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Stroke in Surgical Patients

A Narrative Review

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ABSTRACT

Stroke is associated with substantial morbidity and mortality. The aim of this review is to provide an evidence-based synthesis of the literature related to perioperative stroke, including its etiology, common risk factors, and potential risk reduction strategies. In addition, the authors will discuss screening methods for the detection of postoperative cerebral ischemia and how multidisciplinary collaborations, including endovascular interventions, should be considered to improve patient outcomes. Lastly, the authors will discuss the clinical and scientific knowledge gaps that need to be addressed to reduce the incidence and improve outcomes after perioperative stroke.

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Postoperative stroke is associated with delayed recognition, infrequent intervention, and high rates of mortality and disability.[1,2] In fact, the risk of death or major disability at discharge exceeds 80% for noncardiac surgery patients, and long-term care is frequently required.[1] Epidemiologic data also suggest that the incidence of perioperative stroke may be increasing.[3] The risk of stroke ranges from approximately 0.1 to 2% depending on risk factors,[4] although clinically unrecognized (*i.e.*, covert) stroke may occur in 7% of noncardiac surgery patients 65 yr and older.[5] Furthermore, those with clinically unrecognized stroke demonstrate an increased risk of long-term cognitive impairment, similar to cognitive declines observed after clinically detected stroke.[5,6] As such, perioperative stroke occurs with considerable frequency and is associated with substantial morbidity and mortality.

Our understanding of perioperative stroke has advanced over recent years. Details regarding stroke etiology and anatomical distributions have been reported,[7–10] and multiple risk prediction models have been developed.[11] Strategies for preoperative optimization have been identified,[12,13] and the role of endovascular thrombectomy has been clarified for patients with large-vessel occlusion.[14–18] Such advances in knowledge have informed and motivated changes to perioperative guidelines, particularly with respect to surgical timing,[19] anticoagulation strategies,[19–21] and acute stroke management.[22] The purpose of this narrative review is to provide evidence-based updates with respect to perioperative stroke, with a focus on the noncardiac surgery setting. Because the majority of perioperative strokes appear to be ischemic,[7–10] ischemic perioperative stroke will be the primary focus of this review. We will also describe the public health consequences of perioperative stroke and areas in need of continued study to aid in the prevention, identification, and optimization of treatment after perioperative stroke to improve patient outcomes.

Definition, Etiology, and Pathophysiology

Stroke is defined as brain cell death attributable to ischemia, based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury.[23] Such an injury may result in considerable clinical deficits. Alternatively, small infarcts may be clinically unrecognizable (*i.e.*, covert stroke), and a transient ischemic attack reflects a temporary period of cerebral ischemia without permanent infarction. For surgical patients, perioperative stroke will be defined as brain infarction that occurs within 30 days of surgery.[24]

The major causes of ischemic stroke include embolism, thrombosis, and decreased perfusion.[25] In this context, classification systems have been created with the objective of categorizing acute ischemic stroke based on etiology and anatomy. The Trial of Org 10172 in Acute Stroke Treatment (TOAST) offers a system for coherently defining stroke subtypes across clinical trials.[26] This system classifies ischemic stroke into large-vessel or small-vessel categories, and cardioembolic causes are differentiated from atherothrombosis. The Oxfordshire Community Stroke Project provides a classification system based on anatomical location and natural history of acute stroke.[27] One advantage to the TOAST system is a more precise classification of etiology, because the Oxfordshire criteria focus more on anatomical location. The Oxfordshire system does, however, provide additional anatomical detail (*e.g.*, anterior, partial anterior, posterior) compared to the TOAST System (table 1).

These classification systems have been applied to perioperative stroke. The majority of perioperative strokes occur in large-vessel territories, with cardioembolism and thrombotic events causing large-vessel occlusion and subsequent

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Table 1. Stroke Subtype Classification Systems

Trial of Org 10172 in Acute Stroke Treatment	Oxfordshire Community Stroke Project
Large-artery atherosclerosis	Total anterior circulation infarct
Cardioembolism	Partial anterior circulation infarct
Small-vessel occlusion	Posterior circulation infarct
Stroke of other determined etiology	Lacunar infarct
Stroke of undetermined etiology	

Table 2. Independent Risk Factors for Perioperative Stroke

Age
Cerebrovascular disease
Valvular disease
Atrial fibrillation
Coronary artery disease
Acute renal failure *or* hemodialysis
Patent foramen ovale
Diabetes mellitus
Hypertension
Chronic obstructive pulmonary disease
Congestive heart failure

stroke.[7–10] In the case of cardioembolism, interruption of anticoagulation therapy increases risk for cerebral embolism formation. Similarly, interruption of antithrombotic medications (*e.g.*, aspirin) can contribute to cerebral thrombosis, particularly given that surgery induces a prothrombotic state,[28] and cessation of antithrombotic therapy can produce rebound hypercoagulability perioperatively.[29] Indeed, risk of perioperative stroke appears highest within the first 3 days after surgery,[8] when anticoagulation and antithrombotic medications are often just being restarted. Although cerebral hypoperfusion may also lead to perioperative stroke, thromboembolic stroke appears to occur more commonly.[8,9] Lastly, etiology remains undetermined in approximately 30% of perioperative stroke cases based on medical record review.[8,9]

Overall, perioperative stroke most often occurs within the first few days after surgery, in large-vessel territories, due to major thromboembolic events. Etiology frequently nonetheless remains unclassifiable, which impedes pathophysiological understanding.

Risk Factors and Incidence

Identifying patients at risk for perioperative stroke requires determination—and recognition—of underlying risk factors. Given the relative rarity of overt perioperative stroke, risk factors have been largely identified from large-scale epidemiologic studies (table 2). Older age and previous cerebrovascular disease history are among the most commonly and strongly identified risk factors. The presence of patent foramen ovale was recently identified as a risk factor at both 30 days and up to 2 yr after surgery.[7,30] For noncardiac, nonneurologic patients with limited risk factors, overt stroke risk is 0.1%.[4] For patients with five or more risk factors undergoing relatively low-risk procedures, stroke risk is 1.9%, on par with the risk of stroke after high-risk procedures such carotid endarterectomy.[31] In a similarly low surgical risk subset of patients over 65 yr, the incidence of covert (clinically unrecognized) stroke diagnosed by postoperative magnetic resonance imaging was 7%.[5] The Neurological Impact of Cerebrovascular Events in Non-Cardiac Surgery Patients Cohort Evaluation (NeuroVISION) study, in addition to demonstrating a surprisingly high incidence of covert stroke, also suggested that covert stroke may have long-term effects on cognition and risk for recurrent ischemic stroke.[5]

As risk factors have been identified and clarified over the years, prediction models have become available for characterizing perioperative stroke risk. A recent observational study compared the effectiveness of existing prediction models, largely based on cardiovascular risk stratification, for predicting perioperative stroke after noncardiac surgery.[11] Results demonstrated that the American College of Surgeons (Chicago, Illinois) surgical risk calculator[32] and Myocardial Infarction or Cardiac Arrest risk score[33] had the highest discriminative ability for perioperative stroke. The Myocardial Infarction or Cardiac Arrest risk score has the additional advantage of simplicity, incorporating only five patient factors while still offering excellent discrimination for stroke.[11] Stroke risk (%) was not reported in relation to specific scores or thresholds for the majority of these prediction tools. However, in general, patients with high cardiovascular risk based on these models are likely to have high stroke risk as well.

Overall, the Myocardial Infarction or Cardiac Arrest and American College of Surgeons surgical risk calculators serve as easily accessible tools for practicing anesthesiologists preparing high-risk patients for surgery. These models could be used to gauge the overall risk of cardiovascular and cerebrovascular events (*i.e.*, *via* myocardial infarction or cardiac arrest or American College of Surgeons surgical risk calculators) alongside complementary models that provide quantitative estimates of stroke risk.[4] This risk assessment is an important message to convey, because high-risk patients are infrequently counseled regarding perioperative stroke risk.[34]

Clinical Resources and Guidelines

There are many resources available to assist with detection and management of stroke. Several screening tools have been developed for nonspecialists, although none of these scales have been validated in the perioperative setting. An ideal perioperative screening tool should be simple to use, quick to administer, and able to detect neurologic deficits in the setting of residual anesthesia and related confounders (*e.g.*, opioid use, pain). One proposed strategy, the Face, Arm, Anesthesia, Speech, Time (FAAST) stroke scale (table 3), aims to fulfill these criteria by focusing on signs

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Table 3. Face, Arm, Anesthesia, Speech, Time (FAAST) Test for Postsurgical Wards

FACE	Uneven smile?
	Facial droop?
ARM	Arm/leg numbness?
	Arm/leg weakness?
	Not due to surgery (limb procedures)?
ANESTHESIA	Residual anesthetic effect?
SPEECH	Slurring speech?
	Difficulty to speak or to understand?
TIME	*Get help immediately – "Time is Brain"*

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and symptoms of major stroke.[35] For example, occlusion of a large cerebral vessel can be detected by arm or leg paralysis, aphasia, and/or facial droop. These signs may be present either individually or collectively during a major stroke. This scale prompts the clinician to evaluate for these signs in a simple, efficient manner. Such a scale could be used in the early postoperative setting and administered by nonspecialist clinicians.

For comprehensive assessment and management, the American Heart Association (Dallas, Texas)/American Stroke Association (Dallas, Texas) publish recurrent guidelines for acute ischemic stroke.[22] Similar guidelines are available from the European Stroke Organisation (Basel, Switzerland)[36,37] and the Heart and Stroke Foundation of Canada (Ottawa, Canada).[38] These guidelines contain evidence-based recommendations for prehospital evaluation, in-hospital management, and prevention of stroke-related complications. These guidelines generally align with one another, with similar recommendations for supportive care and emergency management. They also each recommend intravenous alteplase within 4.5 h if criteria are met, although administration beyond 4.5 h can be considered in select cases. Likewise, mechanical thrombectomy is recommended within 6 h of symptom onset, although specific patients may be eligible for up to 24 h after time last known well. Although these guidelines serve as a useful resource for clinicians caring for stroke patients, perioperative considerations are not discussed in great detail. The Society for Neuroscience in Anesthesiology and Critical Care (Richmond, Virginia) publishes complementary guidelines for patients at high risk of stroke undergoing noncardiac, nonneurologic procedures.[24] The main focus of these guidelines is to provide evidence-based recommendations for reducing stroke risk in surgical patients. Overall, there are thus many resources available for stroke assessment and management in the perioperative setting.

Preoperative Risk Modification

Optimal perioperative care for patients with high stroke risk begins with preoperative evaluation and the informed consent process. Patient survey data suggest that severe complications, even if uncommon, should be discussed.[39] Those with high stroke risk also tend to underestimate their risk of stroke.[40] As such, appropriate counseling for high-risk patients seems warranted to increase risk awareness and improve the informed consent process. Risk prediction models discussed previously can be used to estimate risk for a noncardiac surgery patient.[4,11] In the following paragraphs, we review evidence-based strategies for risk reduction (fig. 1).

Surgical Timing

As discussed above, cerebrovascular disease history is a risk factor for postoperative stroke.[9,12] Previous stroke can impair cerebral autoregulation, and the presence of cerebrovascular disease is associated with increased oxygen extraction and cerebral malperfusion.[41–43] It is thus unsurprising that surgery is associated with new stroke given the physiologic perturbations inherent to the surgical setting. To assess optimal timing between previous ischemic stroke and elective surgery, a retrospective epidemiologic cohort study of more than 480,000 noncardiac surgery patients was conducted using Danish National Patient Register data.[12] Stroke history was associated with new postoperative stroke, and risk was highest within the first 3 months after a previous stroke. Risk then leveled off by 9 months. Important limitations are worth noting. This was a large-scale observational study, and factors other than previous stroke may have driven increased postoperative stroke risk. Previous stroke also predisposes to recurrent risk outside of the surgical setting.[44] The authors addressed this latter possibility by comparing stroke risk in surgical and nonsurgical patients using population data from Denmark. In this analysis, stroke incidence remained higher in surgical patients across each time point studied.[45] As such, surgery seems to impose stroke risk, and delaying elective surgery for at least 9 months after a previous ischemic stroke may be warranted, when possible.[12]

Medication Optimization

Preoperative medication optimization represents one strategy for the mitigating risk of adverse perioperative outcomes. For example, β-blocker therapy can attenuate catecholaminergic tone and, by extension, risk of adverse cardiac events.[46] However, β-adrenergic receptor antagonism can also create conditions for reduced cerebral perfusion pressure by reducing cardiac output and cerebrovascular vasodilatation.[47–49] In the landmark PeriOperative ISchemic Evaluation (POISE) trial, patients randomized to metoprolol demonstrated a significantly higher stroke risk (approximately two-fold) compared to placebo.[46] A follow-up 2014 systematic analysis of nine randomized controlled trials, including POISE, demonstrated that preoperative β blockade initiation was associated with increased risk of nonfatal

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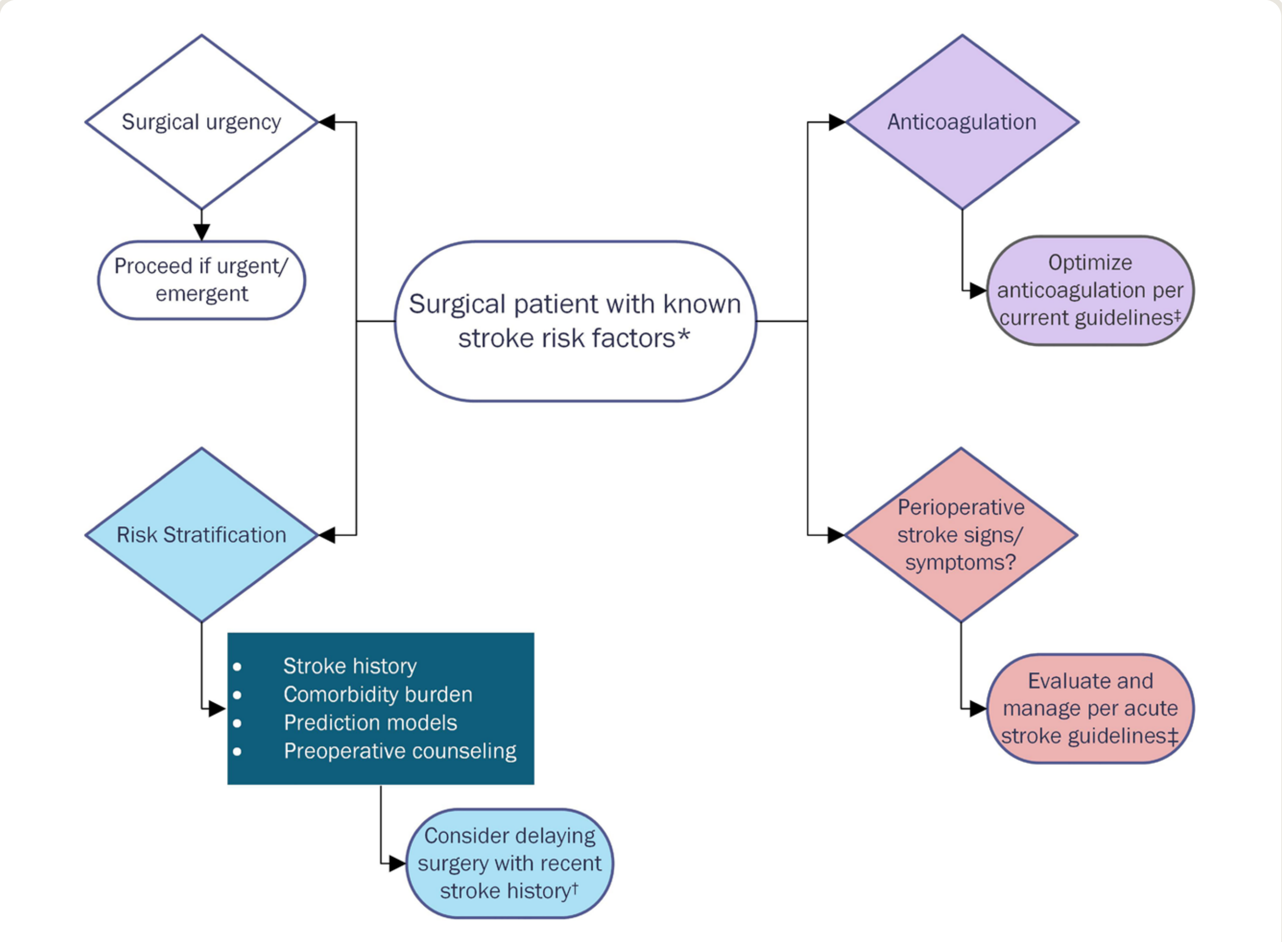

Fig. 1. Proposed framework for evaluating patients with high risk of perioperative stroke. *Independent risk factors have been elucidated across large-scale, epidemiologic studies as described in the text and outlined in table 2. †Longitudinal epidemiologic analysis suggests that risk of new perioperative stroke levels off by approximately 9 months after previous stroke. ‡The Canadian Cardiovascular Society, the American College of Surgeons, and the American College of Cardiology have all published recent anticoagulation guideline updates (see text for references). Likewise, the American Heart Association/American Stroke Association, the European Stroke Association, and Heart and Stroke Foundation of Canada have published recurrent guidelines for the early management of patients with acute ischemic stroke (see text for references).

stroke.[13] These results stand in contrast to observational studies reporting on stroke risk in relation to chronic β blockade. For patients with hypertension,[50] previous coronary revascularization,[51] diabetes mellitus,[52] and multiple cardiovascular risk factors,[53] there does not appear to be an association between chronic β blockade and perioperative stroke. One explanation is that chronic administration allows for appropriate titration. In the POISE trial, patients were started on 200 mg of metoprolol extended release 2 to 4 h before surgery, and daily administration continued postoperatively. Appropriate dose titration over an extended period of time, before surgical interventions, may allow for appropriate dosing and hemodynamic optimization.

Like β blockers, statins have been studied in relation to perioperative cardiovascular and cerebrovascular outcomes. Postulated mechanisms of action include modification of endothelial function,[54] attenuation of inflammatory processes,[55] and increased atherosclerotic plaque stability.[56] These properties are relevant to the perioperative setting, because these mechanisms might reduce atherothrombotic events (*e.g.*, myocardial infarction, stroke) in surgical patients. In 2018, a meta-analysis of 12 randomized controlled trials (2004 to 2017) involving more than 4,700 noncardiac surgery patients was conducted to investigate whether statins improve such perioperative outcomes.[57] Compared to the control arms, the statin groups demonstrated a reduced incidence of myocardial infarction, atrial fibrillation, and a composite outcome including mortality. However, groups randomized to statin therapy did not demonstrate a significant reduction in perioperative stroke or transient ischemic attack risk. These findings align with large-scale observational studies involving noncardiac

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surgery patients that demonstrate reduced mortality and risk of major adverse cardiac events but no effect on stroke risk.[53,58] Thus, although perioperative statin administration is associated with reduced mortality and adverse cardiovascular events, there does not appear to be a clearly defined association with stroke risk. Continuation of perioperative statin therapy may nonetheless be helpful for reducing cardiovascular morbidity and mortality.

Perioperative Anticoagulation

Anticoagulation strategies must balance the need for thromboembolic prevention against the risk of major surgical bleeding. Table 4 illustrates the current anticoagulation strategy proposed by the American College of Surgeons. For vitamin K antagonists, such as warfarin, heparin-based bridging therapies are generally reserved for high-risk patients, such as those with mechanical heart valves, rheumatic heart disease, high CHA_2DS_2–VASc (Congestive heart failure/left ventricular dysfunction, Hypertension, Age ≥75, Diabetes mellitus, Stroke/transient ischemic attack/thromboembolism, Vascular disease, Age 65–74, Female sex) scores (6 or higher), recent thromboembolism, thromboembolism while on anticoagulation therapy, or known cardiac thrombus.[19–21] For low- to moderate-risk patients, bridging therapy increases the risk of hemorrhage without reducing the incidence of thromboembolism.[59] For direct oral anticoagulants, the last dose is typically administered 2 to 3 days before the surgical procedure depending on thromboembolic risk, surgical bleeding risk, and comorbidities (*e.g.*, renal function).[19] Bridging is not required for these anticoagulants, because such therapy tends to increase the risk of major bleeding without reducing thromboembolic events.[60] The Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) study prospectively evaluated the safety of a standardized protocol for perioperative management of direct oral anticoagulants (apixaban, dabigatran, rivaroxaban).[61] The risks of stroke and major perioperative bleeding were both low across the study cohort. The last dose of each anticoagulant was administered 2 to 3 days before surgery for those with creatinine clearance of more than 50 ml/min, and protocol adherence was high throughout the study. This study mirrored the strategy outlined in table 4 for direct oral anticoagulants and demonstrates feasibility with implementing such a protocol in practical settings. Overall, anticoagulation bridging is reserved only for high-risk patients on vitamin K antagonists, such as warfarin. For direct oral anticoagulants, these medications are held 2 to 3 days before surgery and resumed 1 to 3 days postoperatively, depending on thromboembolic and bleeding risks (table 4).

Intraoperative Considerations

Blood Pressure

Intraoperative hypotension is often implicated as a possible contributor to perioperative stroke, but specific thresholds that portend increased risk remain unclear for the noncardiac surgery patient. For example, in a recent retrospective, case-control study, the duration and severity of hypotension below a mean arterial pressure (MAP) of 70 mmHg were not associated with perioperative stroke.[62] One limitation of the study was that the results were primarily restricted to very mild hypotension (*i.e.*, MAP of less than 70 mmHg). The data nonetheless suggest that factors other than mild intraoperative hypotension probably

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 days before operation, bridge with low-molecular-weight heparin or unfractionated heparin, resume 24 h postoperatively	Give last dose 6 days before operation, bridge with low-molecular-weight heparin or unfractionated heparin, resume 24 h postoperatively
Direct oral anticoagulants	Give last dose 3 days before operation,* resume 2 to 3 days postoperatively	Give last dose 2 days before operation,* resume 24 h postoperatively
Intermediate thromboembolic risk		
Warfarin	Give last dose 6 days before operation, determine need for bridging by clinician judgment and current evidence, resume 24 h postoperatively	Give last dose 6 days before operation, determine need for bridging by clinician judgment and current evidence, resume 24 h postoperatively
Direct oral anticoagulants	Give last dose 3 days before operation,* resume 2 to 3 days postoperatively	Give last dose 2 days before operation,* resume 24 h postoperatively
Low thromboembolic risk		
Warfarin	Give last dose 6 days before operation, bridging not recommended, resume 24 h postoperatively	Give last dose 6 days before operation, bridging not recommended, resume 24 h postoperatively
Direct oral anticoagulants	Give last dose 3 days before operation,* resume 2 to 3 days postoperatively	Give last dose 2 days before operation,* resume 24 h postoperatively

*In patients with creatinine clearance < 50 ml/min on dabigatran, the last dose should be given 3 days before the procedure for low bleeding risk surgery and 4 to 5 days before the procedure for high bleeding risk operation.
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contribute substantially to postoperative stroke, although this conclusion is restricted to the institution studied. In a similar retrospective, case-control study, the investigators tested associations between stroke risk and time spent below various systolic and MAP thresholds in a broad, noncardiac surgery population (n = 48,241).[63] Time spent with MAP more than 30% below baseline was associated with stroke (odds ratio = 1.013/min hypotension). It is important to note, however, that none of the other absolute or relative thresholds studied, including MAP more than 40% below baseline, were associated with stroke. Of note, because there is no uniform definition for baseline blood pressure, measuring relative blood pressure changes with respect to stroke risk is fundamentally challenging. In summary, there is no clearly defined intraoperative blood pressure threshold below which noncardiac surgery patients are at increased risk for perioperative stroke. This supports the notion that intraoperative blood pressure is one of many possible factors that contribute to the risk of perioperative stroke.

Anesthetic Technique

Anesthetic technique has also been studied in relation to stroke risk. General anesthesia has been reported as an independent predictor of perioperative stroke in a large-scale investigation (more than 380,000 subjects) of hip and knee arthroplasty patients.[64] These results stand in contrast to smaller-scale investigations involving vascular[65] and gynecologic surgery[66] patients that demonstrated no associations with anesthetic technique and stroke risk. One explanation is that the effect size of anesthetic technique on stroke risk is small, requiring a large-scale investigation for detection. Alternatively, findings may be specific to surgical subtypes. Regional techniques are associated with less blood loss[67] and thromboembolic phenomena[68] in orthopedic surgery patients. Large-scale investigations involving broad surgical subtypes may provide further insights.

Last, large-scale, multicenter trials have investigated outcomes in relation to specific maintenance techniques (*e.g.*, propofol, nitrous oxide, volatile agents). The Mortality in Cardiac Surgery Randomized Controlled Trial of Volatile Anesthetics (MYRIAD) Trial randomized 5,400 cardiac surgery patients to a volatile-based technique or propofol anesthesia. Stroke risk was similar between the volatile anesthetic group (0.8%) and propofol group (0.6%) in the per-protocol analysis. The Evaluation of Nitrous Oxide in the Gas Mixture for Anaesthesia (ENIGMA)-II trial randomized 7,112 noncardiac surgery patients with cardiovascular risk factors to nitrous oxide (70% N_2O in 30% O_2) or no nitrous oxide (70% N_2 in 30% O_2) during surgical anesthesia.[70] There was no association between nitrous oxide and stroke at the 30-day or 1-year follow-up periods. Thus, for general anesthesia, the choice of maintenance technique does not appear to impact stroke risk. Similarly, the decision to choose general anesthesia *versus* regional anesthesia does not appear to impact stroke risk with the possible exception of patients undergoing joint arthroplasty.

Postoperative Management

Screening and Diagnostic Considerations

Stroke detection is challenging postoperatively. The signs and symptoms of stroke can be masked in the setting of opioid and sedative administration, pain, and delayed neurocognitive recovery after surgery and anesthesia. In fact, perioperative stroke is associated with delayed recognition, diagnosis, and neuroimaging compared to out-of-hospital stroke.[1,2] Various clinical screening tools are available for stroke detection,[35] but these assessments have not been validated in the perioperative setting. Furthermore, perioperative changes in cognition and physical exam findings can trigger false-positive results. A recent prospective cohort study of noncardiac surgery patients revealed that modified National Institutes of Health (Bethesda, Maryland) stroke scale changes were common postoperatively.[71] Increased scores, compared with preoperative baseline, were found in 20% of low-risk patients and more than 30% of high-risk patients. Such tools may thus have a low positive predictive value in the immediate postoperative setting. In the absence of reliable physical examination findings or clinical assessment tools, serum biomarkers may serve in a complementary role to assist with disease screening and diagnosis. However, currently, there are no clinically validated, reliable biomarkers for detecting cerebral ischemia and infarction.[71] Thus, currently available clinical screening tools and serum biomarkers are not presently recommended for routine postoperative screening. A targeted examination that focuses on signs and symptoms of large-vessel occlusion (table 3) may improve stroke detection.

In the event of suspected stroke, urgent noncontrast computed tomography or magnetic resonance imaging should be ordered to rule out intracranial hemorrhage. If large-vessel occlusion is suspected, concurrent computed tomography angiography and perfusion or diffusion-weighted magnetic resonance imaging should be performed. Such perfusion-guided imaging can assess for viable penumbra and eligibility for endovascular intervention. Recent trials have demonstrated improved functional outcomes in patients who underwent endovascular thrombectomy for large-vessel stroke, even with intervals of 16 to 24 h since the patient was last known to be well.[17] Thus, surgical patients with a large-vessel postoperative stroke may benefit from endovascular interventions even several hours after time last known well.

Stroke Management

Once acute ischemic stroke is identified, subsequent evaluation and clinical decision-making should occur within a multidisciplinary framework that includes neurology,

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interventional neuroradiology, and the primary surgical service. Intravenous recombinant tissue plasminogen activator remains standard therapy for acute thromboembolic stroke; however, the decision to administer recombinant tissue plasminogen activator should occur carefully in the postoperative patient and in close collaboration with neurologic and surgical services. The thrombolytic potential of rtPA should be weighed against the documented risk of postoperative hemorrhage.[72] Although recent intracranial or major spinal surgery is a contraindication to intravenous recombinant tissue plasminogen activator, other types of major surgery are relative, rather than absolute, contraindications.[73]

Endovascular interventions may be appealing for large-vessel occlusion given the targeted anatomical approach without need for systemic thrombolytic therapy. Within the past 5 years, multiple clinical trials have demonstrated improved functional outcomes in patients who underwent endovascular mechanical thrombectomy with retrievable stent devices,[14–16] with a pooled number needed to treat of 2.6 for reducing major disability.[74] Guidelines are available for anesthetic management of endovascular treatment for acute ischemic stroke by the Society for Neuroscience in Anesthesiology and Critical Care.[75] These guidelines include optimal strategies for preoperative evaluation, intraoperative management, and postoperative disposition. To review key recommendations, general anesthesia is usually elected for patients with profoundly decreased levels of consciousness or difficulty with protecting the airway. Outcomes otherwise appear to be similar between general anesthesia and conscious sedation techniques.[76–78] In fact, pooled meta-analytical data suggest that patients who undergo general anesthesia may demonstrate improved functional outcomes and recanalization rates compared to conscious sedation techniques.[79,80] Additionally, implementation of hemodynamic protocols during general anesthesia, with targeted thresholds for blood pressure treatment, may further mitigate risk of poor outcomes.[81] Patients should then be admitted to dedicated intensive care units specializing in stroke care after the procedure.

Last, optimal physiologic management during stroke is imperative, both in conjunction with interventional treatments and in the *absence* of interventions (*i.e.*, if ineligible, for example). The American Heart Association/American Stroke Association published guidelines for such supportive management in the acute stroke setting.[22] Intubation and mechanical ventilation are recommended for those with severely decreased consciousness or brainstem dysfunction that compromises the airway. Systolic blood pressure (SBP) should be lowered to less than 185 mmHg, and diastolic blood pressure should be lowered to less than 110 mmHg, if IV alteplase and/or mechanical thrombectomy are being considered. For patients ineligible for such therapies, SBP should be maintained at less than 220 mmHg, and diastolic blood pressure should be less than 120 mmHg. Epidemiologic data reveal an association between increased mortality and SBP of less than 130 mmHg during stroke presentation, although this association does not necessarily reflect causality.[82] Nonetheless, there appears to be a "U-shaped" relationship between stroke mortality and admission blood pressure, with extreme values of hypo- and hypertension most strongly associated with increased mortality. Hyperglycemia (greater than 180 mg/dl) is also associated with worse stroke outcomes,[83] although aggressive efforts to reduce hyperglycemia (less than 130 mg/dl) do not appear to improve outcomes and may increase risk of hypoglycemic events.[84] Reserving treatment for glucose more than 180 mg/dl thus appears reasonable. Hyperthermia within 24 h after stroke has been associated with increased mortality and should be treated.[85]

In summary, new studies support endovascular intervention for large-vessel occlusion, even with prolonged time between stroke onset and clinical recognition. This makes identification of new neurologic symptoms critical in surgical patients, who may be candidates for endovascular intervention. A coordinated, multispecialty response, careful blood pressure management, and determination of anesthetic technique (based on individual patient needs) are all essential to optimizing patient care in this setting.

Consequences of Postoperative Stroke

There are nearly 20 million surgeries per year in patients 65 yr of age and older requiring inpatient admission in the United States alone.[86] Risk of covert stroke may reach 7% in such patients,[5] and overt perioperative stroke risk ranges from approximately 0.1 to 2%[4] depending on risk factors. Taken together, these data suggest that nearly 1.4 million older surgical patients per year may experience covert stroke (with attendant consequences, such as delirium and cognitive decline),[5] and approximately 20,000 to 400,000 will suffer an overt perioperative stroke and associated complications, such as death, disability, prolonged hospitalization, and discharge to rehabilitation facilities. These estimates are even higher worldwide. Perioperative stroke is thus a major public health issue, and the time is ripe for developing programmatic initiatives and research agendas to better understand, predict, and prevent stroke and related perioperative complications.

Future Directions

There is currently no system for preoperatively testing physiologic factors that may contribute to stroke risk. A targeted assessment of cerebrovascular reserve may help to identify high-risk patients and guide perioperative management. For example, patients with preexisting cerebrovascular disease could undergo preoperative functional magnetic resonance imaging testing for determining cerebrovascular reserve. Such testing would be analogous to neurosurgical patients who undergo mapping for cerebrovascular insufficiency.[87] This mapping could reveal regions of impaired

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cerebral autoregulation, such that these vascular territories may be passively dependent on blood pressure for adequate cerebral perfusion. This line of investigation may thus ultimately help to identify personalized intraoperative blood pressure and end-tidal carbon dioxide goals for optimizing cerebrovascular perfusion. Such preoperative imaging could also help to detect significant stenosis (*e.g.*, atherosclerotic plaque). Patients at high risk for cardioembolic phenomena could be tested perioperatively with transcranial Doppler high-intensity transient signal analysis. Signs of cerebral emboli could guide perioperative anticoagulation strategies. Updated prediction models are also needed. As discussed previously, risk classification systems generated from National Surgical Quality Improvement Program data do not include key risk factors (*e.g.*, atrial fibrillation, valvular heart disease).[4] Although cardiovascular risk prediction models have been compared for perioperative stroke discriminative ability,[11] information was not reported on stroke risk for given scores or thresholds. As such, a risk prediction model is still needed that comprehensively incorporates all relevant risk factors while presenting quantitative data for stroke risk stratification.

Intraoperative risk factors also warrant further study. For example, emerging data suggest that intraoperative blood pressure commonly falls below lower autoregulatory thresholds,[88–90] and both hypo- and hyperventilation may further reduce cerebral blood flow below thresholds required for hypoxic–ischemic injury.[41] As such, the combination of hypotension and end-tidal carbon dioxide perturbations could be studied in relation to stroke risk using multicenter databases with intraoperative physiologic data points.[91] Near-infrared spectroscopy- and bioimpedance-based strategies can be also tested intraoperatively for defining critical thresholds for cerebral blood flow.[89,92] Postoperative screening and monitoring strategies also require further development. Current clinical assessment tools and serum biomarkers do not appear to have high specificity in the perioperative setting.[71] Neurophysiologic methods (*e.g.*, electroencephalography, transcranial Doppler, bioimpedance) could be tested for detecting cerebrovascular vulnerability postoperatively. Last, a perioperative stroke registry could be created to curate granular detail on preoperative risk factors, surgical subtypes, intraoperative physiology and events, postoperative management, reported etiologies, and long-term trajectory. Detailed clinical information, particularly involving clinical and physiologic events before stroke, along with neuroradiologic imaging (where available), could inform pathophysiologic understanding. These candidate strategies are outlined in table 5.

Table 5. Proposed Strategies for Advancing Perioperative Stroke Care and Research

Preoperative evaluation
Advanced risk prediction modeling
Cerebrovascular reserve mapping
Plaque-stenosis identification
Intraoperative management
Identify critical cerebral blood flow thresholds
Near-infrared spectroscopy
Bioimpedance
Postoperative assessment
Embolism detection (*e.g.*, transcranial Doppler)
Novel screening strategies (*e.g.*, electroencephalography)

Conclusions

Perioperative stroke is a detrimental outcome for surgical patients. Furthermore, stroke recognition is often delayed in the perioperative setting, and consequences include death, severe disability, and discharge to long-term care facilities. Risk reduction strategies include delaying elective surgery after recent stroke and medication optimization. Further investigation is required to determine the role of intraoperative physiologic management and stroke risk, and novel strategies are required to improve stroke detection postoperatively. Anesthesiologists can play a vital role in leading the required scientific and clinical efforts to advance perioperative stroke understanding and improve clinical management.

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Competing Interests

The authors declare no competing interests.

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References

1. Saltman AP, Silver FL, Fang J, Stamplecoski M, Kapral MK: Care and outcomes of patients with in-hospital stroke. JAMA Neurol 2015; 72:749–55
2. Vlisides PE, Mashour GA, Didier TJ, Shanks AM, Weightman A, Gelb AW, Moore LE: Recognition and management of perioperative stroke in hospitalized patients. A Case Rep 2016; 7:55–6
3. Smilowitz NR, Gupta N, Ramakrishna H, Guo Y, Berger JS, Bangalore S: Perioperative major adverse cardiovascular and cerebrovascular events associated with noncardiac surgery. JAMA Cardiol 2017; 2:181–7

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4. Mashour GA, Shanks AM, Kheterpal S: Perioperative stroke and associated mortality after noncardiac, non-neurologic surgery. ANESTHESIOLOGY 2011; 114:1289–96
5. Perioperative covert stroke in patients undergoing non-cardiac surgery (NeuroVISION): A prospective cohort study. Lancet 2019; 394:1022–9
6. Tan HH, Xu J, Teoh HL, Chan BP, Seet RC, Venketasubramanian N, Sharma VK, Chen CL, Dong Y: Decline in changing Montreal Cognitive Assessment (MoCA) scores is associated with post-stroke cognitive decline determined by a formal neuropsychological evaluation. PLoS One 2017; 12:e0173291
7. Ng PY, Ng AK, Subramaniam B, Burns SM, Herisson F, Timm FP, Med C, Rudolph MI, Med C, Scheffenbichler F, Med C, Friedrich S, Med C, Houle TT, Bhatt DL, Eikermann M: Association of preoperatively diagnosed patent foramen ovale with perioperative ischemic stroke. JAMA 2018; 319:452–62
8. Grau AJ, Eicke M, Burmeister C, Hardt R, Schmitt E, Dienlin S: Risk of ischemic stroke and transient ischemic attack is increased up to 90 days after non-carotid and non-cardiac surgery. Cerebrovasc Dis 2017; 43:242–9
9. Vasivej T, Sathirapanya P, Kongkamol C: Incidence and risk factors of perioperative stroke in noncardiac, and nonaortic and its major branches surgery. J Stroke Cerebrovasc Dis 2016; 25:1172–6
10. Dong Y, Cao W, Cheng X, Fang K, Zhang X, Gu Y, Leng B, Dong Q: Risk factors and stroke characteristic in patients with postoperative strokes. J Stroke Cerebrovasc Dis 2017; 26:1635–40
11. Wilcox T, Smilowitz NR, Xia Y, Berger JS: Cardiovascular risk scores to predict perioperative stroke in noncardiac surgery. Stroke 2019; 50:2002–6
12. Jørgensen ME, Torp-Pedersen C, Gislason GH, Jensen PF, Berger SM, Christiansen CB, Overgaard C, Schmiegelow MD, Andersson C: Time elapsed after ischemic stroke and risk of adverse cardiovascular events and mortality following elective noncardiac surgery. JAMA 2014; 312:269–77
13. Wijeysundera DN, Duncan D, Nkonde-Price C, Virani SS, Washam JB, Fleischmann KE, Fleisher LA; ACC/AHA Task Force Members: Perioperative β 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; 130:2246–64
14. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, van Walderveen MA, Staals J, Hofmeijer J, van Oostayen JA, Lycklama à Nijeholt GJ, Boiten J, Brouwer PA, Emmer BJ, de Bruijn SF, van Dijk LC, Kappelle LJ, Lo RH, van Dijk EJ, de Vries J, de Kort PL, van Rooij WJ, van den Berg JS, van Hasselt BA, Aerden LA, Dallinga RJ, Visser MC, Bot JC, Vroomen PC, Eshghi O, Schreuder TH, Heijboer RJ, Keizer K, Tielbeek AV, den Hertog HM, Gerrits DG, van den Berg-Vos RM, Karas GB, Steyerberg EW, Flach HZ, Marquering HA, Sprengers ME, Jenniskens SF, Beenen LF, van den Berg R, Koudstaal PJ, van Zwam WH, Roos YB, van der Lugt A, van Oostenbrugge RJ, Majoie CB, Dippel DW; MR CLEAN Investigators: A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015; 372:11–20
15. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, Albers GW, Cognard C, Cohen DJ, Hacke W, Jansen O, Jovin TG, Mattle HP, Nogueira RG, Siddiqui AH, Yavagal DR, Baxter BW, Devlin TG, Lopes DK, Reddy VK, du Mesnil de Rochemont R, Singer OC, Jahan R; SWIFT PRIME Investigators: Stent-retriever thrombectomy after intravenous t-PA *vs.* t-PA alone in stroke. N Engl J Med 2015; 372:2285–95
16. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, San Román L, Serena J, Abilleira S, Ribó M, Millán M, Urra X, Cardona P, López-Cancio E, Tomasello A, Castaño C, Blasco J, Aja L, Dorado L, Quesada H, Rubiera M, Hernandez-Pérez M, Goyal M, Demchuk AM, von Kummer R, Gallofré M, Dávalos A; REVASCAT Trial Investigators: Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 2015; 372:2296–306
17. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, Yavagal DR, Ribo M, Cognard C, Hanel RA, Sila CA, Hassan AE, Millan M, Levy EI, Mitchell P, Chen M, English JD, Shah QA, Silver FL, Pereira VM, Mehta BP, Baxter BW, Abraham MG, Cardona P, Veznedaroglu E, Hellinger FR, Feng L, Kirmani JF, Lopes DK, Jankowitz BT, Frankel MR, Costalat V, Vora NA, Yoo AJ, Malik AM, Furlan AJ, Rubiera M, Aghaebrahim A, Olivot JM, Tekle WG, Shields R, Graves T, Lewis RJ, Smith WS, Liebeskind DS, Saver JL, Jovin TG; DAWN Trial Investigators: Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Engl J Med 2018; 378:11–21
18. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, McTaggart RA, Torbey MT, Kim-Tenser M, Leslie-Mazwi T, Sarraj A, Kasner SE, Ansari SA, Yeatts SD, Hamilton S, Mlynash M, Heit JJ, Zaharchuk G, Kim S, Carrozzella J, Palesch YY, Demchuk AM, Bammer R, Lavori PW, Broderick JP, Lansberg MG; DEFUSE 3 Investigators: Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. N Engl J Med 2018; 378:708–18
19. Hornor MA, Duane TM, Ehlers AP, Jensen EH, Brown PS Jr, Pohl D, da Costa PM, Ko CY, Laronga C: American College of Surgeons' guidelines for the

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perioperative management of antithrombotic medication. J Am Coll Surg 2018; 227:521–536.e1
20. Macle L, Cairns J, Leblanc K, Tsang T, Skanes A, Cox JL, Healey JS, Bell A, Pilote L, Andrade JG, Mitchell LB, Atzema C, Gladstone D, Sharma M, Verma S, Connolly S, Dorian P, Parkash R, Talajic M, Nattel S, Verma A; CCS Atrial Fibrillation Guidelines Committee: 2016 focused update of the Canadian Cardiovascular Society guidelines for the management of atrial fibrillation. Can J Cardiol 2016; 32:1170–85
21. Doherty JU, Gluckman TJ, Hucker WJ, Januzzi JL Jr, Ortel TL, Saxonhouse SJ, Spinler SA: 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; 69:871–98
22. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL: 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:e344–418
23. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MS, George MG, Hamdan AD, Higashida RT, Hoh BL, Janis LS, Kase CS, Kleindorfer DO, Lee JM, Moseley ME, Peterson ED, Turan TN, Valderrama AL, Vinters HV; American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Council on Nutrition, Physical Activity and Metabolism: An updated definition of stroke for the 21st century: A statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013; 44:2064–89
24. Vlisides PE, Moore LE, Whalin MK, Robicsek SA, Gelb AW, Lele AV, Mashour GA: 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. J Neurosurg Anesthesiol 2020; 32:210–26
25. Mohr JP, Albers GW, Amarenco P, Babikian VL, Biller J, Brey RL, Coull B, Easton JD, Gomez CR, Helgason CM, Kase CS, Pullicino PM, Turpie AG: American Heart Association Prevention Conference. IV. Prevention and rehabilitation of stroke: Etiology of stroke. Stroke 1997; 28:1501–6
26. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE 3rd: 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
27. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C: Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet 1991; 337:1521–6
28. Schietroma M, Carlei F, Mownah A, Franchi L, Mazzotta C, Sozio A, Amicucci G: Changes in the blood coagulation, fibrinolysis, and cytokine profile during laparoscopic and open cholecystectomy. Surg Endosc 2004; 18:1090–6
29. Cundiff DK: Clinical evidence for rebound hypercoagulability after discontinuing oral anticoagulants for venous thromboembolism. Medscape J Med 2008; 10:258
30. Friedrich S, Ng PY, Platzbecker K, Burns SM, Banner-Goodspeed V, Weimar C, Subramaniam B, Houle TT, Bhatt DL, Eikermann M: Patent foramen ovale and long-term risk of ischaemic stroke after surgery. Eur Heart J 2019; 40:914–24
31. Paraskevas KI, Kalmykov EL, Naylor AR: Stroke/death rates following carotid artery stenting and carotid endarterectomy in contemporary administrative dataset registries: A systematic review. Eur J Vasc Endovasc Surg 2016; 51:3–12
32. Bilimoria KY, Liu Y, Paruch JL, Zhou L, Kmiecik TE, Ko CY, Cohen ME: Development and evaluation of the universal ACS NSQIP surgical risk calculator: A decision aid and informed consent tool for patients and surgeons. J Am Coll Surg 2013; 217:833–42.e1–3
33. Gupta PK, Gupta H, Sundaram A, Kaushik M, Fang X, Miller WJ, Esterbrooks DJ, Hunter CB, Pipinos II, Johanning JM, Lynch TG, Forse RA, Mohiuddin SM, Mooss AN: Development and validation of a risk calculator for prediction of cardiac risk after surgery. Circulation 2011; 124:381–7
34. Sewell D, Gelb AW, Meng L, Chui J, Flexman AM: Anesthesiologists' perception of perioperative stroke risk during non-neurologic and non-cardiac surgery. Can J Anaesth 2018; 65:225–6
35. Sun Z, Yue Y, Leung CC, Chan MT, Gelb AW; Study Group for Perioperative Stroke In China (POSIC): Clinical diagnostic tools for screening of perioperative stroke in general surgery: A systematic review. Br J Anaesth 2016; 116:328–38
36. Ahmed N, Audebert H, Turc G, Cordonnier C, Christensen H, Sacco S, Sandset EC, Ntaios G, Charidimou A, Toni D, Pristipino C, Köhrmann M, Kuramatsu JB, Thomalla G, Mikulik R, Ford GA, Martí-Fàbregas J, Fischer U, Thoren M, Lundström

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E, Rinkel GJ, van der Worp HB, Matusevicius M, Tsivgoulis G, Milionis H, Rubiera M, Hart R, Moreira T, Lantz M, Sjöstrand C, Andersen G, Schellinger P, Kostulas K, Sunnerhagen KS, Keselman B, Korompoki E, Purrucker J, Khatri P, Whiteley W, Berge E, Mazya M, Dippel DW, Mustanoja S, Rasmussen M, Söderqvist ÅK, Escudero-Martínez I, Steiner T: Consensus statements and recommendations from the ESO–Karolinska Stroke Update Conference, Stockholm 11–13 November 2018. Eur Stroke J 2019; 4:307–17
37. Turc G, Bhogal P, Fischer U, Khatri P, Lobotesis K, Mazighi M, Schellinger PD, Toni D, de Vries J, White P, Fiehler J: European Stroke Organisation (ESO)–European Society for Minimally Invasive Neurological Therapy (ESMINT) guidelines on mechanical thrombectomy in acute ischaemic stroke: Endorsed by Stroke Alliance for Europe (SAFE). Eur Stroke J 2019; 4:6–12
38. Boulanger JM, Lindsay MP, Gubitz G, Smith EE, Stotts G, Foley N, Bhogal S, Boyle K, Braun L, Goddard T, Heran M, Kanya-Forster N, Lang E, Lavoie P, McClelland M, O'Kelly C, Pageau P, Pettersen J, Purvis H, Shamy M, Tampieri D, vanAdel B, Verbeek R, Blacquiere D, Casaubon L, Ferguson D, Hegedus Y, Jacquin GJ, Kelly M, Kamal N, Linkewich B, Lum C, Mann B, Milot G, Newcommon N, Poirier P, Simpkin W, Snieder E, Trivedi A, Whelan R, Eustace M, Smitko E, Butcher K: Canadian Stroke best practice recommendations for acute stroke management: Prehospital, emergency department, and acute inpatient stroke care, 6th edition, update 2018. Int J Stroke 2018; 13:949–84
39. Burkle CM, Pasternak JJ, Armstrong MH, Keegan MT: Patient perspectives on informed consent for anaesthesia and surgery: American attitudes. Acta Anaesthesiol Scand 2013; 57:342–9
40. Roughead T, Chui J, Gelb AW, Meng L, Sewell D, Flexman AM: 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
41. Fisher JA, Venkatraghavan L, Mikulis DJ: Magnetic resonance imaging–based cerebrovascular reactivity and hemodynamic reserve. Stroke 2018; 49:2011–8
42. Yamauchi H, Fukuyama H, Fujimoto N, Nabatame H, Kimura J: Significance of low perfusion with increased oxygen extraction fraction in a case of internal carotid artery stenosis. Stroke 1992; 23:431–2
43. Yamauchi H, Fukuyama H, Nagahama Y, Nabatame H, Nakamura K, Yamamoto Y, Yonekura Y, Konishi J, Kimura J: 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
44. Burn J, Dennis M, Bamford J, Sandercock P, Wade D, Warlow C: Long-term risk of recurrent stroke after a first-ever stroke: The Oxfordshire Community Stroke Project. Stroke 1994; 25:333–7
45. Jørgensen ME, Gislason GH, Andersson C: Time since stroke and risk of adverse outcomes after surgery: Reply. JAMA 2014; 312:1930–1
46. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Malaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P: Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): A randomised controlled trial. Lancet 2008; 371:1839–47
47. El Beheiry MH, Heximer SP, Voigtlaender-Bolz J, Mazer CD, Connelly KA, Wilson DF, Beattie WS, Tsui AK, Zhang H, Golam K, Hu T, Liu E, Lidington D, Bolz SS, Hare GM: Metoprolol impairs resistance artery function in mice. J Appl Physiol (1985) 2011; 111:1125–33
48. Hare GM, Worrall JM, Baker AJ, Liu E, Sikich N, Mazer CD: β2 Adrenergic antagonist inhibits cerebral cortical oxygen delivery after severe haemodilution in rats. Br J Anaesth 2006; 97:617–23
49. Ragoonanan TE, Beattie WS, Mazer CD, Tsui AK, Leong-Poi H, Wilson DF, Tait G, Yu J, Liu E, Noronha M, Dattani ND, Mitsakakis N, Hare GM: Metoprolol reduces cerebral tissue oxygen tension after acute hemodilution in rats. Anesthesiology 2009; 111:988–1000
50. Jørgensen ME, Hlatky MA, Køber L, Sanders RD, Torp-Pedersen C, Gislason GH, Jensen PF, Andersson C: β-Blocker–associated risks in patients with uncomplicated hypertension undergoing noncardiac surgery. JAMA Intern Med 2015; 175:1923–31
51. Park J, Kim J, Kwon JH, Park SJ, Min JJ, Lee SM, Gwon HC, Lee YT, Park M, Lee SH: Association between perioperative β-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
52. Chen RJ, Chu H, Tsai LW: Impact of β-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
53. Richman JS, Graham LA, DeRussy A, Maddox TM, Itani KMF, Hawn MT: Perioperative β blockers and statins for noncardiac surgery patients with coronary stents. Am J Surg 2017; 214:180–5
54. Laufs U, La Fata V, Plutzky J, Liao JK: Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. Circulation 1998; 97:1129–35
55. Jialal I, Stein D, Balis D, Grundy SM, Adams-Huet B, Devaraj S: Effect of hydroxymethyl glutaryl coenzyme a reductase inhibitor therapy on high sensitive C-reactive protein levels. Circulation 2001; 103:1933–5
56. Crisby M, Nordin-Fredriksson G, Shah PK, Yano J, Zhu J, Nilsson J: Pravastatin treatment increases collagen content and decreases lipid content, inflammation, metalloproteinases, and cell death in human

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carotid plaques: Implications for plaque stabilization. Circulation 2001; 103:926–33
57. Ma B, Sun J, Diao S, Zheng B, Li H: Effects of perioperative statins on patient outcomes after noncardiac surgery: A meta-analysis. Ann Med 2018; 50:402–9
58. London MJ, Schwartz GG, Hur K, Henderson WG: Association of perioperative statin use with mortality and morbidity after major noncardiac surgery. JAMA Intern Med 2017; 177:231–42
59. Douketis JD, Spyropoulos AC, Kaatz S, Becker RC, Caprini JA, Dunn AS, Garcia DA, Jacobson A, Jaffer AK, Kong DF, Schulman S, Turpie AG, Hasselblad V, Ortel TL; BRIDGE Investigators: Perioperative bridging anticoagulation in patients with atrial fibrillation. N Engl J Med 2015; 373:823–33
60. Beyer-Westendorf J, Gelbricht V, Förster K, Ebertz F, Köhler C, Werth S, Kuhlisch E, Stange T, Thieme C, Daschkow K, Weiss N: Peri-interventional management of novel oral anticoagulants in daily care: Results from the prospective Dresden NOAC registry. Eur Heart J 2014; 35:1888–96
61. Douketis JD, Spyropoulos AC, Duncan J, Carrier M, Le Gal G, Tafur AJ, Vanassche T, Verhamme P, Shivakumar S, Gross PL, Lee AYY, Yeo E, Solymoss S, Kassis J, Le Templier G, Kowalski S, Blostein M, Shah V, MacKay E, Wu C, Clark NP, Bates SM, Spencer FA, Arnaoutoglou E, Coppens M, Arnold DM, Caprini JA, Li N, Moffat KA, Syed S, Schulman S: Perioperative management of patients with atrial fibrillation receiving a direct oral anticoagulant. JAMA Intern Med 2019; 179:1469–1478
62. Hsieh JK, Dalton JE, Yang D, Farag ES, Sessler DI, Kurz AM: The association between mild intraoperative hypotension and stroke in general surgery patients. Anesth Analg 2016; 123:933–9
63. Bijker JB, Persoon S, Peelen LM, Moons KG, Kalkman CJ, Kappelle LJ, van Klei WA: Intraoperative hypotension and perioperative ischemic stroke after general surgery: A nested case-control study. Anesthesiology 2012; 116:658–64
64. Memtsoudis SG, Sun X, Chiu YL, Stundner O, Liu SS, Banerjee S, Mazumdar M, Sharrock NE: Perioperative comparative effectiveness of anesthetic technique in orthopedic patients. Anesthesiology 2013; 118:1046–58
65. Sgroi MD, McFarland G, Mell MW: Utilization of regional *versus* general anesthesia and its impact on lower extremity bypass outcomes. J Vasc Surg 2019; 69:1874–9
66. Smith PE, Hade EM, Tan Y, Pandya LK, Hundley AF, Hudson CO: Mode of anesthesia and major perioperative outcomes associated with vaginal surgery. Int Urogynecol J 2020; 31:181–9
67. Richman JM, Rowlingson AJ, Maine DN, Courpas GE, Weller JF, Wu CL: Does neuraxial anesthesia reduce intraoperative blood loss?: A meta-analysis. J Clin Anesth 2006; 18:427–35
68. Hu S, Zhang ZY, Hua YQ, Li J, Cai ZD: A comparison of regional and general anaesthesia for total replacement of the hip or knee: A meta-analysis. J Bone Joint Surg Br 2009; 91:935–42
69. Landoni G, Lomivorotov VV, Nigro Neto C, Monaco F, Pasyuga VV, Bradic N, Lembo R, Gazivoda G, Likhvantsev VV, Lei C, Lozovskiy A, Di Tomasso N, Bukamal NAR, Silva FS, Bautin AE, Ma J, Crivellari M, Farag AMGA, Uvaliev NS, Carollo C, Pieri M, Kunstýř J, Wang CY, Belletti A, Hajjar LA, Grigoryev EV, Agrò FE, Riha H, El-Tahan MR, Scandroglio AM, Elnakera AM, Baiocchi M, Navalesi P, Shmyrev VA, Severi L, Hegazy MA, Crescenzi G, Ponomarev DN, Brazzi L, Arnoni R, Tarasov DG, Jovic M, Calabrò MG, Bove T, Bellomo R, Zangrillo A; MYRIAD Study Group: Volatile anesthetics *versus* total intravenous anesthesia for cardiac surgery. N Engl J Med 2019; 380:1214–25
70. Leslie K, Myles PS, Kasza J, Forbes A, Peyton PJ, Chan MT, Paech MJ, Sessler DI, Beattie WS, Devereaux PJ, Wallace S: 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; 123:1267–80
71. Vlisides PE, Kunkler B, Thompson A, Zierau M, Lobo R, Strasser MO, Cantley MJ, McKinney A, Everett AD, Mashour GA, Picton P: Cerebrovascular disease and perioperative neurologic vulnerability: A prospective cohort study. Front Neurol 2019; 10:560
72. Voelkel N, Hubert ND, Backhaus R, Haberl RL, Hubert GJ: Thrombolysis in postoperative stroke. Stroke 2017; 48:3034–9
73. Demaerschalk BM, Kleindorfer DO, Adeoye OM, Demchuk AM, Fugate JE, Grotta JC, Khalessi AA, Levy EI, Palesch YY, Prabhakaran S, Saposnik G, Saver JL, Smith EE; American Heart Association Stroke Council and Council on Epidemiology and Prevention: 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
74. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, Dávalos A, Majoie CB, van der Lugt A, de Miquel MA, Donnan GA, Roos YB, Bonafe A, Jahan R, Diener HC, van den Berg LA, Levy EI, Berkhemer OA, Pereira VM, Rempel J, Millán M, Davis SM, Roy D, Thornton J, Román LS, Ribó M, Beumer D, Stouch B, Brown S, Campbell BC, van Oostenbrugge RJ, Saver JL, Hill MD, Jovin TG; HERMES collaborators: Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. Lancet 2016; 387:1723–31

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75. Talke PO, Sharma D, Heyer EJ, Bergese SD, Blackham KA, Stevens RD: 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
76. Schönenberger S, Uhlmann L, Hacke W, Schieber S, Mundiyanapurath S, Purrucker JC, Nagel S, Klose C, Pfaff J, Bendszus M, Ringleb PA, Kieser M, Möhlenbruch MA, Bösel J: Effect of conscious sedation *vs.* general anesthesia on early neurological improvement among patients with ischemic stroke undergoing endovascular thrombectomy: A randomized clinical trial. JAMA 2016; 316:1986–96
77. Löwhagen Hendén P, Rentzos A, Karlsson JE, Rosengren L, Leiram B, Sundeman H, Dunker D, Schnabel K, Wikholm G, Hellström M, Ricksten SE: General anesthesia *versus* conscious sedation for endovascular treatment of acute ischemic stroke: The AnStroke Trial (Anesthesia During Stroke). Stroke 2017; 48:1601–7
78. Simonsen CZ, Yoo AJ, Sørensen LH, Juul N, Johnsen SP, Andersen G, Rasmussen M: Effect of general anesthesia and conscious sedation during endovascular therapy on infarct growth and clinical outcomes in acute ischemic stroke: A randomized clinical trial. JAMA Neurol 2018; 75:470–7
79. Zhang Y, Jia L, Fang F, Ma L, Cai B, Faramand A: General anesthesia *versus* conscious sedation for intracranial mechanical thrombectomy: A systematic review and meta-analysis of randomized clinical trials. J Am Heart Assoc 2019; 8:e011754
80. Campbell D, Diprose WK, Deng C, Barber PA: General anesthesia versus conscious sedation in endovascular thrombectomy for stroke: A meta-analysis of 4 randomized controlled trials. J Neurosurg Anesthesiol 2021; 33:21–7
81. Rasmussen M, Espelund US, Juul N, Yoo AJ, Sørensen LH, Sørensen KE, Johnsen SP, Andersen G, Simonsen CZ: The influence of blood pressure management on neurological outcome in endovascular therapy for acute ischaemic stroke. Br J Anaesth 2018; 120:1287–94
82. Vemmos KN, Tsivgoulis G, Spengos K, Zakopoulos N, Synetos A, Manios E, Konstantopoulou P, Mavrikakis M: U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. J Intern Med 2004; 255:257–65
83. Baird TA, Parsons MW, Phan T, Phanh T, Butcher KS, Desmond PM, Tress BM, Colman PG, Chambers BR, Davis SM: Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. Stroke 2003; 34:2208–14
84. Johnston KC, Bruno A, Pauls Q, Hall CE, Barrett KM, Barsan W, Fansler A, Van de Bruinhorst K, Janis S, Durkalski-Mauldin VL; Neurological Emergencies Treatment Trials Network and the SHINE Trial Investigators: Intensive *vs.* standard treatment of hyperglycemia and functional outcome in patients with acute ischemic stroke: The SHINE randomized clinical trial. JAMA 2019; 322:326–35
85. Saxena M, Young P, Pilcher D, Bailey M, Harrison D, Bellomo R, Finfer S, Beasley R, Hyam J, Menon D, Rowan K, Myburgh J: Early temperature and mortality in critically ill patients with acute neurological diseases: Trauma and stroke differ from infection. Intensive Care Med 2015; 41:823–32
86. Centers for Disease Control and National Center for Health Statistics (2010): Number of all-listed procedures for discharges from short-stay hospitals, by procedure category and age: United States, 2010. Available at: https://www.cdc.gov/nchs/data/nhds/4procedures/2010pro4_numberprocedureage.pdf. Accessed December 21, 2020.
87. McKetton L, Venkatraghavan L, Rosen C, Mandell DM, Sam K, Sobczyk O, Poublanc J, Gray E, Crawley A, Duffin J, Fisher JA, Mikulis DJ: Improved white matter cerebrovascular reactivity after revascularization in patients with steno-occlusive disease. AJNR Am J Neuroradiol 2019; 40:45–50
88. Brady K, Joshi B, Zweifel C, Smielewski P, Czosnyka M, Easley RB, Hogue CW Jr: Real-time continuous monitoring of cerebral blood flow autoregulation using near-infrared spectroscopy in patients undergoing cardiopulmonary bypass. Stroke 2010; 41:1951–6
89. Joshi B, Ono M, Brown C, Brady K, Easley RB, Yenokyan G, Gottesman RF, Hogue CW: Predicting the limits of cerebral autoregulation during cardiopulmonary bypass. Anesth Analg 2012; 114:503–10
90. Ono M, Joshi B, Brady K, Easley RB, Zheng Y, Brown C, Baumgartner W, Hogue CW: Risks for impaired cerebral autoregulation during cardiopulmonary bypass and postoperative stroke. Br J Anaesth 2012; 109:391–8
91. Kheterpal S: Clinical research using an information system: The Multicenter Perioperative Outcomes Group. Anesthesiol Clin 2011; 29:377–88
92. Tiba MH, McCracken BM, Ansari S, Belle A, Cummings BC, Rajajee V, Patil PG, Alam HB, Ward KR: Novel noninvasive method of cerebrovascular blood volume assessment using brain bioimpedance. J Neurotrauma 2017; 34:3089–96

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