Title

Perioperative Care of Patients at High Risk for Stroke During or After Non-cardiac, Non-neurological Surgery: 2020 Guidelines From the Society for Neuroscience in Anesthesiology and Critical Care

Journal

Journal of Neurosurgical Anesthesiology, 32(3)

ISSN

0898-4921

Authors

Vlisides, Phillip E
Moore, Laurel E
Whalin, Matthew K
et al.

Publication Date

2020-07-01

DOI

10.1097/ana.0000000000000686

Peer reviewed

Perioperative Care of Patients at High Risk for Stroke During or After Non-Cardiac, Non-Neurological Surgery: 2020 Guidelines From the Society for Neuroscience in Anesthesiology and Critical Care

Phillip E. Vlisides, MD,† Laurel E. Moore, MD,* Matthew K. Whalin, MD,‡§ Steven A. Robicsek, MD, PhD,‖ Adrian W. Gelb, MBChB,¶ Abhijit V. Lele, MBBS, MD, MS, FNCS,# and George A. Mashour, MD, PhD*†*

Abstract: Perioperative stroke is associated with considerable morbidity and mortality. Stroke recognition and diagnosis are challenging perioperatively, and surgical patients receive therapeutic interventions less frequently compared with stroke patients in the outpatient setting. These updated guidelines from the Society for Neuroscience in Anesthesiology and Critical Care provide evidence-based recommendations regarding perioperative care of patients at high risk for stroke. Recommended areas for future investigation are also proposed.

Key Words: anesthesia, cerebrovascular disorders, neurological outcomes, perioperative care, postoperative complications, stroke

(*J Neurosurg Anesthesiol* 2020;00:000–000)

Received for publication March 4, 2020; accepted March 13, 2020.

From the *Department of Anesthesiology; †Center for Consciousness Science, University of Michigan Medical School, Ann Arbor, MI; ‡Department of Anesthesiology, Emory University School of Medicine; §Department of Anesthesiology, Grady Memorial Hospital, Atlanta, GA; ‖Department of Anesthesiology, University of Florida, Gainesville, FL; ¶Department of Anesthesia and Perioperative Care, University of California, San Francisco, CA; and #Department of Anesthesiology and Pain Medicine, University of Washington, Seattle, WA.

These clinical guidelines have been reviewed and approved by the Society for Neuroscience in Anesthesiology and Critical. The manuscript has not undergone review by the Editorial Board of the Journal of Neurosurgical Anesthesiology.

A.W.G. serves as a consultant for Masimo and Haisco Pharmaceutical Company, and A.V.L. receives research support from Aqueduct Critical Care and salary support from LifeCenter Northwest. These relationships are not relevant to this publication. The reminaing authors have no funding or conflicts of interest to disclose.

Address correspondence to: Phillip E. Vlisides, MD, E-mail: pvliside@med.umich.edu.

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.jnsa.com.

DOI: 10.1097/ANA.0000000000000686

Stroke can be a devastating outcome for surgical patients and is associated with an adjusted 8-fold increase in mortality.[1] Unfortunately, the incidence of perioperative stroke has been increasing,[2] and the risk of clinically silent stroke may reach 7% in patients 65 years and older undergoing major noncardiac surgery.[3] Furthermore, perioperative stroke is associated with delayed recognition, less frequent intervention, and higher rates of death and disability compared with a stroke occurring in the nonoperative setting.[4,5] In these practice guidelines, we systematically review past and current evidence regarding incidence, pathogenesis, prevention, and management of perioperative stroke. These recommendations build upon the initial consensus statement published by the Society for Neuroscience in Anesthesiology and Critical Care (SNACC) in 2014.[6]

METHODOLOGY

Definition of Perioperative Stroke

For the purposes of these guidelines, "perioperative stroke" is defined as a brain infarction of ischemic or hemorrhagic etiology that occurs during surgery or within 30 days after surgery. We recommend that this definition be adopted as the standardized definition of perioperative stroke. These guidelines focus on care for surgical patients with high stroke risk or suspected stroke; periprocedural guidelines for endovascular stroke interventions are described separately.[7]

Purpose of the Guidelines

The purpose of these guidelines is to provide current evidence-based recommendations regarding the following: (1) preoperative risk stratification and optimization, (2) intraoperative management to mitigate risk, and (3) appropriate steps for clinical care if the stroke is suspected or identified in the postoperative period. Since the initial SNACC consensus statement was published,[6] several major studies have been conducted that have influenced clinical care and prompted changes in other perioperative guidelines (as discussed in relevant sections). The present

guidelines were thus written to reflect the updated medical literature and are not intended as clinical standards. Rather, the recommendations are meant to assist with individual clinical decision-making in patients at high risk for perioperative stroke.

Focus

As previously outlined,[6] the focus of these guidelines remains on the prevention and management of ischemic stroke in adult patients undergoing noncardiac, nonmajor vascular, and nonneurological surgery. These recommendations also apply to nonsurgical interventions (eg, interventional radiology procedures) requiring anesthesia provision.

Application

These guidelines are intended for use by perioperative care teams, including anesthesiologists, nurse anesthetists, anesthesiologist assistants, surgeons, nurses, and other care providers. They may also serve additional health care professionals such as intensivists, neurologists, internists, or other clinicians who evaluate either: (1) surgical patients, and/or (2) those with a suspected stroke. For the purposes of these guidelines, anesthesia care refers primarily to general anesthesia, regional anesthesia, or monitored anesthesia care. The principles and recommendations discussed can also be considered for procedures not involving anesthesia care teams.

Task Force Members and Consultants

Since the initial consensus statement was published,[6] the task force was expanded to include additional members (P.E.V., M.K.W.) with clinical and scientific expertise in perioperative stroke and cerebrovascular disease. The guidelines were made available to active SNACC members for review and comment before publication, and the final task force roster and updated guidelines were approved by the Executive Committee and Board of Directors of SNACC.

AVAILABILITY AND STRENGTH OF EVIDENCE

The literature search was conducted with PubMed, Google Scholar, Embase, Web of Science, and direct internet searches. Database queries for updated studies were restricted to humans, publication from January 1, 2014, to present, and availability in English. The following search terms and keywords were used: "stroke," "cerebrovascular disease," "perioperative," "surgical," "surgery," "noncardiac," postoperative," "perioperative," "endovascular," "anticoagulation," "bridging," "bridge," and "management." All retrieved articles were reviewed manually for inclusion relevance.

These updated guidelines follow the American College of Cardiology/American Heart Association (ACC/AHA) methodology for assessing the quality of evidence (Supplemental Digital Content: Supplementary Table, http://links.lww.com/JNA/A275).[8] This method was chosen for multiple reasons. First, by using the ACC/AHA methodology, direct comparisons can be made to related clinical guidelines in terms of the supporting strength of evidence. For example, this methodology is used by the American Stroke Association,[9] the ACC/AHA for perioperative management guidelines,[10] and by SNACC for anesthetic management of endovascular treatment of acute ischemic stroke.[7] Thus, using the ACC/AHA criteria will allow for coherent evidence-grading methodology across guidelines related to stroke or cerebrovascular disease. In addition, although other strategies are available (eg, GRADE Criteria[11]), the ACC/AHA methodology allows for a flexible analysis of underlying evidence when point estimates are not available for relevant clinical questions and topics. Lastly, by consistently aligning with this system, temporal comparisons can be made within these guidelines to determine how evidence quality evolves over time. Major chronological updates since the original consensus statement can be found in Table 1.

PREOPERATIVE GUIDELINES

Stroke Pathophysiology and Etiology

Prospective, multicenter stroke registry data confirm that noncardiac, nonmajor vascular surgical procedures are associated with increased risk of stroke and/or transient ischemic attack (TIA), with the highest risk occurring between 1 and 3 days after surgery (rate ratio = 34.0, 95% confidence interval [CI]: 26.9-42.8).[12] To mitigate the risk of any adverse perioperative outcome, a fundamental step is to understand the underlying pathophysiology and etiology. Multiple large-scale, retrospective cohort studies have sought to classify perioperative stroke etiology based on available data in medical records.[12–15] Overall, large-vessel and cardioembolic etiologies are commonly identified, particularly in the anterior circulation (anterior cerebral artery, middle cerebral artery)[15]; however, a substantial proportion of cases (~25% to 30%) do not have a classified etiology per medical records (Fig. 1). Limited cerebrovascular reserve may also insidiously contribute to risk. For example, patients with preexisting cerebrovascular disease demonstrate reduced cerebrovascular reserve, whereby vascular dilation is maximized distal to sites of anatomical occlusion.[18] Additional deleterious perturbations (eg, hypotension, hypocapnia/hypercapnia) throughout such vascular beds may further predispose to hypoxic-ischemic injury.[18] Ultimately, to inform prevention strategies, further investigation is required to better understand stroke etiology and pathogenesis in the perioperative setting.

Preoperative Evaluation and Risk Evaluation

In contrast to the cardiovascular system, for which physiological and clinical risk can be tested with multiple tools (eg, electrocardiogram, echocardiogram, stress testing), there is no standard preoperative system for evaluating cerebrovascular physiology. Various strategies have been tested for determining cerebrovascular vulnerability, though testing has been largely restricted to nonsurgical or neurosurgical settings. For example, the cerebrovascular reserve has been mapped via blood oxygen level-dependent signal and vasoactive stimuli (eg, CO_2) in human volunteers and neurosurgical patients.[19,20] Cerebral microembolic events have been detected via high-intensity transcranial Doppler signals in

TABLE 1. Major Recommendation Updates

	Strength of Evidence	Class of Recommendation
Preoperative recommendations		
Consider delaying elective surgery for at least 9 mo after prior stroke	Level B-NR	Class IIa
For patients on vitamin K anticoagulants (eg, warfarin), stop medication 5 d preoperatively, and only implement bridging anticoagulation for patients with moderate-to-high thromboembolic risk	Level A	Class I
For patients on direct oral anticoagulants, stop anticoagulation 1-3 d preoperatively, resume 1-3 d postoperatively based on clinical risk factors. Avoid bridging therapy	Level A	Class I
Intraoperative recommendations		
In patients at high risk of perioperative stroke, maintaining normocapnia may prevent further risk of cerebrovascular compromise	Level C-LD	Class I
Intensive efforts to maintain tight control of serum glucose (eg, <130 mg/dL) may result in hypoglycemia and related adverse events	Level B-R	Class III: Harm
Postoperative recommendations		
Routine clinical screening for stroke is not recommended given the low positive predictive value of current screening instruments	Level B-NR	Class III: No Benefit
Currently available serum-based biomarkers are not recommended for stroke screening given the low positive predictive value	Level B-NR	Class III: No Benefit
For suspected large-vessel occlusion, computed tomography angiography and diffusion/perfusion imaging should be obtained within 24 h of time last known well for endovascular therapy consideration (Level A, Class I)	Level A	Class I
Patients with large-vessel occlusion should receive mechanical thrombectomy as soon as possible if criteria are met	Level A	Class I

high-risk nonsurgical patients,[21,22] and distinct electroencephalographic patterns, such as oscillatory asymmetry and increased delta/alpha ratios, have been identified during acute stroke.[23–25] The utility of such methodologies for predicting or detecting cerebral ischemia has not been defined in the noncardiac, nonmajor vascular, non-neurological surgery setting. Rigorous clinical testing is required as an initial step. As such, cerebrovascular risk evaluation presently remains guided by comorbidity-based risk factors in these surgical populations.

Three commonly and consistently identified clinical risk factors for perioperative stroke include advanced age, prior cerebrovascular disease, and renal failure.[1,14,26–28] Recent large-scale, database analyses (of administrative billing data) extend this set of risk factors to include recent ischemic stroke, emergency surgery, valvular heart disease, postoperative hypotension, and patent foramen ovale (Table 2).[13,14,26] These additional risk factors can be incorporated into clinical assessment alongside previously established risk factors, such as age, cerebrovascular disease, and renal failure. Lastly, Wilcox et al[29] recently compared multiple cardiovascular risk stratification models for predicting stroke in noncardiac surgery patients. The Myocardial Infarction or Cardiac Arrest (MICA) risk score[30] and American College of Surgeons Surgical Risk Calculator (ACS-SRC)[31] were the most highly discriminative for perioperative stroke (*c*-statistic area under the curve 0.833 and 0.836, respectively). The MICA score only contains 5 components, compared with the 23-item ACS-SRC, and thus may serve as a pragmatic and useful tool for predicting perioperative stroke. However, quantitative stroke risk (ie, percentage likelihood) is not reported based on specific scores, nor are optimal sensitivity/specificity thresholds presented. Nonetheless, relatively high scores within the framework of each respective tool are likely to reflect increased stroke risk.

Recommendations

(1) Preoperative physiological testing is not recommended for determining cerebrovascular vulnerability (Level C-LD, Class III: No Benefit).
(2) Screen for risk factors of postoperative stroke, most notably recent or remote stroke history, and communicate such risk to patients and clinical care teams (Level C-EO, Class IIb).

Informed Consent

The previous SNACC consensus statement recommended discussing perioperative stroke with high-risk patients.[6] Stroke risk approaches 2–3% in such patients with multiple risk factors,[1,32] and patient survey data suggest that major complications with an incidence > 1% should be discussed.[33,34] A recent survey administered to Canadian anesthesiologists revealed that <50% of respondents routinely discuss perioperative stroke with high-risk patients.[35] Furthermore, <50% correctly identified stroke incidence, most common stroke etiology, or mortality rates. From the patient perspective, a follow-up cross-sectional survey demonstrated that surgical patients may underestimate their risk of stroke and less than half of respondents endorsed previously discussing perioperative stroke.[36] These survey data suggest room for improvement with regards to perioperative stroke education and counseling.

Recommendations

For those with high-stroke risk, such risk should be communicated to patients and clinical care teams (Level C-EO, Class IIb).

Timing of Elective Surgery After Stroke

Patients with prior stroke may have impaired cerebrovascular autoregulation and chemoregulation for months

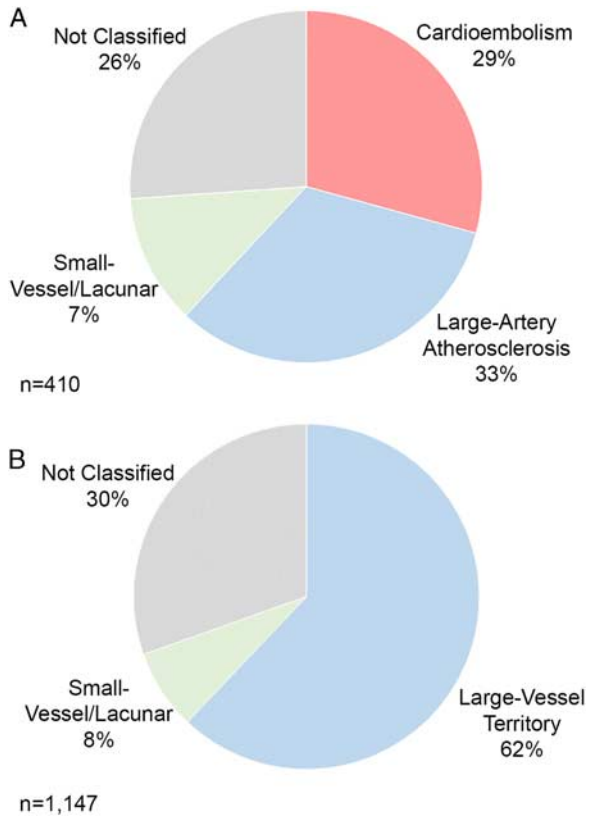

FIGURE 1. Reported etiologies and vascular distribution of perioperative stroke. A, Etiologies are reported based on Trial of Org 10172 in Acute Stroke Treatment (TOAST) Criteria (large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology).[12,14,16] For studies that report stroke etiology,[12,14] large-vessel and small-vessel stroke subtypes are reported separately from cardioembolism. B, Vascular territory is presented via Oxfordshire Criteria.[12–14,17] Large-vessel territory includes total anterior, partial anterior, and posterior circulation strokes.

to years after the initial insult,[37,38] and multiple strokes may further compromise cerebrovascular reactivity.[39] In addition, patients with cerebral artery occlusive disease may demonstrate increased oxygen extraction, compromised cerebral blood flow, and inadequate cerebral perfusion.[18,40–42] These physiological vulnerabilities may lead to increased perioperative stroke risk in patients with prior stroke and cerebrovascular disease history. A recent large-scale observational study has supported this notion.[3]

In 2014, Jørgensen et al[26] conducted a retrospective cohort study including >480,000 patients that underwent elective, noncardiac surgery using Danish nationwide registry data (2005-2011). For patients with prior ischemic stroke, the risk of new postoperative stroke was increased compared with those with no stroke history, with the highest adjusted risk within the first 3 months after prior stroke (adjusted odds ratio [AOR] = 67.60, 95% CI: 52.27-87.42). New stroke risk stabilized by 9 months but remained elevated compared with those with no prior stroke history (AOR = 8.17, 95% CI: 6.19-10.80). To further support these findings, the authors then conducted a secondary analysis to determine whether surgery itself was associated with the risk of a new stroke, as the prior cerebrovascular disease itself predisposes to recurrent stroke risk. After assessing recurrent stroke risk in >72,000 nonsurgical patients from the same dataset, stroke risk remained significantly elevated in surgical patients across all time points up to 12 months after surgery.[43] Of note, the incidence of major cardiovascular events was temporally increased in parallel with recurrent stroke risk. Similar temporal patterns have been observed in patients with previous stroke presenting for emergency noncardiac, nonintracranial surgery.[44] Thus, delaying elective surgery for at least 9 months after a prior stroke may be warranted. This position was also recently endorsed by the American College of Surgeons.[45] Lastly, to prevent perioperative stroke in patients with recent cerebrovascular insult, it is likely beneficial to identify the cause of the initial stroke in conjunction with guideline-based diagnostic recommendations.[9]

Recommendations

Consider delaying elective surgical cases for at least 9 months after a prior stroke (Level B-NR, Class IIa).

Management of Anticoagulant and Antiplatelet Drugs

Major studies have been published within the past 5 years that have prompted changes in anticoagulation guidelines. In 2015, the Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation (BRIDGE) Trial examined whether forgoing bridging anticoagulation would impact the risk of arterial thromboembolism or major bleeding in patients with atrial fibrillation.[46] Only patients with vitamin K antagonist therapy (eg, warfarin) were included. The trial found that forgoing bridging was noninferior to bridging therapy with respect to thromboembolism risk (0.4% vs. 0.3%, respectively, risk difference = 0.1%, 95% CI: −0.6 to 0.8; $P = 0.01$) and superior to bridging for risk of major bleeding (1.3% vs. 3.2%, respectively, relative risk [RR] = 0.41, 95% CI: 0.20-0.78; $P = 0.005$). These findings align with prior a meta-analysis of 34 studies and >12,000 patients that reported an increased risk of major bleeding events for patients who received perioperative heparin bridging.[47] Of note, the mean $CHADS_2$ score in the BRIDGE Trial was 2.3, and <3% of patients had a $CHADS_2$ score of ≥5. Patients with mechanical heart valves or recent thromboembolic events were also excluded. Thus, findings from the trial may not apply to high-risk patients. In addition, multiple studies have examined the safety and effectiveness of newer, direct oral anticoagulant agents.[48–50] These drugs directly inhibit prothrombotic proteins in the coagulation cascade. Because of their relatively short, predictable half-life, direct oral anticoagulants can be interrupted for a shorter period of time compared with warfarin. Furthermore, bridging is not required with these agents, because this practice appears to increase bleeding risk without reducing thromboembolic events.[51] Collectively, these studies have

TABLE 2. Independent Risk Factors for Perioperative Stroke Identified in Large Epidemiologic Studies

Risk Factor	Adjusted OR (95% CI)	Surgical Population	Sample Size (n)
Ng et al[13]		Noncardiac surgery	150,198
Patent foramen ovale	2.66 (1.96-3.63)		
Vasivej et al[14]		Noncardiac, nonmajor vascular, nonintracranial	55,648
Emergency surgery	8.13 (2.05-32.25)		
Previous stroke or TIA	7.06 (1.74-28.75)		
Valvular heart disease	6.18 (1.35- 28.33)		
Postoperative hypotension	5.1 (1.11-23.45)		
Jørgensen et al[26]		Nonemergent, noncardiac	481,183
Prior stroke anytime	16.24 (13.23-19.94)		
Stroke <3 mo prior	67.60 (52.27-87.42)		
Stroke 3 to <6 mo prior	24.02 (15.03-38.39)		
Stroke 6 <12 mo prior	10.39 (6.18-17.44)		
Stroke ≥12 mo prior	8.17 (6.19-10.80)		
Sharifpour et al[28]		Vascular surgery (noncarotid)	47,750
Acute renal failure	2.03 (1.39-2.97)		
History of TIA, stroke, existing hemiplegia	1.72 (1.29-2.30)		
Female sex	1.47 (1.12-1.93)		
Cardiac disease*	1.42 (1.07-1.87)		
Mashour et al[1]		Noncardiac, nonvascular, non-neurological	523,059
Age >62 y	3.9 (3.0-5.0)		
MI within 6 mo	3.8 (2.4-6.0)		
Acute renal failure	3.6 (2.3-5.8)		
History of stroke	2.9 (2.3-3.8)		
Bateman et al[27]		Hemicolectomy, THA, lobectomy/segmental lung resection	371,641
Renal disease	2.98 (2.52-3.54)		
Atrial fibrillation	1.95 (1.69-2.26)		
History of stroke	1.64 (1.25-2.14)		
Valvular disease	1.54 (1.25-1.90)		

*History of myocardial infarction or congestive heart failure within 6 months, angina within 1 month, or previous cardiac intervention.
MI indicates myocardial infarction; THA, total hip arthroplasty; TIA, transient ischemic attack.

motivated and informed recent guideline updates. Specifically, the Canadian Cardiovascular Society (2016),[52] American College of Cardiology (2017),[53] and American College of Surgeons (2018)[45] have all published recent, focused updates with regards to perioperative anticoagulation management. These guidelines converge on similar themes: for direct oral anticoagulants, no bridging therapy is required; for vitamin K antagonist therapy (eg, warfarin), bridging anticoagulation is reserved for patients with moderate-to-high thromboembolic risk (Table 3). To summarize, direct oral anticoagulants are generally held for 2 to 3 days preoperatively depending on clinical risk factors and bleeding risk (Tables 4, 5), and bridging therapy is deferred. For vitamin K antagonist therapy, bridging is generally recommended only in the following, high-risk situations: mechanical heart valve, high CHA_2DS_2-VASc scores[56] (generally ≥6), recent (within 3 mo) thromboembolism, history of thromboembolism while on anticoagulation, known cardiac thrombus, and rheumatic valve disease.[45,52,53] Finally, the Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) study was recently published, which prospectively evaluated the safety of a standardized, clinical protocol for interrupting direct oral anticoagulants (dabigatran, apixaban, and rivaroxaban) in relation to risk of major bleeding and stroke.[57] Anticoagulants were stopped 1 to 2 days before surgery based on clinical considerations (eg, renal function, bleeding risk) and resumed 1 to 3 days postoperatively. Rates of stroke (<1%) and major bleeding (0.9% to 2.96%) were consistent with population averages.[1,27,46] Thus, a standardized clinical protocol for stopping direct oral anticoagulants can minimize the risk of stroke and major bleeding with a minimal interruption window and no requirement for heparin bridging.

In terms of antiplatelet therapy, there is a paucity of high-quality data to inform perioperative management, particularly for high-risk patients with established atherosclerotic disease. Substudy analysis of the POISE-2 Trial was recently published to analyze outcomes in patients with a history of percutaneous coronary intervention.[58] While aspirin reduced the risk of mortality or nonfatal myocardial infarction (primary composite outcome) in those with prior percutaneous coronary intervention, the overall incidence of stroke was low (2/470, 0.4%), precluding definitive conclusions. Patients undergoing vascular surgery were also separately analyzed in the main POISE-2 Trial.[59] Similarly, the incidence of stroke was rare in this cohort (1/537, 0.1%). Thus, further investigation is required to determine the effects of aspirin on stroke risk in high-risk patients. Wolff et al[60] conducted a meta-analysis of randomized clinical trials of patients randomized to aspirin therapy for noncardiac surgery. The majority of patients (>13,000) came from the Pulmonary Embolism Prevention Trial,[61] which analyzed venous thromboembolism risk in orthopedic surgery patients, or the POISE-2 Trial.[62] There was no difference in stroke or TIA risk between groups in either of these trials. However, the risk of major perioperative bleeding was

TABLE 3. Proposed Risk Classification System for Perioperative Anticoagulation

Risk Category	Mechanical Heart Valve	Atrial Fibrillation	Venous Thromboembolism
High	Mitral valve prosthesis; caged-ball or tilting disk aortic prosthesis; stroke or TIA within 6 mo	CHA_2DS_2-VASc score ≥ 6; stroke or TIA within previous 3 mo; rheumatic valvular heart disease	VTE within 3 mo; severe thrombophilia*
Moderate	Bileaflet aortic valve prosthesis and at least one of the following risk factors: atrial fibrillation, previous stroke or TIA, hypertension, diabetes, congestive heart failure, age > 75 y	CHA_2DS_2-VASc score 4-5 or previous stroke or TIA > 3 mo before	VTE within 3 to 12 mo; nonsevere thrombophilia†; recurrent VTE; active cancer
Low	Bileaflet aortic valve prosthesis and no other risk factors for stroke	CHA_2DS_2-VASc score 2-3 (assuming no previous stroke or TIA)	VTE > 12 mo previous and no other risk factor

*Severe thrombophilia is defined as deficiency in protein C, protein S, or antithrombin; antiphospholipid antibodies; and those with multiple abnormalities.
†Nonsevere thrombophilia is defined as heterozygous factor V Leiden or prothrombin gene mutation.
TIA indicates transient ischemic attack; VTE, venous thromboembolism.
Reprinted from Horner et al[45] and Douketis et al.[54] Copyright [Elsevier Inc.], [Amsterdam, Netherlands]. All permission requests for this image should be made to the copyright holder.

significantly higher in patients randomized to receive aspirin (odds artio [OR] = 1.18, 95% CI: 1.05-1.33, $P = 0.007$). This aligns with findings from the BRIDGE Trial, which demonstrated that aspirin use was a time-dependent predictor of major bleeding (OR = 3.6, 95% CI: 1.1-11.9, $P = 0.038$).[46] Additional meta-analyses include trials and observational studies with small sample sizes that render inconclusive findings related to cerebrovascular events.[63–65] Overall, recent studies suggest that aspirin probably does not reduce stroke risk for the majority of noncardiac patients. Further investigation is required for those at high risk of stroke, though potential benefits of aspirin must be weighed against the documented risk of major perioperative hemorrhage.

Recommendations

(1) For patients on vitamin K anticoagulants (eg, warfarin), stop medication 5 days preoperatively, and consider bridging anticoagulation only for those with moderate-to-high thromboembolic risk (Level A, Class I).
(2) For patients on direct oral anticoagulants, administer last dose 2 to 3 days preoperatively and resume 1 to 3 days postoperatively based on clinical risk factors. Avoid heparin bridging (Level A, Class I).
(3) For patients with prior percutaneous coronary intervention, a continuation of aspirin may reduce perioperative mortality and myocardial infarction risk (Level B-R, Class IIa). However, there is insufficient evidence to determine whether aspirin mitigates stroke risk in such patients (Level C-LD, Class IIb).

Role of Preoperative Beta-blockers and Statins in Perioperative Stroke

In 2014, a systematic review was published for the ACC/AHA perioperative guidelines that focused on stroke

TABLE 4. Approach to Perioperative Bridging of Anticoagulation Management

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
Direct oral anticoagulants	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
Direct oral anticoagulants	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
Direct oral anticoagulants	Give last dose 3 d before operation,* resume 2-3 d postoperatively	Give last dose 2 d before operation,* resume 24 h postoperatively

*In patients with CrCl <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.
CrCl indicates creatinine clearance; LMWH, low–molecular-weight heparin; UFH, unfractionated heparin.
Reprinted from Horner et al.[45] Copyright [Elsevier Inc.], [Amsterdam, Netherlands]. All permission requests for this image should be made to the copyright holder.

TABLE 5. Suggested Risk Classification for Bleeding According to Type of Surgery/Procedure

Bleeding Risk Category	Type of Surgery/Procedure
High risk	Intracranial or spinal surgery
	Major vascular surgery (aortic aneurysm repair, aortofemoral bypass)
	Major urologic surgery (prostatectomy, bladder tumor resection)
	Major orthopedic surgery (hip/knee joint replacement)
	Lung resection surgery
	Intestinal anastomosis surgery
	Permanent pacemaker or internal defibrillator placement
	Selected procedures: colonic polypectomy of large polyp, endoscopic retrograde cholangiopancreatography with sphincterotomy, kidney biopsy
Moderate risk	Other intra-abdominal surgery
	Other intrathoracic surgery
	Other orthopedic surgery
	Other vascular surgery
	Selected procedures: colonic polypectomy of small polyp, prostate biopsy, cervical biopsy
Low risk	Laparoscopic cholecystectomy
	Laparoscopic inguinal hernia repair
	Noncataract ophthalmologic procedures
	Coronary angiography
	Gastroscopy or colonoscopy (with/without biopsy)
	Selected procedures: thoracentesis, paracentesis, arthrocentesis, bone marrow aspiration, and biopsy
Very low risk (anticoagulation interruption not required)	Single tooth extraction or teeth cleaning
	Skin biopsy or selected skin cancer removal
	Cataract removal

Of note, bleeding risk also relates to the consequences of bleeding rather than the mere volume of blood loss.

CrCl indicates creatinine clearance.

Reprinted from Darvish-Kazem and Douketis.[55] Copyright [Georg Thieme Verlag KG], [Stuttgart, Germany]. All permission requests for this image should be made to the copyright holder.

risk in relation to beta-blockade initiation in the immediate preoperative setting.[66] The final analysis included 9 randomized control trials, and results demonstrated that beta-blockade was associated with an increased risk of nonfatal stroke (RR = 1.86, 95% CI: 1.09-3.16). These results were driven in part by the POISE Trial,[67] which randomized beta-blocker–naive patients to the administration of extended-release metoprolol. Multiple observational studies have since examined whether chronic beta-blocker use is associated with perioperative stroke. In 2015, Jørgensen et al[68] examined perioperative major adverse cardiovascular events in patients on long-term beta-blocker therapy with a retrospective case-control design. The incidence of nonfatal stroke was not significantly increased in patients on chronic beta-blocker therapy compared with those on alternative antihypertensives (0.23% vs. 0.21%, respectively, $P = 0.68$).[68] This group then examined perioperative adverse events in relation to beta-blocker subtype using Danish Nationwide Cohort data.[69] For patients on long-term beta-blocker therapy preoperatively, stroke risk did not differ among various beta-blocker subtypes. Taken together, these results align with findings from related observational studies. In 2018, Park et al[70] studied associations between preoperative beta-blocker therapy and noncardiac surgery outcomes in patients with previous coronary revascularization. There was no adjusted increased risk of stroke in those on prior beta-blocker therapy (AOR = 0.33, 95% CI: 0.06-1.75). With additional propensity-matched analysis, there remained no statistically significant association between preoperative beta-blocker use and stroke risk (AOR = 0.33, 95% CI: 0.03-3.18). A large-scale, retrospective cohort study of Veterans Affairs patients undergoing noncardiac surgery also demonstrated no association between chronic beta-blockade and perioperative stroke risk across different risk profiles based on the Revised Cardiac Risk Index.[71] Chen et al[72] reported outcomes associated with the timing of beta-blocker initiation using population-based cohort data in patients with diabetes mellitus. There was no statistically significant association with preoperative beta-blocker use and stroke in the studied cohort (OR = 1.33, 95% CI: 0.94-1.88). However, temporal associations between the timing of beta-blocker initiation and stroke risk were not specifically reported. Collectively, these observational data support the updated ACC/AHA guidelines, which recommends avoiding beta-blocker initiation immediately before surgery while continuing beta-blockade for those already on chronic therapy.[10,66]

The role of perioperative statin use has also been refined in recent years given large-scale investigations and associated findings. In 2017, London et al[73] evaluated associations between perioperative statin use (previously prescribed) and multiple outcomes in a retrospective, observational cohort analysis involving >180,000 patients using the Veterans Affairs Surgical Quality Improvement Program. Using propensity-matched cohort analysis, there was no difference in stroke incidence between groups with statin exposure (0.4%) and no preoperative statin use (0.5%, $P = 0.39$). Perioperative statin use was, however, associated with significant reductions in all-cause mortality and both cardiovascular and noncardiovascular morbidity. Richman et al[71] performed a similar retrospective cohort investigation of noncardiac surgery patients, with prior cardiac stent placement, and outcomes associated with preoperative statin use. Likewise, perioperative statin use was not associated with stroke across any level of preoperative risk, as stratified by the Revised Cardiac Risk Index.[74] However, statin use was associated with decreased adjusted mortality across multiple cohorts studied. Lastly, a meta-analysis was recently published that examined outcomes associated with perioperative statin administration across twelve randomized controlled trials.[75] While perioperative statin administration was not associated with perioperative stroke or TIA (OR = 0.584,

95%: CI: 0.226-1.505, $P = 0.265$), multiple cardiovascular endpoints (eg, major adverse cardiac events, new atrial fibrillation) were improved in groups randomized to statin therapy. Thus, while perioperative statin use may not reduce stroke risk, statin administration has been consistently associated with reductions in mortality and major morbidity in the noncardiac surgery setting.

Recommendations

(1) Avoid initiating beta-blocker therapy in the immediate preoperative setting (Level A, Class I).
(2) Continue beta-blockers (Level B-NR, Class IIa) and statins (Level B-R, Class IIa) throughout the perioperative period in patients already taking them.

INTRAOPERATIVE GUIDELINES

Most perioperative strokes occur or manifest after the day of surgery, which suggests that postoperative factors contribute to stroke risk.[76] However, intraoperative events may nonetheless contribute to cerebrovascular injury. In the following section, we present available data to guide intraoperative management in relation to stroke risk. Specifically, anesthetic technique, blood pressure management, ventilation strategy, hemorrhage/blood transfusion, glycemic management, and intraoperative beta-blockade will be reviewed.

Anesthetic Technique

Studies investigating the anesthetic technique in relation to stroke risk for noncardiac, nonmajor vascular surgery have produced mixed results. In 2019, Sgroi et al[77] retrospectively analyzed clinical outcomes in lower extremity vascular surgery patients (> 16,000) in relation to anesthetic technique (ie, general anesthesia vs. epidural or spinal anesthesia). While certain outcomes, such as heart failure, acute kidney injury, and length of stay favored regional techniques, there was no statistically significant difference in stroke incidence between general (0.7%) and regional (1.2%; $P = 0.10$) anesthesia groups. Likewise, Smith et al[78] retrospectively studied outcomes in relation to anesthetic technique in gynecologic surgery patients (> 37,000). While stroke data were not analyzed separately in this analysis, stroke was included as part of a composite outcome of major complications, which was not significantly different for those receiving regional techniques (adjusted RR = 1.23, 95% CI: 0.92-1.65) or monitored anesthesia care (adjusted RR = 0.74, 95% CI: 0.45-1.20) compared with general anesthesia. Results from these 2 studies stand in contrast to a large-scale retrospective analysis (> 380,000 patients) by Memtsoudis et al,[79] which found that general anesthesia was an independent predictor of perioperative stroke (AOR = 3.15, 95% CI: 1.11-8.92, $P = 0.0271$) in hip and knee arthroplasty patients. There are thus mixed data as to whether regional anesthetic techniques reduce stroke risk. One explanation might be that neuraxial techniques are particularly helpful for orthopedic surgery patients, given that regional techniques are associated with less blood loss[80] and thromboembolic phenomena[81] in these patients. Alternatively, the study by Memtsoudis et al[79] may have detected a difference because of the larger sample size, which was approximately an order of magnitude larger than the vascular and gynecologic surgery investigations. Regional techniques may thus confer a reduced risk of stroke, but the effect size may be small, requiring a large sample size for detection. Furthermore, sedative depth during regional anesthesia serves as an additional confounder for consideration.

In terms of inhalational anesthetic agents, the MYRIAD Trial[82] recently compared volatile and propofol anesthesia during coronary artery bypass surgery in relation to clinical outcomes. The trial randomized > 5000 patients to either volatile anesthesia (eg, isoflurane, sevoflurane, desflurane) or total intravenous anesthesia with propofol. Stroke was assessed both as part of the primary composite outcome and separately as a safety outcome. There was no difference in stroke incidence between the volatile anesthetic group (0.8%) or propofol group (0.6%, RR = 1.38, 95% CI: 0.70-1.25) in the per-protocol analysis. Similarly, in the as-treated analysis, there remained no significant difference in stroke risk between the volatile anesthesia (0.8%) and propofol groups (0.6%, RR = 1.41, 95% CI: 0.73-2.72). Thus, while these data are derived from the cardiac surgery literature, cardiac surgery patients tend to have multiple risk factors for perioperative stroke (eg, coronary artery disease, diabetes mellitus, hypertension)[1] and remain at high risk for perioperative stroke.[83] There were nonetheless no associations between stroke and choice of anesthetic agent.

Lastly, nitrous oxide is associated with an acute increase in plasma homocysteine concentrations, which could impair endothelial function and theoretically increase adverse cardiovascular events.[84,85] In a basic science model of ischemic stroke, nitrous oxide use was found to bind to tissue plasminogen activator (tPA), and dose-dependently inhibit tPA-induced thrombolysis, disrupt the blood-brain barrier, and increase hemorrhagic complications.[86] However, no association has been demonstrated in several large studies between intraoperative nitrous oxide and postoperative stroke.[76,87–90] This was confirmed in the ENIGMA-II Trial, which randomized > 7000 noncardiac surgery patients with known or suspected cardiovascular disease to nitrous oxide use or no nitrous oxide during surgical anesthesia.[89] During the 1-year follow-up period, nitrous oxide was not associated with stroke (OR = 1.08, 95% CI: 0.74-1.58, $P = 0.70$).

Recommendations

(1) When appropriate given a particular surgery, regional anesthetic techniques may be considered for reducing stroke risk, though the effect is likely to be small (Level B-NR, Class IIb).
(2) Either propofol or inhalational anesthesia can be used for maintenance techniques, given that there does not appear to be a difference in relation to stroke risk (Level A, Class III: No Benefit).
(3) Nitrous oxide appears safe across broad surgical populations (Level A, Class I).

Blood Pressure Management

Intraoperative hypotension has been cited as a cause of postoperative stroke. While there is evidence from cardiac surgery patients that intraoperative hypotension, particularly during cardiopulmonary bypass, is associated with perioperative stroke,[91,92] this relationship is less clear in the noncardiac surgical population. In a single-center, retrospective, propensity-matched case-control study, Hsieh et al[93] found no association between intraoperative hypotension and perioperative stroke. Hypotension was measured as the time-integrated area under a mean arterial pressure (MAP) of 70 mm Hg; as such, both depth and duration of MAP <70 mm Hg were measured. The median (first quartile, third quartile) values were 19 (4, 55) mm Hg-minutes in stroke cases and 19 (6, 48) mm Hg-minutes in controls. Regression modeling demonstrated no association between time-integrated area under the curve (MAP <70 mm Hg) in stroke patients versus controls (ratio of geometric means = 1.07, 95% CI: 0.76-1.53). Sensitivity analyses with lower MAP thresholds (eg, 65, 60 mm Hg) also demonstrated no association with stroke. The authors concluded that factors other than intraoperative blood pressure probably contribute more to overt postoperative stroke (a conclusion restricted to the institution studied). These findings are similar to a previous retrospective, case-control study conducted by Bijker et al,[94] which investigated the relationship between intraoperative hypotension and stroke in a broad noncardiac, non-neurosurgical population (>48,000 patients). Time spent with MAP >30% below baseline was associated with postoperative stroke (OR = 1.013/min hypotension, 99.9% CI: 1.000-1.025). However, the effect size is of unclear clinical significance, particularly given that no other threshold studied, including time spent with MAP >40% below baseline, was associated with stroke. Thus, routine intraoperative blood pressures (ie, MAPs ≥60 to 70 mm Hg) are unlikely to be a major driver of overt perioperative stroke.

Postural hypotension may also play a role in stroke after noncardiac surgery. As described in previous guidelines, there are case reports of the ischemic brain and spinal cord injury after shoulder surgery in the beach chair position.[95] Such reports, along with changes in cerebral oxygen saturation in the beach chair position,[96,97] have prompted discussion about optimal blood pressure management and cerebrovascular risk.[98] Fortunately, large-scale analyses report that overt stroke risk and severe neurocognitive deficits appear to be rare after shoulder surgery in the beach chair position.[99] Of relevance, a selected cohort study by Laflam et al[100] reported diminished cerebral autoregulation in patients undergoing shoulder surgery in the beach chair position compared with the lateral decubitus position. There were no differences in composite cognitive outcomes or serum ischemic biomarkers between the 2 groups. Nonetheless, covert ischemic injury remains a possibility with beach chair positioning, and future studies with perioperative neuroimaging may be required to further delineate risk of cerebrovascular vulnerability and injury. In this context, blood pressure should be measured with the understanding that a gradient exists between the upper extremity (eg, brachial artery, radial artery) and brain, such that MAP may be 12 to 24 mm Hg lower in the brainstem compared with the nonoperative upper extremity.[6]

Overall, there seems to be a well-defined relationship between mild hypotension and end-organ injury, including acute kidney injury,[101–103] myocardial injury,[102,103] and even mortality.[104] This relationship, unfortunately, remains poorly defined for the central nervous system.

Recommendations

(1) While no specific thresholds are recommended to reduce stroke risk, an effect of relative hypotension cannot be excluded based on current evidence (Level B-NR, Class IIb).
(2) For surgery in the beach chair position, blood pressure measurement should be performed on the nonoperative upper arm (as opposed to lower extremity) and consideration should be given to the blood pressure gradient between the brachial artery and brain (Level C-LD, Class I).
(3) Induced hypotension for shoulder surgery in the beach chair position should always be approached with caution, especially in patients at risk for stroke (Level C-LD, Class I).

Respiratory Physiology and Cerebrovascular Reserve

Although there is some evidence that normocapnia is associated with improved outcomes in patients undergoing intervention for acute ischemic stroke,[105] there are limited data on the interaction between intraoperative $PaCO_2$ or $EtCO_2$ and cerebrovascular reserve. Recent translational investigations have studied computer-controlled changes in $PaCO_2$ in relation to cerebral blood flow and cerebrovascular resistance.[18,19,106,107] Of relevance to the perioperative setting, these studies included older patient populations both with and without cerebrovascular disease. Hypocapnia increases cerebrovascular resistance, and maximal resistance may be achieved with $PaCO_2$ levels that approach 30 mm Hg.[19] Alternatively, hypercapnia may also impair cerebral blood flow in high-risk brain regions via the steal phenomenon, where there is an asymmetric cerebrovascular reserve in parallel vascular beds.[18] As such, the combination of reduced cerebrovascular inflow (eg, hypotension) and impaired vasodilatory reserve (mediated by hypocapnia or hypercapnia), may create conditions for hypoxic-ischemic injury.[18] Interestingly, patients with the steno-occlusive disease who undergo revascularization demonstrate significantly improved white matter cerebrovascular reactivity.[20] Thus, for patients with preexisting cerebrovascular disease, $PaCO_2$ may be relevant for cerebrovascular perfusion, with derangements in $PaCO_2$ reducing cerebrovascular reserve, particular in the setting of hypotension and/or steno-occlusive disease.

Recommendations

In patients at high risk of perioperative stroke, maintaining normocapnia may prevent further risk of cerebrovascular compromise (Level C-LD, Class I).

Hemorrhage and Blood Transfusion

Intraoperative hemorrhage and transfusion have been associated with perioperative stroke. The decision to transfuse packed red blood cells must balance the need to optimize physiological oxygen delivery while minimizing risks associated with transfusions. Reduced serum hemoglobin concentration, and thus arterial oxygen content, leads to reduced cerebral oxygenation and increased markers of brain tissue hypoxia.[108,109] Hemorrhage and anemia may thus predispose to cerebral hypoxic-ischemic injury. Conversely, transfusion itself may increase stroke risk via distinct pathways, such as red blood cell aggregation, increased thrombogenic potential, and impaired microcirculation.[110–112] Indeed, large-scale observational data demonstrate an increased association between transfusion and perioperative stroke, even after adjusting for relevant clinical and physiological confounders.[113–116] Important caveats do apply with such retrospective, observational analyses. Detailed clinical data, such as transfusion thresholds, hemodynamic function, and indications for transfusion, are often unavailable.[114] Baseline imbalance may be present between groups, particularly with respect to comorbidities, blood loss, and preoperative hemoglobin, though associations remain present despite propensity score matching for relevant confounders.[115] Of note, tranexamic acid is used to reduce blood loss and transfusion requirements across broad surgical populations without evidence of increased stroke risk.[117–119]

Lastly, as mentioned in the prior consensus statement,[6] a retrospective, observational study involving >44,000 noncardiac surgery patients demonstrated an increased risk of stroke as postoperative hemoglobin decreased <9 g/dL.[120] Mechanistic studies suggest that reduced cardiac output, combined with impaired $beta_2$-mediated cerebrovascular vasodilatation, may reduce cerebral blood flow and oxygen delivery.[121,122]

Recommendations

For noncardiac, non-neurological surgical in patients already taking a beta-blocker, a relatively high transfusion threshold (hemoglobin 9.0 g/dL) may reduce perioperative stroke risk (Level B-NR, Class IIb).

Glycemic Management

Perioperative stroke is more likely to be associated with an elevated fasting blood sugar than nonoperative stroke,[15] and vascular surgery patients with perioperative hyperglycemia (glucose >180 mg/dL within 72 h of surgery) have a higher perioperative stroke risk than normoglycemic patients, particularly those not previously identified as being diabetic.[123] Both a history of diabetes and elevated blood glucose are associated with poor clinical outcomes in patients undergoing thrombolysis for acute ischemic stroke,[124] though hyperglycemia in this setting may be indicative of stroke severity rather than the cause of injury. Extrapolating from these data, it seems intuitive that perioperative glycemic control is desirable, but the optimal glucose range is not yet defined. The recent SHINE Trial[125] compared standard (sliding scale insulin, mean glucose 179 mg/dL) and intensive (insulin infusion, mean glucose 118 mg/dL) insulin therapy for 1151 acute ischemic stroke patients who were hyperglycemic at admission. Results from this study of nonoperative stroke in the community demonstrated no benefit of intensive therapy on outcomes at 90 days poststroke; in fact, hypoglycemia and other adverse events were more common in the intensive treatment group (11.2%) compared with the standard treatment group (3.2%), and severe hypoglycemia only occurred in the intensive treatment group (2.6%). Of note, however, the mean glucose level was still <180 mg/dL in both groups.

Recommendations

(1) Treat hyperglycemia to maintain serum glucose between 130 and 180 mg/dL (Level B-NR, Class IIa).
(2) Intensive efforts to maintain tight control of serum glucose (eg, <130 mg/dL) may result in hypoglycemia and related adverse events (Level B-R, Class III: Harm).

Intraoperative Beta-blockade

As discussed in previous guidelines,[6] intraoperative metoprolol administration has been associated with an increased risk of perioperative stroke (OR = 3.3, 95% CI: 1.4-7.8, $P = 0.003$).[76] This was based on a single-center, retrospective analysis of >57,000 noncardiac surgery patients, and the association between intraoperative metoprolol and stroke was based on an unadjusted, univariate analysis. However, no such association was found for other intraoperative beta-blockers studied. Furthermore, no colinearity existed between intraoperative metoprolol administration and hypotension. Mechanistically, animal data suggest that metoprolol, as a relatively nonselective $beta_1$-antagonist, may reduce brain tissue oxygenation by impairing $beta_2$-mediated cerebral vasodilation in mice.[121] There have otherwise been no updates with respect to intraoperative beta-blocker use and stroke risk since the previous consensus statement.[6]

Recommendations

Intraoperative metoprolol has been associated with perioperative stroke; alternative intraoperative beta-blockers may be reasonable for avoiding an increased risk of stroke (Level C-LD, Class IIb).

POSTOPERATIVE GUIDELINES

Stroke Team, Networks, and Triage

Rapid recognition, communication, and timely management are imperative for optimizing outcomes related to acute stroke. Indeed, the American Heart Association/American Stroke Association Guidelines recommend an organized protocol for emergency evaluation of patients with a suspected stroke.[9] This is particularly important given that stroke in hospitalized patients is associated with

delayed recognition, infrequent intervention, and poor outcomes.[4,5] Institutional pathways can promote higher efficiency, rapid therapeutic intervention, and reliable communication pertinent to optimizing patient care.[126] Stand-alone facilities without access to stroke teams or emergency brain imaging should have an established protocol for rapidly transferring potential perioperative stroke patients to the most appropriate stroke center. Potential resources to guide the choice of transfer facility include telestroke networks and stroke severity scales.[9]

Recommendations

An organized protocol for emergency evaluation of surgical patients with suspected perioperative stroke is recommended (Level B-NR, Class I).

Assessing Stroke

In 2016, Sun et al[127] performed a systematic review of the clinical diagnostic tools available for perioperative stroke screening. The authors outlined the following characteristics of an ideal perioperative stroke assessment scale: (1) easy to administer, (2) quick, (3) ability to detect neurological deficits that reflect acute cerebrovascular events (validity), (4) ability to distinguish from confounding factors, like residual anesthetics and analgesic effects, (5) simple to use for nonspecialists, and (6) high interrater reliability among observers. In practice, meeting these conditions proves challenging, and there are currently no perioperative stroke assessment scales that satisfy all such criteria. In fact, a recent selected cohort study involving noncardiac surgery patients revealed that modified National Institutes of Health Stroke Scale (mNIHSS) changes are common postoperatively.[128] Approximately 20% to 30% of patients in this cohort were reported to have acute increases in mNIHSS scores within the first 3 postoperative days. This 20% to 30% incidence exceeds the published prevalence of overt stroke by 1 to 2 orders of magnitude (0.1% to 1.9%),[1] and covert stroke (7%)[3] by ~3- to 4-fold. Thus, clinical screening tests will likely generate many false positives and, accordingly, a low positive predictive value. This issue is complicated further by the possibility of unmasking prior neurological deficits in the setting of residual GABAergic anesthetic and sedative medications.[129,130] Such deficits, however, do not necessarily reflect acute ischemic injury. Rather, drugs that potentiate GABAergic transmission may impair adaptive neural mechanisms that compensate for prior, covert deficits from preexisting neuropathology.[131] Thus, current screening assessments for stroke have limited validity in the immediate postoperative setting. Targeted assessments that focus on large-vessel pathology (eg, middle cerebral artery syndrome) may be of greater utility given the (1) distinct, robust pattern of neurological deficits that manifest, and (2) availability of effective neurointerventional therapies, such as endovascular thrombectomy.

Complementary to clinical assessment, biochemical and neurophysiological methods have also been studied for monitoring cerebrovascular vulnerability. Preliminary evidence has suggested that glial fibrillary acid protein may correlate with ischemic injury[132]; however, recent data from a noncardiac surgery cohort study demonstrate wide variability in perioperative glial fibrillary acid protein levels.[128] Furthermore, S-100β, neuron-specific enolase, and matrix metalloproteinase-9 values also vary greatly in the perioperative period and were not significantly elevated in a patient with hypoxic-ischemic injury.[128] In terms of neurophysiology, electroencephalographic slow-wave activity and oscillatory asymmetry correlate with stroke severity and outcomes,[23–25] and high-intensity transient signals from transcranial Doppler analysis can detect cerebral emboli.[21,22] However, these measures have not been rigorously tested in noncardiac, nonmajor vascular, or nonneurosurgical patients for the detection of cerebral ischemia.

Immediate diagnostic studies of all patients with suspected stroke should include noncontrast computed tomography (CT) or magnetic resonance imaging of the brain to determine whether the stroke is ischemic or hemorrhagic in origin, and to correlate neurological deficit with radiologic findings.[133] For patients with a significant neurological deficit suggestive of large-vessel occlusion, CT angiography and urgent CT perfusion or diffusion-weighted magnetic resonance imaging should be performed concurrently to facilitate rapid assessment for endovascular thrombectomy. Results from the DAWN[134] and DEFUSE 3[135] trials demonstrated improved functional outcomes in patients who received late endovascular therapy based on perfusion imaging, even with intervention time windows up to 24 hours. Thus, surgical patients with large-vessel occlusion may still benefit from endovascular therapy several hours after time last known well.

Recommendations

(1) Currently available clinical assessment tools (eg, mNIHSS) are not recommended for routine screening given the high likelihood of false-positive results (Level B-NR, Class III: No Benefit).
(2) A targeted postoperative evaluation, which focuses on signs and symptoms of large-vessel occlusion, may be reasonable in high-risk patients (Level C-EO, Class IIb).
(3) Neither serum-based biomarkers (Level B-NR, Class III: No Benefit) nor neurophysiological monitoring (Level C-EO, Class III: No Benefit) are recommended for clinical detection of perioperative cerebral ischemia.
(4) Emergency imaging of the brain is recommended before initiating any specific therapy to treat acute postoperative stroke (Level A, Class I).
(5) For suspected large-vessel occlusion, CT angiography and diffusion/perfusion imaging should be obtained urgently for consideration of endovascular therapy (Level A, Class I).

Acute Interventions for Ischemic Stroke

Many aspects of the management of acute perioperative stroke will mirror therapeutic strategies for ischemic

stroke in nonsurgical settings. Identification of a hemorrhagic stroke with head CT will prompt a distinct pathway of investigation and management, with separate recommendations for blood pressure control.[136,137] Interventions for acute ischemic stroke, such as recombinant tissue plasminogen activator (rtPA) or mechanical thrombectomy, should be considered with a multidisciplinary team that includes stroke neurology, interventional neuroradiology, and the primary surgical service. The risk/benefit balance of therapeutic interventions will vary depending on the patient, severity and location of the stroke, and type of surgical intervention. Intravenous rtPA remains the standard therapy for thrombotic strokes, but it is contraindicated in a number of relevant situations, such as intracranial or spinal surgery within 3 months.[138] Importantly, other major surgery within 14 days is a relative, rather than absolute, contraindication to intravenous rtPA.[138] Data in the postsurgical population are limited, but one retrospective study reported (nonfatal) surgical site hemorrhage in 7 of 49 (14%) patients given rtPA within ten days of surgery.[139]

There is an expanding role for endovascular mechanical thrombectomy in surgical patients. In 2015, 3 separate clinical trials—MR CLEAN,[140] SWIFT PRIME,[141] and REVASCAT[142]—all demonstrated improved functional outcomes, including increased likelihood of independence, in patients randomized to mechanical thrombectomy with retrievable stents. The number needed to treat for reducing disability (based on modified Rankin Score) is 2.6 based on pooled analysis from recent trials.[143] In addition, as described above, the time window for intervention may be as long as 24 hours after time last known well based on viable penumbra.[144] Thus, for surgical patients with a large thrombus in a major vessel, perfusion imaging and urgent endovascular thrombectomy should be considered. Anesthetic management for these cases is covered by a separate set of SNACC guidelines.[7]

Recommendations

(1) Initiate multidisciplinary discussion regarding the benefits of intravenous rtPA versus risks of hemorrhage for the surgical patient with an acute ischemic stroke (Level C-EO, Class I).
(2) Patients with large-vessel occlusion should receive mechanical thrombectomy as soon as possible if criteria are met (Level A, Class I).

Supportive Care for Acute Ischemic Stroke Patients

The initial management of stroke is usually best achieved in a subspecialty acute care setting such as neurocritical care or stroke unit, as optimizing physiology is critical during acute stroke care. From a cardiovascular standpoint, stroke patients should have cardiac monitoring for at least the first 24 hours, given that arrhythmias are common in the setting of stroke.[9] Myocardial ischemia and cardiac arrhythmias are potential sequelae of acute cerebrovascular events, and systemic hypertension is common after stroke. Common postoperative conditions that may contribute to hypertension include stress response to surgery, pain, and nausea, and these should be managed accordingly. Unless the patient is eligible for acute reperfusion intervention, systolic blood pressure is usually treated only if it is >220 mm Hg, and diastolic pressure is treated only if it is >120 mm Hg, though the benefits of targeting these parameters remain uncertain.[9] In patients who receive rtPA (intravenous or intra-arterial), systolic blood pressure >180 mm Hg and diastolic pressure >105 mm Hg should be treated with antihypertensive drugs such as labetolol or nicardipine.[9] Recommendations for thrombectomy patients are the same, largely because many patients in clinical trials also received rtPA and the trial protocols were written with this in mind. Hypotension during a stroke can also significantly worsen outcomes,[145–148] and mortality risk may follow a U-shaped pattern, whereby incremental reductions (and increases) in blood pressure from a systolic blood pressure of 130 mm Hg may be associated with increased mortality.[148] Ideal blood pressure thresholds during cerebral ischemia are unknown, but physiological derangements that contribute to hypotension (eg, hypovolemia, unstable arrhythmias) should be corrected as soon as possible. These blood pressure considerations should also be appreciated intraoperatively for stroke patients requiring incidental surgery. Blood pressure management during acute interventions, such as endovascular thrombectomy, is reviewed separately.[7]

Hypoxia is associated with poor neurological outcomes,[149] and patients should, therefore, be monitored with pulse oximetry during acute stroke. Although there is no benefit to supplemental oxygen in nonhypoxic stroke patients,[150] it should be used when needed to maintain SaO_2 saturation $>94\%$.[9] Patients with depressed levels of consciousness (Glasgow Coma Scale <8), signs of brainstem dysfunction, or inability to protect the airway should be intubated and mechanically ventilated. These interventions may also be helpful in the management of increased intracranial pressure or for those who have suspected malignant brain edema. In addition, hyperthermia, hypothermia, and both hyperglycemia and hypoglycemia are all linked with adverse outcomes in acute stroke and should be avoided or rapidly corrected.[151,152]

Lastly, oral administration of aspirin (the initial dose is 325 mg) within 24 to 48 hours after stroke onset is recommended but is not a substitute for other acute interventions such as rtPA or thrombectomy.[153] Furthermore, the administration of aspirin (or other antiplatelet agents) as an adjunctive therapy within 24 hours of intravenous fibrinolysis is usually avoided unless there is a high risk of interrupting antiplatelet therapy.[9] Urgent anticoagulation with the goal of preventing early recurrent stroke, halting neurological deterioration, or improving outcomes after ischemic stroke is not recommended, nor is the initiation of anticoagulation therapy within 24 hours of treatment with intravenous rtPA.[9]

Recommendations

(1) Baseline electrocardiogram (Level B-NR, Class I) and troponin assessments (Level C-LD, Class I) are recommended.

(2) Cardiac telemetry monitoring is recommended to detect potentially deleterious arrhythmias for at least the first 24 hours (Level B-NR, Class I).
(3) In patients who receive rtPA (intravenous or intra-arterial) or undergo mechanical clot retrieval, systolic blood pressure > 180 mm Hg and diastolic pressure > 105 mm Hg should be treated with antihypertensive drugs such as labetolol or nicardipine (Level B-NR, Class I).
(4) Relative hypotension should be avoided in acute ischemic stroke patients, though optimal blood pressure targets have not been established (Level C-EO, Class I).
(5) Aspirin is generally recommended within 24 to 48 hours after stroke onset. The administration is delayed until at least 24 hours in patients treated with IV alteplase (Level A, Class I).
(6) Supplemental oxygen should be provided to maintain oxygen saturation > 94% (Level C-LD, Class I).
(7) Tracheal intubation and mechanical ventilation are recommended in patients with decreased consciousness or bulbar dysfunction that causes a compromise of respiration (Level C-EO, Class I).
(8) Both hypoglycemia and hyperglycemia should be treated with a goal of 140 to 180 mg/dL (Level C-LD, Class IIa).

CONCLUSIONS

Stroke is a potentially devastating complication for surgical patients. In addition to the considerable morbidity and mortality associated with perioperative stroke, the incidence may also be underappreciated. Age, prior cerebrovascular disease history, and renal dysfunction are all risk factors for perioperative stroke. Large-scale population analysis suggests that elective surgeries should be deferred until at least 9 months after a prior stroke. In terms of anticoagulation, bridging therapy should be reserved for moderate-to-high-risk patients receiving vitamin K antagonists, and bridging should be deferred for patients on direct oral anticoagulants. Neither clinical assessment tools nor serum-based biomarkers are currently recommended for routine screening in the perioperative setting due to limited positive predictive value and validity. When a stroke is suspected, however, urgent neuroimaging should be obtained, and perfusion-guided imaging can guide the decision-making process for endovascular thrombectomy. Multidisciplinary protocols should also be implemented for the triage and management of patients with perioperative ischemic stroke. Looking ahead, further investigation is required to: (1) advance pathophysiological understanding of perioperative stroke, (2) create updated, comprehensive risk prediction models, (3) advance understanding and optimization of the perioperative cerebrovascular reserve, and (4) develop validated screening and monitoring strategies perioperatively.

REFERENCES

1. Mashour GA, Shanks AM, Kheterpal S. Perioperative stroke and associated mortality after noncardiac, nonneurologic surgery. *Anesthesiology*. 2011;114:1289–1296.
2. Smilowitz NR, Gupta N, Ramakrishna H, et al. Perioperative major adverse cardiovascular and cerebrovascular events associated with noncardiac surgery. *JAMA Cardiol*. 2017;2:181–187.
3. The NeuroVISION Investigators. Perioperative covert stroke in patients undergoing non-cardiac surgery (NeuroVISION): a prospective cohort study. *Lancet*. 2019;394:1022–1029.
4. Saltman AP, Silver FL, Fang J, et al. Care and outcomes of patients with in-hospital stroke. *JAMA Neurol*. 2015;72:749–755.
5. Vlisides PE, Mashour GA, Didier TJ, et al. Recognition and management of perioperative stroke in hospitalized patients. *A A Case Rep*. 2016;7:55–56.
6. Mashour GA, Moore LE, Lele AV, et al. 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.
7. Talke PO, Sharma D, Heyer EJ, et al. Society for Neuroscience in Anesthesiology and Critical Care Expert Consensus Statement: anesthetic management of endovascular treatment for acute ischemic stroke: endorsed by the Society of Neurointerventional Surgery and the Neurocritical Care Society. *J Neurosurg Anesthesiol*. 2014;26:95–108.
8. Halperin JL, Levine GN, Al-Khatib SM, et al. Further evolution of the ACC/AHA clinical practice guideline recommendation classification system: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation*. 2016;133:1426–1428.
9. Powers WJ, Rabinstein AA, Ackerson T, et al. 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. *Stroke*. 2019;50:e344–e418.
10. Fleisher LA, Fleischmann KE, Auerbach AD, et al. ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Aeart Association task force on practice guidelines. *Circulation*. 2014;130:e278–e333.
11. Guyatt GH, Oxman AD, Vist GE, et al. Grade: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924–926.
12. Grau AJ, Eicke M, Burmeister C, et al. Risk of ischemic stroke and transient ischemic attack is increased up to 90 days after non-carotid and non-cardiac surgery. *Cerebrovasc Dis*. 2017;43:242–249.
13. Ng PY, Ng AK, Subramaniam B, et al. Association of preoperatively diagnosed patent foramen ovale with perioperative ischemic stroke. *JAMA*. 2018;319:452–462.
14. 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.
15. Dong Y, Cao W, Cheng X, et al. Risk factors and stroke characteristic in patients with postoperative strokes. *J Stroke Cerebrovasc Dis*. 2017;26:1635–1640.
16. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. Toast. Trial of org 10172 in acute stroke treatment. *Stroke*. 1993;24:35–41.
17. Bamford J, Sandercock P, Dennis M, et al. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet*. 1991;337:1521–1526.
18. Fisher JA, Venkatraghavan L, Mikulis DJ. Magnetic resonance imaging-based cerebrovascular reactivity and hemodynamic reserve. *Stroke*. 2018;49:2011–2018.
19. McKetton L, Cohn M, Tang-Wai DF, et al. Cerebrovascular resistance in healthy aging and mild cognitive impairment. *Front Aging Neurosci*. 2019;11:79.
20. McKetton L, Venkatraghavan L, Rosen C, et al. Improved white matter cerebrovascular reactivity after revascularization in patients with steno-occlusive disease. *AJNR Am J Neuroradiol*. 2019;40:45–50.

21. Sliwka U, Job FP, Wissuwa D, et al. Occurrence of transcranial Doppler high-intensity transient signals in patients with potential cardiac sources of embolism. A prospective study. *Stroke*. 1995;26:2067–2070.
22. Niesen WD, Sliwka U, Lingnau A, et al. Cerebral emboli in cryptogenic ischemia: a reason to enforce diagnostic testing. *J Stroke Cerebrovasc Dis*. 2001;10:44–48.
23. Jordan KG. Emergency EEG and continuous EEG monitoring in acute ischemic stroke. *J Clin Neurophysiol*. 2004;21:341–352.
24. van Putten MJ, Tavy DL. Continuous quantitative EEG monitoring in hemispheric stroke patients using the brain symmetry index. *Stroke*. 2004;35:2489–2492.
25. Van Kaam RC, van Putten M, Vermeer SE, et al. Contralesional brain activity in acute ischemic stroke. *Cerebrovasc Dis*. 2018;45:85–92.
26. Jørgensen ME, Torp-Pedersen C, Gislason GH, et al. Time elapsed after ischemic stroke and risk of adverse cardiovascular events and mortality following elective noncardiac surgery. *JAMA*. 2014;312:269–277.
27. Bateman BT, Schumacher HC, Wang S, et al. Perioperative acute ischemic stroke in noncardiac and nonvascular surgery: incidence, risk factors, and outcomes. *Anesthesiology*. 2009;110:231–238.
28. Sharifpour M, Moore LE, Shanks AM, et al. Incidence, predictors, and outcomes of perioperative stroke in noncarotid major vascular surgery. *Anesth Analg*. 2013;116:424–434.
29. Wilcox T, Smilowitz NR, Xia Y, et al. Cardiovascular risk scores to predict perioperative stroke in noncardiac surgery. *Stroke*. 2019;50:2002–2006.
30. Gupta PK, Gupta H, Sundaram A, et al. Development and validation of a risk calculator for prediction of cardiac risk after surgery. *Circulation*. 2011;124:381–387.
31. Bilimoria KY, Liu Y, Paruch JL, et al. 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.e1–842.e3.
32. Kamel H, Johnston SC, Kirkham JC, et al. Association between major perioperative hemorrhage and stroke or q-wave myocardial infarction. *Circulation*. 2012;126:207–212.
33. Jamjoom AA, White S, Walton SM, et al. Anaesthetists' and surgeons' attitudes towards informed consent in the UK: an observational study. *BMC Med Ethics*. 2010;11:2.
34. Burkle CM, Pasternak JJ, Armstrong MH, et al. Patient perspectives on informed consent for anaesthesia and surgery: American attitudes. *Acta Anaesthesiol Scand*. 2013;57:342–349.
35. Sewell D, Gelb AW, Meng L, et al. Anesthesiologists' perception of perioperative stroke risk during non-neurologic and non-cardiac surgery. *Can J Anaesth*. 2018;65:225–226.
36. Roughead T, Chui J, Gelb AW, et al. Knowledge and perceptions about perioperative stroke: a cross-sectional survey of patients scheduled for non-neurologic and non-cardiac surgery. *Can J Anaesth*. 2020;67:13–21.
37. Aries MJ, Elting JW, De Keyser J, et al. Cerebral autoregulation in stroke: a review of transcranial Doppler studies. *Stroke*. 2010;41:2697–2704.
38. Aoi MC, Hu K, Lo MT, et al. Impaired cerebral autoregulation is associated with brain atrophy and worse functional status in chronic ischemic stroke. *PLoS One*. 2012;7:e46794.
39. Molina C, Sabin JA, Montaner J, et al. Impaired cerebrovascular reactivity as a risk marker for first-ever lacunar infarction: a case-control study. *Stroke*. 1999;30:2296–2301.
40. Yamauchi H, Higashi T, Kagawa S, et al. Is misery perfusion still a predictor of stroke in symptomatic major cerebral artery disease? *Brain*. 2012;135:2515–2526.
41. Yamauchi H, Fukuyama H, Nagahama Y, et al. Evidence of misery perfusion and risk for recurrent stroke in major cerebral arterial occlusive diseases from PET. *J Neurol Neurosurg Psychiatry*. 1996;61:18–25.
42. Yamauchi H, Fukuyama H, Fujimoto N, et al. Significance of low perfusion with increased oxygen extraction fraction in a case of internal carotid artery stenosis. *Stroke*. 1992;23:431–432.
43. Jorgensen ME, Gislason GH, Andersson C. Time since stroke and risk of adverse outcomes after surgery—reply. *JAMA*. 2014;312:1930–1931.
44. Christiansen MN, Andersson C, Gislason GH, et al. 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.
45. Horner MA, Duane TM, Ehlers AP, et al. American College of Surgeons' guidelines for the perioperative management of antithrombotic medication. *J Am Coll Surg*. 2018;227:521.e1–536.e1.
46. Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. *N Engl J Med*. 2015;373:823–833.
47. Siegal D, Yudin J, Kaatz S, et al. Periprocedural heparin bridging in patients receiving vitamin K antagonists: systematic review and meta-analysis of bleeding and thromboembolic rates. *Circulation*. 2012;126:1630–1639.
48. Garcia D, Alexander JH, Wallentin L, et al. Management and clinical outcomes in patients treated with apixaban vs warfarin undergoing procedures. *Blood*. 2014;124:3692–3698.
49. Halperin JL, Hankey GJ, Wojdyla DM, et al. Efficacy and safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in the rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF). *Circulation*. 2014;130:138–146.
50. Douketis JD, Healey JS, Brueckmann M, et al. Perioperative bridging anticoagulation during dabigatran or warfarin interruption among patients who had an elective surgery or procedure. Substudy of the RE-LY trial. *Thromb Haemost*. 2015;113:625–632.
51. Beyer-Westendorf J, Gelbricht V, Forster K, et al. Peri-interventional management of novel oral anticoagulants in daily care: results from the prospective Dresden NOAC registry. *Eur Heart J*. 2014;35:1888–1896.
52. Macle L, Cairns J, Leblanc K, et al. 2016 focused update of the Canadian Cardiovascular Society guidelines for the management of atrial fibrillation. *Can J Cardiol*. 2016;32:1170–1185.
53. Doherty JU, Gluckman TJ, Hucker WJ, et al. 2017 ACC expert consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation: a report of the American College of Cardiology clinical expert consensus document task force. *J Am Coll Cardiol*. 2017;69:871–898.
54. Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: a ntithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141:e326S–e350S.
55. Darvish-Kazem S, Douketis JD. Perioperative management of patients having noncardiac surgery who are receiving anticoagulant or antiplatelet therapy: an evidence-based but practical approach. *Semin Thromb Hemost*. 2012;38:652–660.
56. Lip GY, Nieuwlaat R, Pisters R, et al. 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.
57. Douketis JD, Spyropoulos AC, Duncan J, et al. Perioperative management of patients with atrial fibrillation receiving a direct oral anticoagulant. *JAMA Intern Med*. 2019;179:1469–1478.
58. Graham MM, Sessler DI, Parlow JL, et al. Aspirin in patients with previous percutaneous coronary intervention undergoing noncardiac surgery. *Ann Intern Med*. 2018;168:237–244.
59. Biccard BM, Sigamani A, Chan MTV, et al. Effect of aspirin in vascular surgery in patients from a randomized clinical trial (POISE-2). *Br J Surg*. 2018;105:1591–1597.
60. Wolff G, Navarese EP, Brockmeyer M, et al. Perioperative aspirin therapy in non-cardiac surgery: a systematic review and meta-analysis of randomized controlled trials. *Int J Cardiol*. 2018;258:59–67.
61. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: pulmonary embolism prevention (PEP) trial. *Lancet*. 2000;355:1295–1302.
62. Devereaux PJ, Mrkobrada M, Sessler DI, et al. Aspirin in patients undergoing noncardiac surgery. *N Engl J Med*. 2014;370:1494–1503.

63. Columbo JA, Lambour AJ, Sundling RA, et al. A meta-analysis of the impact of aspirin, clopidogrel, and dual antiplatelet therapy on bleeding complications in noncardiac surgery. *Ann Surg*. 2018;267:1–10.
64. Goes R, Muskens IS, Smith TR, et al. Risk of aspirin continuation in spinal surgery: a systematic review and meta-analysis. *Spine J*. 2017;17:1939–1946.
65. Lewis SR, Pritchard MW, Schofield-Robinson OJ, et al. Continuation versus discontinuation of antiplatelet therapy for bleeding and ischaemic events in adults undergoing non-cardiac surgery. *Cochrane Database Syst Rev*. 2018;7:Cd012584.
66. Wijeysundera DN, Duncan D, Nkonde-Price C, et al. Perioperative beta blockade in noncardiac surgery: a systematic review for the 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;130:2246–2264.
67. Devereaux PJ, Yang H, Yusuf S, 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.
68. Jorgensen ME, Hlatky MA, Kober L, et al. Beta-blocker-associated risks in patients with uncomplicated hypertension undergoing noncardiac surgery. *JAMA Intern Med*. 2015;175:1923–1931.
69. Jorgensen ME, Sanders RD, Kober L, 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.
70. Park J, Kim J, Kwon JH, et al. Association between perioperative beta-blocker use and clinical outcome of non-cardiac surgery in coronary revascularized patients without severe ventricular dysfunction or heart failure. *PLoS One*. 2018;13:e0201311.
71. Richman JS, Graham LA, DeRussy A, et al. Perioperative beta blockers and statins for noncardiac surgery patients with coronary stents. *Am J Surg*. 2017;214:180–185.
72. Chen RJ, Chu H, Tsai LW. Impact of beta-blocker initiation timing on mortality risk in patients with diabetes mellitus undergoing noncardiac surgery: a nationwide population-based cohort study. *J Am Heart Assoc*. 2017;6:e004392.
73. London MJ, Schwartz GG, Hur K, et al. Association of perioperative statin use with mortality and morbidity after major noncardiac surgery. *JAMA Intern Med*. 2017;177:231–242.
74. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation*. 1999;100:1043–1049.
75. Ma B, Sun J, Diao S, et al. Effects of perioperative statins on patient outcomes after noncardiac surgery: a meta-analysis. *Ann Med*. 2018;50:402–409.
76. Mashour GA, Sharifpour M, Freundlich RE, et al. Perioperative metoprolol and risk of stroke after noncardiac surgery. *Anesthesiology*. 2013;119:1340–1346.
77. Sgroi MD, McFarland G, Mell MW. Utilization of regional versus general anesthesia and its impact on lower extremity bypass outcomes. *J Vasc Surg*. 2019;69:1874–1879.
78. Smith PE, Hade EM, Tan Y, et al. Mode of anesthesia and major perioperative outcomes associated with vaginal surgery. *Int Urogynecol J*. 2020;31:181–189.
79. Memtsoudis SG, Sun X, Chiu YL, et al. Perioperative comparative effectiveness of anesthetic technique in orthopedic patients. *Anesthesiology*. 2013;118:1046–1058.
80. Richman JM, Rowlingson AJ, Maine DN, et al. Does neuraxial anesthesia reduce intraoperative blood loss? A meta-analysis. *J Clin Anesth*. 2006;18:427–435.
81. Hu S, Zhang ZY, Hua YQ, et al. A comparison of regional and general anaesthesia for total replacement of the hip or knee: a meta-analysis. *J Bone Joint Surg Br*. 2009;91:935–942.
82. Landoni G, Lomivorotov VV, Nigro Neto C, et al. Volatile anesthetics versus total intravenous anesthesia for cardiac surgery. *N Engl J Med*. 2019;380:1214–1225.
83. Bucerius J, Gummert JF, Borger MA, et al. Stroke after cardiac surgery: a risk factor analysis of 16,184 consecutive adult patients. *Ann Thorac Surg*. 2003;75:472–478.
84. Badner NH, Drader K, Freeman D, et al. The use of intraoperative nitrous oxide leads to postoperative increases in plasma homocysteine. *Anesth Analg*. 1998;87:711–713.
85. Myles PS, Chan MT, Leslie K, et al. Effect of nitrous oxide on plasma homocysteine and folate in patients undergoing major surgery. *Br J Anaesth*. 2008;100:780–786.
86. Haelewyn B, David HN, Colloc'h N, et al. Interactions between nitrous oxide and tissue plasminogen activator in a rat model of thromboembolic stroke. *Anesthesiology*. 2011;115:1044–1053.
87. Leslie K, Myles PS, Chan MT, et al. Nitrous oxide and long-term morbidity and mortality in the enigma trial. *Anesth Analg*. 2011; 112:387–393.
88. Sanders RD, Graham C, Lewis SC, et al. Nitrous oxide exposure does not seem to be associated with increased mortality, stroke, and myocardial infarction: a non-randomized subgroup analysis of the general anaesthesia compared with local anaesthesia for carotid surgery (GALA) trial. *Br J Anaesth*. 2012;109:361–367.
89. Leslie K, Myles PS, Kasza J, 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.
90. Leslie K, Myles P, Devereaux PJ, et al. Nitrous oxide and serious morbidity and mortality in the poise trial. *Anesth Analg*. 2013; 116:1034–1040.
91. Ono M, Brady K, Easley RB, et al. Duration and magnitude of blood pressure below cerebral autoregulation threshold during cardiopulmonary bypass is associated with major morbidity and operative mortality. *J Thorac Cardiovasc Surg*. 2014;147:483–489.
92. Sun LY, Chung AM, Farkouh ME, et al. Defining an intraoperative hypotension threshold in association with stroke in cardiac surgery. *Anesthesiology*. 2018;129:440–447.
93. Hsieh JK, Dalton JE, Yang D, et al. The association between mild intraoperative hypotension and stroke in general surgery patients. *Anesth Analg*. 2016;123:933–939.
94. Bijker JB, Persoon S, Peelen LM, et al. Intraoperative hypotension and perioperative ischemic stroke after general surgery: a nested case-control study. *Anesthesiology*. 2012;116:658–664.
95. Pohl A, Cullen DJ. Cerebral ischemia during shoulder surgery in the upright position: a case series. *J Clin Anesth*. 2005;17:463–469.
96. Songy CE, Siegel ER, Stevens M, et al. The effect of the beach-chair position angle on cerebral oxygenation during shoulder surgery. *J Shoulder Elbow Surg*. 2017;26:1670–1675.
97. Murphy GS, Szokol JW, Marymont JH, et al. Cerebral oxygen desaturation events assessed by near-infrared spectroscopy during shoulder arthroscopy in the beach chair and lateral decubitus positions. *Anesth Analg*. 2010;111:496–505.
98. Shear T, Murphy GS. Impact of the beach chair position on cerebral perfusion: what do we know so far? APSF Newsletter 2013;28: 18–20.
99. Salazar D, Hazel A, Tauchen AJ, et al. Neurocognitive deficits and cerebral desaturation during shoulder arthroscopy with patient in beach-chair position: a review of the current literature. *Am J Orthop (Belle Mead NJ)*. 2016;45:E63–E68.
100. Laflam A, Joshi B, Brady K, et al. Shoulder surgery in the beach chair position is associated with diminished cerebral autoregulation but no differences in postoperative cognition or brain injury biomarker levels compared with supine positioning: the Anesthesia Patient Safety Foundation beach chair study. *Anesth Analg*. 2015;120:176–185.
101. Sun LY, Wijeysundera DN, Tait GA, et al. Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. *Anesthesiology*. 2015;123:515–523.
102. Ahuja S, Mascha EJ, Yang D, et al. Associations of intraoperative radial arterial systolic, diastolic, mean, and pulse pressures with myocardial and acute kidney injury after noncardiac surgery: a retrospective cohort analysis. *Anesthesiology*. 2020;132:291–306.
103. Salmasi V, Maheshwari K, Yang D, et al. 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.

104. Monk TG, Bronsert MR, Henderson WG, et al. Association between intraoperative hypotension and hypertension and 30-day postoperative mortality in noncardiac surgery. *Anesthesiology*. 2015;123:307–319.
105. Athiraman U, Sultan-Qurraie A, Nair B, et al. Endovascular treatment of acute ischemic stroke under general anesthesia: predictors of good outcome. *J Neurosurg Anesthesiol*. 2018;30: 223–230.
106. Willie CK, Tzeng YC, Fisher JA, et al. Integrative regulation of human brain blood flow. *J Physiol*. 2014;592:841–859.
107. McKetton L, Sobczyk O, Duffin J, et al. The aging brain and cerebrovascular reactivity. *Neuroimage*. 2018;181:132–141.
108. Duffin J, Hare GMT, Fisher JA. A mathematical model of cerebral blood flow control in anaemia and hypoxia. *J Physiol*. 2020;598: 717–730.
109. Mistry N, Mazer CD, Sled JG, et al. Red blood cell antibody-induced anemia causes differential degrees of tissue hypoxia in kidney and brain. *Am J Physiol Regul Integr Comp Physiol*. 2018;314:R611–R622.
110. Zecher D, Cumpelik A, Schifferli JA. Erythrocyte-derived microvesicles amplify systemic inflammation by thrombin-dependent activation of complement. *Arterioscler Thromb Vasc Biol*. 2014;34:313–320.
111. Hovav T, Yedgar S, Manny N, et al. Alteration of red cell aggregability and shape during blood storage. *Transfusion*. 1999;39:277–281.
112. Tsai AG, Cabrales P, Intaglietta M. Microvascular perfusion upon exchange transfusion with stored red blood cells in normovolemic anemic conditions. *Transfusion*. 2004;44:1626–1634.
113. Moore LE, Sferra JJ, Engoren M. Timing and risk factors associated with postoperative stroke in vascular surgery patients using time-varying coefficients from a cox model. *Anesth Analg*. 2020;130:673–684.
114. Whitlock EL, Kim H, Auerbach AD. Harms associated with single unit perioperative transfusion: retrospective population based analysis. *BMJ*. 2015;350:H3037.
115. Valentijn TM, Hoeks SE, Bakker EJ, et al. The impact of perioperative red blood cell transfusions on postoperative outcomes in vascular surgery patients. *Ann Vasc Surg*. 2015;29:511–519.
116. Rubinstein C, Davenport DL, Dunnagan R, et al. Intraoperative blood transfusion of one or two units of packed red blood cells is associated with a fivefold risk of stroke in patients undergoing elective carotid endarterectomy. *J Vasc Surg*. 2013;57:53S–57S.
117. Dastrup A, Pottegard A, Hallas J, et al. Perioperative tranexamic acid treatment and risk of cardiovascular events or death after total hip arthroplasty: a population-based cohort study from national danish databases. *J Bone Joint Surg Am*. 2018;100:1742–1749.
118. Myles PS, Smith JA, Forbes A, et al. Tranexamic acid in patients undergoing coronary-artery surgery. *N Engl J Med*. 2017;376: 136–148.
119. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. *Lancet*. 2019;394:1713–1723.
120. Ashes C, Judelman S, Wijeysundera DN, et al. Selective β1-antagonism with bisoprolol is associated with fewer postoperative strokes than atenolol or metoprolol: a single-center cohort study of 44,092 consecutive patients. *Anesthesiology*. 2013;119:777–787.
121. El Beheiry MH, Heximer SP, Voigtlaender-Bolz J, et al. Metoprolol impairs resistance artery function in mice. *J Appl Physiol*. 2011;111: 1125–1133.
122. Ragoonanan TE, Beattie WS, Mazer CD, et al. Metoprolol reduces cerebral tissue oxygen tension after acute hemodilution in rats. *Anesthesiology*. 2009;111:988–1000.
123. Long CA, Fang ZB, Hu FY, et al. Poor glycemic control is a strong predictor of postoperative morbidity and mortality in patients undergoing vascular surgery. *J Vasc Surg*. 2019;69:1219–1226.
124. Desilles JP, Meseguer E, Labreuche J, et al. Diabetes mellitus, admission glucose, and outcomes after stroke thrombolysis: a registry and systematic review. *Stroke*. 2013;44:1915–1923.
125. Johnston KC, Bruno A, Pauls Q, et al. Intensive vs standard treatment of hyperglycemia and functional outcome in patients with acute ischemic stroke: the SHINE randomized clinical trial. *JAMA*. 2019;322:326–335.
126. Xian Y, Xu H, Lytle B, et al. Use of strategies to improve door-to-needle times with tissue-type plasminogen activator in acute ischemic stroke in clinical practice: findings from Target: Stroke. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003227.
127. Sun Z, Yue Y, Leung CC, et al. Clinical diagnostic tools for screening of perioperative stroke in general surgery: a systematic review. *Br J Anaesth*. 2016;116:328–338.
128. Vlisides PE, Kunkler B, Thompson A, et al. Cerebrovascular disease and perioperative neurologic vulnerability: a prospective cohort study. *Front Neurol*. 2019;10:560.
129. Lazar RM, Berman MF, Festa JR, et al. Gabaergic but not anticholinergic agents re-induce clinical deficits after stroke. *J Neurol Sci*. 2010;292:72–76.
130. Lin N, Han R, Hui X, et al. Midazolam sedation induces upper limb coordination deficits that are reversed by flumazenil in patients with eloquent area gliomas. *Anesthesiology*. 2019;131:36–45.
131. Vlisides PE, Mashour GA. Pharmacologic unmasking of neurologic deficits: a stress test for the brain. *Anesthesiology*. 2019;131:5–6.
132. Rappold T, Laflam A, Hori D, et al. Evidence of an association between brain cellular injury and cognitive decline after non-cardiac surgery. *Br J Anaesth*. 2016;116:83–89.
133. Adams HP Jr, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Circulation*. 2007;115:e478–e534.
134. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. 2018;378:11–21.
135. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. 2018;378:708–718.
136. Connolly ES Jr, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2012;43: 1711–1737.
137. Hemphill JC III, Greenberg SM, Anderson CS, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46: 2032–2060.
138. Demaerschalk BM, Kleindorfer DO, Adeoye OM, et al. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2016;47:581–641.
139. Voelkel N, Hubert ND, Backhaus R, et al. Thrombolysis in postoperative stroke. *Stroke*. 2017;48:3034–3039.
140. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372:11–20.
141. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-Pa vs. t-Pa alone in stroke. *N Engl J Med*. 2015;372:2285–2295.
142. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med*. 2015;372:2296–2306.
143. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387:1723–1731.

144. Jovin TG, Nogueira RG. Thrombectomy 6 to 24 hours after stroke. *N Engl J Med*. 2018;378:1161–1162.
145. Wohlfahrt P, Krajcoviechova A, Jozifova M, et al. Low blood pressure during the acute period of ischemic stroke is associated with decreased survival. *J Hypertens*. 2015;33:339–345.
146. Castillo J, Leira R, Garcia MM, et al. Blood pressure decrease during the acute phase of ischemic stroke is associated with brain injury and poor stroke outcome. *Stroke*. 2004;35:520–526.
147. Stead LG, Gilmore RM, Decker WW, et al. Initial emergency department blood pressure as predictor of survival after acute ischemic stroke. *Neurology*. 2005;65:1179–1183.
148. Vemmos KN, Tsivgoulis G, Spengos K, et al. U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. *J Intern Med*. 2004;255:257–265.
149. Bravata DM, Wells CK, Lo AC, et al. Processes of care associated with acute stroke outcomes. *Arch Intern Med*. 2010;170:804–810.
150. Roffe C, Nevatte T, Sim J, et al. Effect of routine low-dose oxygen supplementation on death and disability in adults with acute stroke: the Stroke Oxygen Study randomized clinical trial. *JAMA*. 2017; 318:1125–1135.
151. Saxena M, Young P, Pilcher D, et al. Early temperature and mortality in critically ill patients with acute neurological diseases: trauma and stroke differ from infection. *Intensive Care Med*. 2015;41:823–832.
152. Wahlgren N, Ahmed N, Eriksson N, et al. Multivariable analysis of outcome predictors and adjustment of main outcome results to baseline data profile in randomized controlled trials: safe implementation of thrombolysis in stroke-monitoring study (SITS-MOST). *Stroke*. 2008;39:3316–3322.
153. Sandercock PA, Counsell C, Tseng MC, et al. Oral antiplatelet therapy for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2014;3:CD000029.