doi: 10.1097/ALN.0b013e318295a25f
70. Jørgensen ME, Sanders RD, Køber L, Mehta K, Torp-Pedersen C, Hlatky MA, Pallisgaard JL, Shaw RE, Gislason GH, Jensen PF, et al. Beta-blocker subtype and risks of perioperative adverse events following non-cardiac surgery: a nationwide cohort study. *Eur Heart J.* 2017;38:2421–2428. doi: 10.1093/eurheartj/ehx214
71. London MJ, Schwartz GG, Hur K, Henderson WG. Association of perioperative statin use with mortality and morbidity after major noncardiac surgery. *JAMA Intern Med.* 2017;177:231–242. doi: 10.1001/jamainternmed.2016.8005
72. Ma B, Sun J, Diao S, Zheng B, Li H. Effects of perioperative statins on patient outcomes after noncardiac surgery: a meta-analysis. *Ann Med.* 2018;50:402–409. doi: 10.1080/07853890.2018.1471217
73. Berwanger O, Le Manach Y, Suzumura EA, Biccard B, Srinathan SK, Szczeklik W, Santo JA, Santucci E, Cavalcanti AB, Archbold RA, et al; VISION Investigators. Association between pre-operative statin use and major cardiovascular complications among patients undergoing non-cardiac surgery: the VISION study. *Eur Heart J.* 2016;37:177–185. doi: 10.1093/eurheartj/ehv456
74. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest.* 2010;138:1093–1100. doi: 10.1378/chest.10-0134
75. Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, Dunn AS, Kunz R. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(suppl):e326S–e350S. doi: 10.1378/chest.11-2298
76. Hornor MA, Duane TM, Ehlers AP, Jensen EH, Brown PS Jr, Pohl D, da Cost PM, Ko CY, Laronga C. American College of Surgeons' Guidelines for the Perioperative Management of Antithrombotic Medication. *J Am Coll Surg.* 2018;227:521–536 e1. doi: 10.1016/j.jamcollsurg.2018.08.183
77. Douketis JD, Spyropoulos AC, Kaatz S, Becker RC, Caprini JA, Dunn AS, Garcia DA, Jacobson A, Jaffer AK, Kong DF, et al; BRIDGE Investigators. Perioperative bridging anticoagulation in patients with atrial fibrillation. *N Engl J Med.* 2015;373:823–833. doi: 10.1056/NEJMoa1501035
78. Devereaux PJ, Mrkobrada M, Sessler DI, Leslie K, Alonso-Coello P, Kurz A, Villar JC, Sigamani A, Biccard BM, Meyhoff CS, et al; POISE-2 Investigators. Aspirin in patients undergoing noncardiac surgery. *N Engl J Med.* 2014;370:1494–1503. doi: 10.1056/NEJMoa1401105
79. Bijker JB, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KG, Kalkman CJ. Incidence of intraoperative hypotension as a function of the chosen definition: literature definitions applied to a retrospective cohort using automated data collection. *Anesthesiology.* 2007;107:213–220. doi: 10.1097/01.anes.0000270724.40897.8e
80. Rawlings AM, Juraschek SP, Heiss G, Hughes T, Meyer ML, Selvin E, Sharrett AR, Windham BG, Gottesman RF. Association of orthostatic hypotension with incident dementia, stroke, and cognitive decline. *Neurology.* 2018;91:e759–e768. doi: 10.1212/WNL.0000000000006027
81. Jordan JD, Powers WJ. Cerebral autoregulation and acute ischemic stroke. *Am J Hypertens.* 2012;25:946–950. doi: 10.1038/ajh.2012.53
82. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, Cywinski J, Thabane L, Sessler DI. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. *Anesthesiology.* 2013;119:507–515. doi: 10.1097/ALN.0b013e3182a10e26
83. van Waes JA, van Klei WA, Wijeysundera DN, van Wolfswinkel L, Lindsay TF, Beattie WS. Association between intraoperative hypotension and myocardial injury after vascular surgery. *Anesthesiology.* 2016;124:35–44. doi: 10.1097/ALN.0000000000000922
84. Monk TG, Bronsert MR, Henderson WG, Mangione MP, Sum-Ping ST, Bentt DR, Nguyen JD, Richman JS, Meguid RA, Hammermeister KE. Association between intraoperative hypotension and hypertension and 30-day postoperative mortality in noncardiac surgery. *Anesthesiology.* 2015;123:307–319. doi: 10.1097/ALN.0000000000000756
85. Sessler DI, Meyhoff CS, Zimmerman NM, Mao G, Leslie K, Vásquez SM, Balaji P, Alvarez-Garcia J, Cavalcanti AB, Parlow JL, et al. Period-dependent associations between hypotension during and for four days after noncardiac surgery and a composite of myocardial infarction and death: a substudy of the POISE-2 Trial. *Anesthesiology.* 2018;128:317–327. doi: 10.1097/ALN.0000000000001985
86. Sun LY, Wijeysundera DN, Tait GA, Beattie WS. Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. *Anesthesiology.* 2015;123:515–523. doi: 10.1097/ALN.0000000000000765
87. Salmasi V, Maheshwari K, Yang D, Mascha EJ, Singh A, Sessler DI, Kurz A. Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after noncardiac surgery: a retrospective cohort analysis. *Anesthesiology.* 2017;126:47–65. doi: 10.1097/ALN.0000000000001432
88. Bijker JB, Persoon S, Peelen LM, Moons KG, Kalkman CJ, Kappelle LJ, van Klei WA. Intraoperative hypotension and perioperative ischemic stroke after general surgery: a nested case-control study. *Anesthesiology.* 2012;116:658–664. doi: 10.1097/ALN.0b013e3182472320
89. Hsieh JK, Dalton JE, Yang D, Farag ES, Sessler DI, Kurz AM. The Association between mild intraoperative hypotension and stroke in general surgery patients. *Anesth Analg.* 2016;123:933–939. doi: 10.1213/ANE.0000000000001526
90. Sun LY, Chung AM, Farkouh ME, van Diepen S, Weinberger J, Bourke M, Ruel M. Defining an intraoperative hypotension threshold in association with stroke in cardiac surgery. *Anesthesiology.* 2018;129:440–447. doi: 10.1097/ALN.0000000000002298
91. Wesselink EM, Kappen TH, Torn HM, Slooter AJC, van Klei WA. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. *Br J Anaesth.* 2018;121:706–721. doi: 10.1016/j.bja.2018.04.036
92. Futier E, Lefrant JY, Guinot PG, Godet T, Lorne E, Cuvillon P, Bertran S, Leone M, Pastene B, Piriou V, et al; INPRESS Study Group. Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: a randomized clinical trial. *JAMA.* 2017;318:1346–1357. doi: 10.1001/jama.2017.14172
93. Sessler DI, Bloomstone JA, Aronson S, Berry C, Gan TJ, Kellum JA, Plumb J, Mythen MG, Grocott MPW, Edwards MR, et al; Perioperative Quality Initiative-3 Workgroup; POQI Chairs; Physiology Group; Preoperative Blood Pressure Group; Intraoperative Blood Pressure Group; Postoperative Blood Pressure Group. Perioperative Quality Initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery. *Br J Anaesth.* 2019;122:563–574. doi: 10.1016/j.bja.2019.01.013
94. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. *Chest.* 1988;94:1176–1186. doi: 10.1378/chest.94.6.1176
95. Gillies MA, Pearse R, Chew MS. Peri-operative goal-directed therapy: a definitive answer remains elusive. *Eur J Anaesthesiol.* 2018;35:467–468. doi: 10.1097/EJA.0000000000000812
96. Grocott MP, Dushianthan A, Hamilton MA, Mythen MG, Harrison D, Rowan K; Optimisation Systematic Review Steering Group. Perioperative increase in global blood flow to explicit defined goals and outcomes after surgery: a Cochrane systematic review. *Br J Anaesth.* 2013;111:535–548. doi: 10.1093/bja/aet155
97. Pearse RM, Harrison DA, MacDonald N, Gillies MA, Blunt M, Ackland G, Grocott MP, Ahern A, Griggs K, Scott R, et al; OPTIMISE Study Group. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. *JAMA.* 2014;311:2181–2190. doi: 10.1001/jama.2014.5305
98. Calvo-Vecino JM, Ripollés-Melchor J, Mythen MG, Casans-Francés R, Balik A, Artacho JP, Martínez-Hurtado E, Serrano Romero A, Fernández Pérez C, Asuero de Lis S; FEDORA Trial Investigators Group. Effect of goal-directed haemodynamic therapy on postoperative complications in low-moderate risk surgical patients: a multicentre randomised controlled trial (FEDORA trial). *Br J Anaesth.* 2018;120:734–744. doi: 10.1016/j.bja.2017.12.018
99. Lelubre C, Bouzat P, Crippa IA, Taccone FS. Anemia management after acute brain injury. *Crit Care.* 2016;20:152. doi: 10.1186/s13054-016-1321-6
100. Hoiland RL, Bain AR, Rieger MG, Bailey DM, Ainslie PN. Hypoxemia, oxygen content, and the regulation of cerebral blood flow. *Am J Physiol Regul Integr Comp Physiol.* 2016;310:R398–R413. doi: 10.1152/ajpregu.00270.2015
101. Weiskopf RB, Viele MK, Feiner J, Kelley S, Lieberman J, Noorani M, Leung JM, Fisher DM, Murray WR, Toy P, et al. Human cardiovascular and metabolic response to acute, severe isovolemic anemia. *JAMA.* 1998;279:217–221. doi: 10.1001/jama.279.3.217
102. Momjian-Mayor I, Baron JC. The pathophysiology of watershed infarction in internal carotid artery disease: review of cerebral perfusion studies. *Stroke.* 2005;36:567–577. doi: 10.1161/01.STR.0000155727.82242.e1

103. Tsai CF, Yip PK, Chen CC, Yeh SJ, Chung ST, Jeng JS. Cerebral infarction in acute anemia. *J Neurol.* 2010;257:2044–2051. doi: 10.1007/s00415-010-5657-6
104. Weiskopf RB, Kramer JH, Viele M, Neumann M, Feiner JR, Watson JJ, Hopf HW, Toy P. Acute severe isovolemic anemia impairs cognitive function and memory in humans. *Anesthesiology.* 2000;92:1646–1652. doi: 10.1097/00000542-200006000-00023
105. Yamauchi H, Nishii R, Higashi T, Kagawa S, Fukuyama H. Hemodynamic compromise as a cause of internal border-zone infarction and cortical neuronal damage in atherosclerotic middle cerebral artery disease. *Stroke.* 2009;40:3730–3735. doi: 10.1161/STROKEAHA.109.560011
106. Musallam KM, Tamim HM, Richards T, Spahn DR, Rosendaal FR, Habbal A, Khreiss M, Dahdaleh FS, Khavandi K, Sfeir PM, et al. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. *Lancet.* 2011;378:1396–1407. doi: 10.1016/S0140-6736(11)61381-0
107. Saager L, Turan A, Reynolds LF, Dalton JE, Mascha EJ, Kurz A. The association between preoperative anemia and 30-day mortality and morbidity in noncardiac surgical patients. *Anesth Analg.* 2013;117:909–915. doi: 10.1213/ANE.0b013e31828b347d
108. Wu WC, Schifftner TL, Henderson WG, Eaton CB, Poses RM, Uttley G, Sharma SC, Vezeridis M, Khuri SF, Friedmann PD. Preoperative hematocrit levels and postoperative outcomes in older patients undergoing noncardiac surgery. *JAMA.* 2007;297:2481–2488. doi: 10.1001/jama.297.22.2481
109. Baron DM, Hochrieser H, Posch M, Metnitz B, Rhodes A, Moreno RP, Pearse RM, Metnitz P; European Surgical Outcomes Study (EuSOS) Group for Trials Groups of European Society of Intensive Care Medicine; European Society of Anaesthesiology. Preoperative anaemia is associated with poor clinical outcome in non-cardiac surgery patients. *Br J Anaesth.* 2014;113:416–423. doi: 10.1093/bja/aeu098
110. Gagnon DR, Zhang TJ, Brand FN, Kannel WB. Hematocrit and the risk of cardiovascular disease: the Framingham study: a 34-year follow-up. *Am Heart J.* 1994;127:674–682. doi: 10.1016/0002-8703(94)90679-3
111. Kiyohara Y, Ueda K, Hasuo Y, Fujii I, Yanai T, Wada J, Kawano H, Shikata T, Omae T, Fujishima M. Hematocrit as a risk factor of cerebral infarction: long-term prospective population survey in a Japanese rural community. *Stroke.* 1986;17:687–692. doi: 10.1161/01.str.17.4.687
112. Abramson JL, Jurkovitz CT, Vaccarino V, Weintraub WS, McClellan W. Chronic kidney disease, anemia, and incident stroke in a middle-aged, community-based population: the ARIC Study. *Kidney Int.* 2003;64:610–615. doi: 10.1046/j.1523-1755.2003.00109.x
113. Chang YL, Hung SH, Ling W, Lin HC, Li HC, Chung SD. Association between ischemic stroke and iron-deficiency anemia: a population-based study. *PLoS One.* 2013;8:e82952. doi: 10.1371/journal.pone.0082952
114. Panwar B, Judd SE, Warnock DG, McClellan WM, Booth JN 3rd, Muntner P, Gutiérrez OM. Hemoglobin concentration and risk of incident stroke in community-living adults. *Stroke.* 2016;47:2017–2024. doi: 10.1161/STROKEAHA.116.013077
115. Kellert L, Martin E, Sykora M, Bauer H, Gussmann P, Diedler J, Herweh C, Ringleb PA, Hacke W, Steiner T, et al. Cerebral oxygen transport failure? Decreasing hemoglobin and hematocrit levels after ischemic stroke predict poor outcome and mortality: STroke: RelevAnt Impact of hemoGlobin, Hematocrit and Transfusion (STRAIGHT): an observational study. *Stroke.* 2011;42:2832–2837. doi: 10.1161/STROKEAHA.110.606665
116. Sykora M, Diedler J, Poli S, Rizos T, Kellert L, Turcani P, Steiner T. Association of non-diabetic hyperglycemia with autonomic shift in acute ischaemic stroke. *Eur J Neurol.* 2012;19:84–90. doi: 10.1111/j.1468-1331.2011.03438.x
117. Li Z, Zhou T, Li Y, Chen P, Chen L. Anemia increases the mortality risk in patients with stroke: a meta-analysis of cohort studies. *Sci Rep.* 2016;6:26636. doi: 10.1038/srep26636
118. Milionis H, Papavasileiou V, Eskandari A, D'Ambrogio-Remillard S, Ntaios G, Michel P. Anemia on admission predicts short- and long-term outcomes in patients with acute ischemic stroke. *Int J Stroke.* 2015;10:224–230. doi: 10.1111/ijs.12397
119. Barlas RS, Honney K, Loke YK, McCall SJ, Bettencourt-Silva J, Clark AB, Bowles KM, Metcalf AK, Mamas MA, Potter JF, et al. Impact of hemoglobin levels and anemia on mortality in acute stroke: analysis of UK regional registry data, systematic review, and meta-analysis. *J Am Heart Assoc.* 2016;5:e003019. doi: 10.1161/JAHA.115.003019
120. Bellwald S, Balasubramaniam R, Nagler M, Burri MS, Fischer SDA, Hakim A, Dobrocky T, Yu Y, Scalzo F, Heldner MR, et al. Association of anemia and hemoglobin decrease during acute stroke treatment with infarct growth and clinical outcome. *PLoS One.* 2018;13:e0203535. doi: 10.1371/journal.pone.0203535
121. Bernard AC, Davenport DL, Chang PK, Vaughan TB, Zwischenberger JB. Intraoperative transfusion of 1 U to 2 U packed red blood cells is associated with increased 30-day mortality, surgical-site infection, pneumonia, and sepsis in general surgery patients. *J Am Coll Surg.* 2009;208:931–937, 937.e1. doi: 10.1016/j.jamcollsurg.2008.11.019
122. Glance LG, Dick AW, Mukamel DB, Fleming FJ, Zollo RA, Wissler R, Salloum R, Meredith UW, Osler TM. Association between intraoperative blood transfusion and mortality and morbidity in patients undergoing noncardiac surgery. *Anesthesiology.* 2011;114:283–292. doi: 10.1097/ALN.0b013e3182054d06
123. Ferraris VA, Davenport DL, Saha SP, Austin PC, Zwischenberger JB. Surgical outcomes and transfusion of minimal amounts of blood in the operating room. *Arch Surg.* 2012;147:49–55. doi: 10.1001/archsurg.2011.790
124. Karkouti K, Stukel TA, Beattie WS, Elsaadany S, Li P, Berger R, Wijeysundera DN. Relationship of erythrocyte transfusion with short- and long-term mortality in a population-based surgical cohort. *Anesthesiology.* 2012;117:1175–1183. doi: 10.1097/ALN.0b013e318271604e
125. Aquina CT, Blumberg N, Becerra AZ, Boscoe FP, Schymura MJ, Noyes K, Monson JRT, Fleming FJ. Association among blood transfusion, sepsis, and decreased long-term survival after colon cancer resection. *Ann Surg.* 2017;266:311–317. doi: 10.1097/SLA.0000000000001990
126. Hajjar LA, Vincent JL, Galas FR, Nakamura RE, Silva CM, Santos MH, Fukushima J, Kalil Filho R, Sierra DB, Lopes NH, et al. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. *JAMA.* 2010;304:1559–1567. doi: 10.1001/jama.2010.1446
127. Mazer CD, Whitlock RP, Fergusson DA, Hall J, Belley-Cote E, Connolly K, Khanykin B, Gregory AJ, de Médicis É, McGuinness S, et al; TRICS Investigators and Perioperative Anesthesia Clinical Trials Group. Restrictive or liberal red-cell transfusion for cardiac surgery. *N Engl J Med.* 2017;377:2133–2144. doi: 10.1056/NEJMoa1711818
128. Mazer CD, Whitlock RP, Fergusson DA, Belley-Cote E, Connolly K, Khanykin B, Gregory AJ, de Médicis É, Carrier FM, McGuinness S, et al; TRICS Investigators and Perioperative Anesthesia Clinical Trials Group. Six-month outcomes after restrictive or liberal transfusion for cardiac surgery. *N Engl J Med.* 2018;379:1224–1233. doi: 10.1056/NEJMoa1808561
129. Reeves BC, Rogers CA, Murphy GJ. Liberal or restrictive transfusion after cardiac surgery. *N Engl J Med.* 2015;373:193. doi: 10.1056/NEJMc1505810
130. Carson JL, Terrin ML, Noveck H, Sanders DW, Chaitman BR, Rhoads GG, Nemo G, Dragert K, Beaupre L, Hildebrand K, et al; FOCUS Investigators. Liberal or restrictive transfusion in high-risk patients after hip surgery. *N Engl J Med.* 2011;365:2453–2462. doi: 10.1056/NEJMoa1012452
131. Carson JL, Sieber F, Cook DR, Hoover DR, Noveck H, Chaitman BR, Fleisher L, Beaupre L, Macaulay W, Rhoads GG, et al. Liberal versus restrictive blood transfusion strategy: 3-year survival and cause of death results from the FOCUS randomised controlled trial. *Lancet.* 2015;385:1183–1189. doi: 10.1016/S0140-6736(14)62286-8
132. Hébert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care: Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med.* 1999;340:409–417. doi: 10.1056/NEJM199902113400601
133. Holst LB, Haase N, Wetterslev J, Wernerman J, Guttormsen AB, Karlsson S, Johansson PI, Aneman A, Vang ML, Winding R, et al; TRISS Trial Group; Scandinavian Critical Care Trials Group. Lower versus higher hemoglobin threshold for transfusion in septic shock. *N Engl J Med.* 2014;371:1381–1391. doi: 10.1056/NEJMoa1406617
134. Yazer MH, Triulzi DJ. AABB red blood cell transfusion guidelines: something for almost everyone. *JAMA.* 2016;316:1984–1985. doi: 10.1001/jama.2016.10887
135. Carson JL, Stanworth SJ, Alexander JH, Roubinian N, Fergusson DA, Triulzi DJ, Goodman SG, Rao SV, Doree C, Hebert PC. Clinical trials evaluating red blood cell transfusion thresholds: an updated systematic review and with additional focus on patients with cardiovascular disease. *Am Heart J.* 2018;200:96–101. doi: 10.1016/j.ahj.2018.04.007
136. Carson JL, Guyatt G, Heddle NM, Grossman BJ, Cohn CS, Fung MK, Gernsheimer T, Holcomb JB, Kaplan LJ, Katz LM, et al. Clinical practice guidelines from the AABB: red blood cell transfusion thresholds and storage. *JAMA.* 2016;316:2025–2035. doi: 10.1001/jama.2016.9185

137. Carson JL, Triulzi DJ, Ness PM. Indications for and adverse effects of red-cell transfusion. *N Engl J Med.* 2017;377:1261–1272. doi: 10.1056/NEJMra1612789
138. Meybohm P, Lindau S, Treskatsch S, Francis R, Spies C, Velten M, Wittmann M, Gueresir E, Stoppe C, Kowark A, et al; LIBERAL Collaboration Group. Liberal transfusion strategy to prevent mortality and anaemia-associated, ischaemic events in elderly non-cardiac surgical patients: the study design of the LIBERAL-Trial. *Trials.* 2019;20:101. doi: 10.1186/s13063-019-3200-3
139. Ishida K, Berger M, Nadler J, Warner DS. Anesthetic neuroprotection: antecedents and an appraisal of preclinical and clinical data quality. *Curr Pharm Des.* 2014;20:5751–5765. doi: 10.2174/1381612820666140204111701
140. Warner DS, Sheng H. Anesthetic neuroprotection? It's complicated. *Anesthesiology.* 2017;126:579–581. doi: 10.1097/ALN.0000000000001535
141. Vlisides PE, Avidan MS, Mashour GA. Reconceptualising stroke research to inform the question of anaesthetic neurotoxicity. *Br J Anaesth.* 2018;120:430–435. doi: 10.1016/j.bja.2017.10.013
142. Bedford PD. Adverse cerebral effects of anaesthesia on old people. *Lancet.* 1955;269:259–263. doi: 10.1016/s0140-6736(55)92689-1
143. Myles PS, Leslie K, Chan MT, Forbes A, Peyton PJ, Paech MJ, Beattie WS, Sessler DI, Devereaux PJ, Silbert B, et al; ANZCA Trials Group for the ENIGMA-II Investigators. The safety of addition of nitrous oxide to general anaesthesia in at-risk patients having major non-cardiac surgery (ENIGMA-II): a randomised, single-blind trial. *Lancet.* 2014;384:1446–1454. doi: 10.1016/S0140-6736(14)60893-X
144. Leslie K, Myles PS, Kasza J, Forbes A, Peyton PJ, Chan MT, Paech MJ, Sessler DI, Beattie WS, Devereaux PJ, et al. Nitrous oxide and serious long-term morbidity and mortality in the Evaluation of Nitrous Oxide in the Gas Mixture for Anaesthesia (ENIGMA)-II Trial. *Anesthesiology.* 2015;123:1267–1280. doi: 10.1097/ALN.0000000000000908
145. Short TG, Campbell D, Frampton C, Chan MTV, Myles PS, Corcoran TB, Sessler DI, Mills GH, Cata JP, Painter T, et al; Australian and New Zealand College of Anaesthetists Clinical Trials Network; Balanced Anaesthesia Study Group. Anaesthetic depth and complications after major surgery: an international, randomised controlled trial. *Lancet.* 2019;394:1907–1914. doi: 10.1016/S0140-6736(19)32315-3
146. Berger M, Schenning KJ, Brown CH 4th, Deiner SG, Whittington RA, Eckenhoff RG, Angst MS, Avramescu S, Bekker A, Brzezinski M, et al; Perioperative Neurotoxicity Working Group. Best practices for postoperative brain health: recommendations from the Fifth International Perioperative Neurotoxicity Working Group. *Anesth Analg.* 2018;127:1406–1413. doi: 10.1213/ANE.0000000000003841
147. Yeager MP, Glass DD, Neff RK, Brinck-Johnsen T. Epidural anesthesia and analgesia in high-risk surgical patients. *Anesthesiology.* 1987;66:729–736. doi: 10.1097/00000542-198706000-00004
148. Kettner SC, Willschke H, Marhofer P. Does regional anaesthesia really improve outcome? *Br J Anaesth.* 2011;107(suppl 1):i90–i95. doi: 10.1093/bja/aer340
149. Guay J, Parker MJ, Gajendragadkar PR, Kopp S. Anaesthesia for hip fracture surgery in adults. *Cochrane Database Syst Rev.* 2016;2:CD000521. doi: 10.1002/14651858.CD000521.pub3
150. Barbosa FT, Juca MJ, Castro AA, Cavalcante JC. Neuraxial anaesthesia for lower-limb revascularization. *Cochrane Database Syst Rev.* 2013:CD007083. doi: 10.1002/14651858.CD007083.pub3
151. Chu CC, Weng SF, Chen KT, Chien CC, Shieh JP, Chen JY, Wang JJ. Propensity score-matched comparison of postoperative adverse outcomes between geriatric patients given a general or a neuraxial anesthetic for hip surgery: a population-based study. *Anesthesiology.* 2015;123:136–147. doi: 10.1097/ALN.0000000000000695
152. Memtsoudis SG, Sun X, Chiu YL, Stundner O, Liu SS, Banerjee S, Mazumdar M, Sharrock NE. Perioperative comparative effectiveness of anesthetic technique in orthopedic patients. *Anesthesiology.* 2013;118:1046–1058. doi: 10.1097/ALN.0b013e318286061d
153. Smith LM, Cozowicz C, Uda Y, Memtsoudis SG, Barrington MJ. Neuraxial and combined neuraxial/general anesthesia compared to general anesthesia for major truncal and lower limb surgery: a systematic review and meta-analysis. *Anesth Analg.* 2017;125:1931–1945. doi: 10.1213/ANE.0000000000002069
154. Mutch WA, Patel SR, Shahidi AM, Kulasekara SI, Fisher JA, Duffin J, Hudson C. Cerebral oxygen saturation: graded response to carbon dioxide with isoxia and graded response to oxygen with isocapnia. *PLoS One.* 2013;8:e57881. doi: 10.1371/journal.pone.0057881
155. Grüne F, Kazmaier S, Sonntag H, Stolker RJ, Weyland A. Moderate hyperventilation during intravenous anesthesia increases net cerebral lactate efflux. *Anesthesiology.* 2014;120:335–342. doi: 10.1097/ALN.0b013e3182a8eb09
156. Meng L, Gelb AW. Regulation of cerebral autoregulation by carbon dioxide. *Anesthesiology.* 2015;122:196–205. doi: 10.1097/ALN.0000000000000506
157. Curley G, Kavanagh BP, Laffey JG. Hypocapnia and the injured brain: more harm than benefit. *Crit Care Med.* 2010;38:1348–1359. doi: 10.1097/CCM.0b013e3181d8cf2b
158. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, Kairalla RA, Deheinzelin D, Munoz C, Oliveira R, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med.* 1998;338:347–354. doi: 10.1056/NEJM199802053380602
159. Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A; Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med.* 2000;342:1301–1308. doi: 10.1056/NEJM200005043421801
160. Futier E, Constantin JM, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, Marret E, Beaussier M, Gutton C, Lefrant JY, et al; IMPROVE Study Group. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. *N Engl J Med.* 2013;369:428–437. doi: 10.1056/NEJMoa1301082
161. Cumbler E, Wald H, Bhatt DL, Cox M, Xian Y, Reeves M, Smith EE, Schwamm L, Fonarow GC. Quality of care and outcomes for in-hospital ischemic stroke: findings from the National Get With The Guidelines–Stroke. *Stroke.* 2014;45:231–238. doi: 10.1161/STROKEAHA.113.003617
162. Kimura K, Minematsu K, Yamaguchi T. Characteristics of in-hospital onset ischemic stroke. *Eur Neurol.* 2006;55:155–159. doi: 10.1159/000093574
163. Saltman AP, Silver FL, Fang J, Stamplecoski M, Kapral MK. Care and outcomes of patients with in-hospital stroke. *JAMA Neurol.* 2015;72:749–755. doi: 10.1001/jamaneurol.2015.0284
164. Rudd M, Buck D, Ford GA, Price CI. A systematic review of stroke recognition instruments in hospital and prehospital settings. *Emerg Med J.* 2016;33:818–822. doi: 10.1136/emermed-2015-205197
165. Sun Z, Yue Y, Leung CC, Chan MT, Gelb AW; Study Group for Perioperative Stroke In China (POSIC). Clinical diagnostic tools for screening of perioperative stroke in general surgery: a systematic review. *Br J Anaesth.* 2016;116:328–338. doi: 10.1093/bja/aev452
166. Lyden PD, Lu M, Levine SR, Brott TG, Broderick J; NINDS rtPA Stroke Study Group. A modified National Institutes of Health Stroke Scale for use in stroke clinical trials: preliminary reliability and validity. *Stroke.* 2001;32:1310–1317. doi: 10.1161/01.str.32.6.1310
167. Tirschwell DL, Longstreth WT Jr, Becker KJ, Gammans RE Sr, Sabounjian LA, Hamilton S, Morgenstern LB. Shortening the NIH Stroke Scale for use in the prehospital setting. *Stroke.* 2002;33:2801–2806. doi: 10.1161/01.str.0000044166.28481.bc
168. Kothari RU, Pancioli A, Liu T, Brott T, Broderick J. Cincinnati Prehospital Stroke Scale: reproducibility and validity. *Ann Emerg Med.* 1999;33:373–378. doi: 10.1016/s0196-0644(99)70299-4
169. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, et al; on behalf of the American Heart Association Stroke Council. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association [published correction appears in *Stroke.* 2019;50:e440–e441]. *Stroke.* 2019;50:e344–e418. doi: 10.1161/STR.0000000000000211
170. Blacker DJ. In-hospital stroke. *Lancet Neurol.* 2003;2:741–746. doi: 10.1016/s1474-4422(03)00586-6
171. Nolan S, Naylor G, Burns M. Code gray: an organized approach to inpatient stroke. *Crit Care Nurs Q.* 2003;26:296–302. doi: 10.1097/00002727-200310000-00005
172. Kassardjian CD, Willems JD, Skrabka K, Nisenbaum R, Barnaby J, Kostyrko P, Selchen D, Saposnik G. In-patient code stroke: a quality improvement strategy to overcome knowledge-to-action gaps in response time. *Stroke.* 2017;48:2176–2183. doi: 10.1161/STROKEAHA.117.017622
173. American Heart Association. Clinical tools and resources. Accessed March 12, 2021. https://www.heart.org/en/professional/quality-improvement/target-stroke/clinical-tools-and-resources

174. Lakomkin N, Dhamoon M, Carroll K, Singh IP, Tuhrim S, Lee J, Fifi JT, Mocco J. Prevalence of large vessel occlusion in patients presenting with acute ischemic stroke: a 10-year systematic review of the literature. *J Neurointerv Surg.* 2019;11:241–245. doi: 10.1136/neurintsurg-2018-014239
175. Sheriff F, Hirsch J, Shelton K, D'Alessandro D, Stapleton C, Koch M, Rabinov J, Jassar A, Patel A, Leslie-Mazwi T. Large-vessel occlusion stroke after cardiothoracic surgery: expanding time windows offer new salvage opportunities. *J Thorac Cardiovasc Surg.* 2019;158:186–196.e2. doi: 10.1016/j.jtcvs.2018.11.106
176. Glance LG, Holloway RG. Raising the alarm on brain attacks in surgical patients: are we doing enough to prevent and treat postoperative strokes? *Anesthesiology.* 2017;127:3–5. doi: 10.1097/ALN.0000000000001686
177. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, Dávalos A, Majoie CB, van der Lugt A, de Miquel MA, et al; HERMES Collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet.* 2016;387:1723–1731. doi: 10.1016/S0140-6736(16)00163-X
178. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, Yavagal DR, Ribo M, Cognard C, Hanel RA, et al; DAWN Trial Investigators. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med.* 2018;378:11–21. doi: 10.1056/NEJMoa1706442
179. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, McTaggart RA, Torbey MT, Kim-Tenser M, Leslie-Mazwi T, et al; DEFUSE 3 Investigators. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med.* 2018;378:708–718. doi: 10.1056/NEJMoa1713973
180. Haider AS, Garg P, Watson IT, Leonard D, Khan U, Haque A, Nguyen P, Layton KF. Mechanical thrombectomy for acute ischemic stroke after cardiac surgery. *Cureus.* 2017;9:e1150. doi: 10.7759/cureus.1150
181. Madeira M, Martins C, Koukoulis G, Marques M, Reis J, Abecassis M. Mechanical thrombectomy for stroke after cardiac surgery. *J Card Surg.* 2016;31:517–520. doi: 10.1111/jocs.12776
182. Premat K, Clovet O, Frasca Polara G, Shotar E, Bartolini B, Yger M, Di Maria F, Baronnet F, Pistocchi S, Le Bouc R, et al. Mechanical thrombectomy in perioperative strokes: a case-control study. *Stroke.* 2017;48:3149–3151. doi: 10.1161/STROKEAHA.117.018033
183. Román LS, Menon BK, Blasco J, Hernández-Pérez M, Dávalos A, Majoie CBLM, Campbell BCV, Guillemin F, Lingsma H, Anxionnat R, et al; HERMES Collaborators. Imaging features and safety and efficacy of endovascular stroke treatment: a meta-analysis of individual patient-level data. *Lancet Neurol.* 2018;17:895–904. doi: 10.1016/S1474-4422(18)30242-4
184. Cagnazzo F, Derraz I, Dargazanli C, Lefevre PH, Gascou G, Riquelme C, Bonafe A, Costalat V. Mechanical thrombectomy in patients with acute ischemic stroke and ASPECTS ≤6: a meta-analysis. *J Neurointerv Surg.* 2020;12:350–355. doi: 10.1136/neurintsurg-2019-015237
185. Menon BK, Hill MD, Davalos A, Roos YBWEM, Campbell BCV, Dippel DWJ, Guillemin F, Saver JL, van der Lugt A, Demchuk AM, et al. Efficacy of endovascular thrombectomy in patients with M2 segment middle cerebral artery occlusions: meta-analysis of data from the HERMES Collaboration. *J Neurointerv Surg.* 2019;11:1065–1069. doi: 10.1136/neurintsurg-2018-014678
186. Meretoja A, Putaala J, Tatlisumak T, Atula S, Artto V, Curtze S, Häppölä O, Lindsberg PJ, Mustanoja S, Piironen K, et al. Off-label thrombolysis is not associated with poor outcome in patients with stroke. *Stroke.* 2010;41:1450–1458. doi: 10.1161/STROKEAHA.109.576140
187. De Keyser J, Gdovinová Z, Uyttenboogaart M, Vroomen PC, Luijckx GJ. Intravenous alteplase for stroke: beyond the guidelines and in particular clinical situations. *Stroke.* 2007;38:2612–2618. doi: 10.1161/STROKEAHA.106.480566
188. Guillan M, Alonso-Canovas A, Garcia-Caldentey J, Sanchez-Gonzalez V, Hernandez-Medrano I, Defelipe-Mimbrera A, Matute MC, Alonso-Arias MA, Alonso de Leciñana M, Masjuan J. Off-label intravenous thrombolysis in acute stroke. *Eur J Neurol.* 2012;19:390–394. doi: 10.1111/j.1468-1331.2011.03517.x
189. Voelkel N, Hubert ND, Backhaus R, Haberl RL, Hubert GJ. Thrombolysis in postoperative stroke. *Stroke.* 2017;48:3034–3039. doi: 10.1161/STROKEAHA.117.017957
190. Thomalla G, Simonsen CZ, Boutitie F, Andersen G, Berthezene Y, Cheng B, Cheripelli B, Cho TH, Fazekas F, Fiehler J, et al; WAKE-UP Investigators. MRI-guided thrombolysis for stroke with unknown time of onset. *N Engl J Med.* 2018;379:611–622. doi: 10.1056/NEJMoa1804355
191. Campbell BCV, Ma H, Ringleb PA, Parsons MW, Churilov L, Bendszus M, Levi CR, Hsu C, Kleinig TJ, Fatar M, et al; EXTEND, ECASS-4, and EPITHET Investigators. Extending thrombolysis to 4·5-9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data. *Lancet.* 2019;394:139–147. doi: 10.1016/S0140-6736(19)31053-0