Can J Anesth/J Can Anesth (2016) 63:193–204
DOI 10.1007/s12630-015-0494-9

REVIEW ARTICLE/BRIEF REVIEW

Perioperative stroke
AVC périopératoire

Phillip Vlisides, MD · George A. Mashour, MD, PhD

Received: 23 April 2015 / Revised: 2 July 2015 / Accepted: 11 September 2015 / Published online: 21 September 2015

Abstract

Purpose *Perioperative stroke is associated with significant morbidity and mortality, with an incidence that may be underappreciated. In this review, we examine the significance, pathophysiology, risk factors, and evidence-based recommendations for the prevention and management of perioperative stroke.*

Source *This is a narrative review based on literature from the PubMed database regarding perioperative stroke across a broad surgical population. The Society for Neuroscience in Anesthesiology and Critical Care recently published evidence-based recommendations for perioperative management of patients at high risk for stroke; these recommendations were analyzed and incorporated into this review.*

Principal findings *The incidence of overt perioperative stroke is highest in patients presenting for cardiac and major vascular surgery, although preliminary data suggest that the incidence of covert stroke may be as high as 10% in non-cardiac surgery patients. The pathophysiology of perioperative stroke involves different pathways. Thrombotic stroke can result from increased inflammation and hypercoagulability; cardioembolic stroke can result from disease states such as atrial fibrillation, and tissue hypoxia from anemia can result from the combination of anemia and beta-blockade. Across large-scale database studies, common risk factors for perioperative stroke include advanced age, history of cerebrovascular disease, ischemic heart disease, congestive heart failure, atrial fibrillation, and renal disease. Recommendations for prevention and management of perioperative stroke are evolving, though further work is needed to clarify the role of proposed modifiable risk factors such as perioperative anticoagulation, antiplatelet therapy, appropriate transfusion thresholds, and perioperative beta-blockade.*

Conclusions *Perioperative stroke carries a significant clinical burden. The incidence of perioperative stroke may be higher than previously recognized, and there are diverse pathophysiologic mechanisms. There are many opportunities for further investigation of the pathophysiology, prevention, and management of perioperative stroke.*

Résumé

Objectif *L'AVC périopératoire est associé à une morbi-mortalité significative, dont l'incidence pourrait être sous-évaluée. Dans cette analyse, nous examinons la signification, la physiopathologie, les facteurs de risque et les recommandations basées sur des données probantes concernant la prévention et la gestion de l'AVC périopératoire.*

Source *Il s'agit d'une étude narrative basée sur la documentation publiée dans la base de données PubMed sur les AVC périopératoires dans des populations chirurgicales variées. La Society for Neuroscience in Anesthesiology and Critical Care a récemment publié des recommandations basées sur des données probantes pour la gestion périopératoire des patients à risque élevé*

Author contributions *Phillip Vlisides* and *George A. Mashour* contributed substantially to all aspects of this manuscript, including conception, design and drafting the article.

P. Vlisides, MD · G. A. Mashour, MD, PhD (✉)
Department of Anesthesiology, University of Michigan Health System, University Hospital 1H247, 1500 East Medical Center Drive, SPC 5048, Ann Arbor, MI 48109, USA
e-mail: gmashour@med.umich.edu

d'AVC; ces recommandations ont été analysées et incorporées dans la présente étude.

Constatations principales *L'incidence des AVC périopératoires évidents est plus élevée chez les patients subissant une chirurgie cardiaque et/ou vasculaire majeure bien que des données préliminaires suggèrent que l'incidence des AVC non apparents puisse atteindre 10 % chez les patients subissant une chirurgie non cardiaque. La physiopathologie des AVC périopératoires passe par différentes voies. Un AVC thrombotique peut résulter d'une augmentation de l'inflammation et d'une hypercoagulabilité; un AVC cardio-embolique peut être la conséquence de maladies telles qu'une fibrillation auriculaire, et l'hypoxie tissulaire de l'anémie peut résulter de la combinaison d'une anémie et d'un blocage bêta. Dans les études de grande envergure de bases de données, les facteurs de risque fréquents de l'AVC périopératoire incluent l'âge avancé, les antécédents de maladie cérébrovasculaire, la maladie cardiaque ischémique, l'insuffisance cardiaque congestive, la fibrillation auriculaire et l'insuffisance rénale. Les recommandations pour la prévention et la gestion des AVC périopératoires évoluent, bien que des recherches supplémentaires soient nécessaires pour clarifier le rôle des facteurs de risque modifiables proposés, comme l'anticoagulation et le traitement antiagrégant plaquettaire périopératoire, les seuils adaptés de transfusion et le blocage bêta-adrénergique périopératoire.*

Conclusions *Un AVC périopératoire entraîne une morbidité clinique significative. L'incidence des AVC périopératoires pourrait être supérieure à ce qui a été identifié à ce jour et différents mécanismes physiopathologiques sont en cause. Il existe de nombreuses opportunités de nouvelles recherches sur la physiopathologie, la prévention et la gestion des AVC périopératoires.*

Stroke is responsible for approximately 6.2 million deaths annually, making cerebrovascular disease a leading global cause of premature death and disability.[1] Additionally, cerebrovascular disease is projected to be the second leading cause of death worldwide by the year 2030.[2] Given the global burden, many efforts have focused on the prevention and treatment of stroke and other sequelae of cerebrovascular disease. One area of particular concern is the perioperative setting where patients may be at particular risk of stroke.[3] In the United States alone, significant increases (14-47%) in demand for surgical services are expected over the coming years,[4] and it follows that the number of perioperative strokes may increase accordingly. Perioperative stroke in high-risk cardiovascular surgery has been well-documented, with an incidence in the range of approximately 1.9-9.7%.[5] Currently, the incidence of perioperative ischemic stroke (IS) in non-cardiac, non-neurologic, and non-major vascular surgery is in the range of approximately 0.1-1.9% depending on associated risk factors.[6,7] Pilot data from the Neurovision study, however, suggest that the incidence of *covert* stroke in high-risk non-cardiac surgery patients may be as high as 10%.[8] This is relevant because clinically silent cerebral ischemia has been proportionally correlated with postoperative cognitive impairment in cardiac surgery patients.[9] In addition to the potentially underappreciated incidence and significance of perioperative stroke, recent data have shown that mortality from perioperative stroke may be particularly high, with an approximate incidence in the range of 20-60% depending on type of stroke, operation, and patient.[10-12] As such, interest has grown in the identification of those at risk for perioperative stroke as well as in potentially modifiable risk factors. This focus has culminated in a consensus statement by the Society for Neuroscience in Anesthesiology and Critical Care (SNACC) for perioperative care of non-cardiac, non-neurological surgery patients at high risk of stroke.[13]

The SNACC Consensus Statement defines perioperative stroke as a brain infarction of ischemic or hemorrhagic etiology that occurs during surgery or within 30 days after surgery.[13] The remainder of this review will focus on stroke based on this definition. Specifically, the pathophysiology and risk factors of perioperative stroke are reviewed, and the recently released SNACC perioperative stroke recommendations are also reviewed. Lastly, directions for future investigations are suggested.

Pathophysiology

Because stroke is caused by a diverse array of etiologies, different stroke subtypes may be a function of varying pathophysiologic pathways. Thus, discussion of the pathophysiology of perioperative stroke first begins with a classification framework for stroke etiology. Though stroke is classified in many different ways (e.g., arterial *vs* venous and ischemic *vs* hemorrhagic), for the purpose of this review, perioperative stroke is classified as either *ischemic* or *hemorrhagic*.

Ischemic stroke

Categorization of ischemic stroke (IS) based on etiology has been outlined in the Trial of Org 10172 in Acute Stroke Treatment (TOAST).[14] The TOAST classification system

divides IS subtypes into large-artery atherosclerosis, cardioembolism, small-artery occlusion (lacunar), stroke of other determined etiology, and stroke of undetermined etiology. Much of the recent literature on perioperative stroke focuses on IS, as the incidence of ischemic perioperative stroke seems to be higher than that of hemorrhagic stroke (HS).[15,16] As such, pathophysiologic cascades that may facilitate perioperative IS have been considered in this context. Though Ng *et al.*[17] reviewed major studies that reported the etiologies of perioperative stroke in the non-cardiac surgery setting, estimated incidences of subtypes are difficult to ascertain, as many population-based studies do not analyze stroke subtypes with the required level of granularity.[6,7,18] Based on available data, thrombosis, embolism, anemic tissue hypoxia, and cerebral hypoperfusion have all been described as etiologic pathways contributing to perioperative IS.[10,19-21] Following is a review of three of the major pathophysiologic mechanisms of IS—thrombosis, cardioembolism, and anemic tissue hypoxia.

Large- and small-vessel occlusion: thrombosis

Surgery precipitates systemic inflammation and hypercoagulability,[22-24] and this state may contribute to thrombogenesis and vessel plaque rupture in the perioperative setting. Further, patients receiving anticoagulation or antiplatelet therapy preoperatively may be at risk for rebound hypercoagulation[25] and subsequent IS upon withdrawal.[26] Taken together, this indicates that some patients—especially those on preoperative anticoagulation or antiplatelet therapy—may be at an increased risk for perioperative thromboembolic events via a hypercoagulable state that may be driven by both surgical intervention and rebound hypercoagulation. This hypercoagulable state may be exacerbated by systemic inflammation, which is also increased perioperatively.[22,23,27] An elevation of inflammatory biomarkers has been shown to predict future stroke,[28-30] and it follows that anti-inflammatory measures may conceivably reduce the risk of stroke. One such possible anti-inflammatory intervention is statin administration, which has been associated with decreased perioperative stroke across multiple surgical populations.[31,32] Though statins act through various pathways, there is evidence to suggest that the anti-inflammatory effects, in particular, confer stroke protection.[33-37] Given the clinical evidence, inflammatory and hypercoagulable factors may indeed combine to increase the risk of perioperative thrombogenic stroke.

Cardioembolism

Ischemic stroke of embolic origin is often due to cardioembolism. In this review, cardioembolism refers to any embolic phenomenon originating from the heart, including both valvular and non-valvular sources. In the perioperative setting, atrial fibrillation combined with a hypercoagulable state (as discussed above) may be a source of cardioembolic phenomena. Atrial fibrillation has indeed been a consistent risk factor for perioperative stroke across various surgical populations.[5,6,38,39] An additional source of cardioembolic stroke is cardiovascular manipulation of the heart and aortic arch, both of which occur during major cardiac and some vascular surgery (e.g., endovascular stent grafting). In fact, these surgeries have been linked with a relatively high incidence of perioperative stroke, with embolic stroke representing a relatively high proportion of these events.[5,38]

Other determined stroke etiologies—anemia-associated tissue hypoxia

One potential mechanism by which IS may occur involves cerebral hypoxia in the setting of hemodilution and anemia.[40] With anemic states, increased cardiac output (CO) and cerebral blood flow act as compensatory mechanisms to preserve oxygenation.[41-46] In the setting of use of a non-specific beta-blocker (i.e., metoprolol) and anemia, both CO and cerebral vasodilation become impaired, which may result in cerebral tissue hypoxia.[46-48] Mechanistically, animal models have shown that the β2-mediated reduction in cerebral vasodilatory function may be integral to the reduction in cerebral oxygenation.[47,48] In animal studies, minimizing β2-mediated cerebrovascular antagonism improved cerebral oxygenation in the setting of anemia.[49] Ultimately, this aberrant physiology may render vulnerable brain regions at risk for ischemia and stroke. Indeed, clinical data have shown an increased risk of stroke in surgical patients on beta-blockade with hemoglobin levels below 9 $g \cdot dL^{-1}$; those taking metoprolol were at highest risk.[20] The risk of stroke also increased in the Perioperative Ischemic Evaluation (POISE) trial in patients who experienced significant bleeding.[21]

Hemorrhagic stroke

According to the American Heart Association and American Stroke Association (AHA/ASA), stroke of hemorrhagic etiology can be attributed to a focal collection of blood within the brain parenchyma, subarachnoid space, or ventricular system that is not caused by trauma.[50] Perioperatively, this may plausibly occur *via* factors such as uncontrolled hypertension, cerebral vascular malformations, and administration of anticoagulant or antiplatelet therapy. Fortunately, however, this seems to be an infrequent occurrence, as HS represents

approximately only 1-4% of all perioperative strokes as shown by incidence data.[15,16] As such, much of the research into the mechanisms of perioperative stroke to date centres on IS, which remains the focus for the rest of this review.

Risk factors

Many risk factors for perioperative stroke have been elucidated over the years, and several of those factors seem to fit well within the pathophysiologic framework as outlined above. These risk factors have been derived largely from case series and large database studies, [5-7,51] as the rarity of perioperative stroke makes it difficult to collect and analyze prospective data. In particular, factors that reflect pre-existing vascular disease or propagation of vascular disease have been consistently shown across studies. Examples include advanced age, previous stroke or transient ischemic attacks, coronary artery disease, and renal disease (Table 1).[6,7,51] These factors may reflect less cerebrovascular reserve and thus higher susceptibility to deleterious cerebral thromboembolic phenomena. Major cardiovascular surgery has a relatively high incidence of perioperative stroke (Figure),[5,52] as these surgeries carry the additional risk of cardioembolism from cardiac and vascular manipulation. Along similar lines, atrial fibrillation serves as a risk factor for perioperative embolic stroke.[5,6,38,39] Recently, in fact, patients with new-onset atrial fibrillation after non-cardiac surgery were shown to be at increased risk of IS beyond the perioperative setting alone.[53]

Perioperative beta-blockade has emerged as a risk factor for stroke across the general surgical population.[16,20,21,54] Both prospective randomized controlled trials and retrospective observational studies have shown an increased risk of stroke in patients taking beta-blockers in the perioperative setting.[16,20,21] Further, there may be a differentially increased risk with relatively non-selective beta-blockers.[16,20] As previously outlined, this may be due to impaired cerebral vasodilation and CO in the setting of malperfusion and non-selective beta-blockade.[46-48]

The SNACC Consensus Statement

In 2014, the SNACC released the first set of recommendations regarding care for patients at high risk for perioperative stroke in the setting of non-cardiac non-neurologic surgery.[13] Based on a review of the literature as well as expert opinion, recommendations to minimize the risk of perioperative stroke in the preoperative, intraoperative, and postoperative periods were presented. Considerations for prevention and management of stroke across the perioperative spectrum are reviewed below. These factors are derived from both the SNACC Consensus Statement as well as from other subsequent influential studies.[55-57]

Preoperative management

Phenotype of the high-risk patient

Prevention of perioperative stroke begins with the identification of high-risk patients in the preoperative setting. By initially stratifying risk based on the type of surgery, non-cardiac, non-neurologic, and non-major vascular surgery are all associated with the lowest incidence of perioperative stroke—approximately 1 per 1,000 cases (0.1%).[7] The SNACC Consensus Statement focuses largely on this population. The incidence then climbs with major vascular and cardiac surgery, with reported incidences as high as 5.6% and 9.7%, respectively.[5,58] In addition to the type of surgery, patient-specific risk factors also play a role. Across major epidemiologic studies examining risk factors for stroke in the general surgical population, advanced age, history of renal failure, history of stroke, and cardiac disease all confer an increased risk of perioperative stroke.[6,7] The existence of such conditions in a patient's medical history should alert the perioperative physician to an increased risk of cerebrovascular compromise and raise the index of suspicion for stroke in the setting of postoperative neurologic changes. Thus, the phenotype of the high-risk patient may appear as someone presenting for major surgery (especially cardiovascular) with comorbidities such as advanced age, renal dysfunction, history of cerebrovascular compromise, and history of cardiac disease.

Identifying modifiable risk factors

Although many risk factors for perioperative stroke are largely non-modifiable, the discussion below encompasses elements that the perioperative physician may be able to modulate for risk reduction. As may become evident, there are noticeably few large-scale randomized prospective trials available to help guide management for the factors below. Possible modifiable risk factors, along with proposed strategies for minimizing the risk of perioperative stroke, are outlined in the sections below and presented in Table 2.

Table 1 Stroke risk factors across various surgical populations

Study	Year	Population	Patients (*n*)	OR (CI, 95%)
Sharifpour et al.	2013	Vascular surgery (noncarotid)	47,750	
Acute renal failure				2.03 (1.39 to 2.97)
History of TIA, stroke, existing hemiplegia				1.72 (1.29 to 2.30)
Female sex				1.47 (1.12 to 1.93)
History of cardiac disease[a]				1.42 (1.07 to 1.87)
Age				1.02 (1.01 to 1.04)
Mashour et al.	2011	Non-cardiac, non-vascular, non-neurologic surgery	523,059	
Age > 62 yr				3.9 (3.0 to 5.0)
MI within 6 months				3.8 (2.4 to 6.0)
Acute renal failure				3.6 (2.3 to 5.8)
History of stroke				2.9 (2.3 to 3.8)
Dialysis				2.3 (1.6 to 3.4)
Bateman et al.	2009	Hemicolectomy, THA, lobectomy/segmental lung resection patients	371,641	
Renal disease				2.98 (2.52 to 3.54)
Atrial fibrillation				1.95 (1.69 to 2.26)
History of stroke				1.64 (1.25 to 2.14)
Valvular disease				1.54 (1.25 to 1.90)
CHF				1.44 (1.21 to 1.70)
Bucerius et al.	2003	Cardiac surgery	16,184	
High transfusion requirement				6.04 (5.05 to 7.23)
History of cerebrovascular disease				3.55 (2.71 to 4.66)
Preoperative infection				2.39 (1.69 to 3.40)
Urgent operation				1.47 (1.23 to 1.76)
CPB > 2 hours				1.42 (1.17 to 1.72)

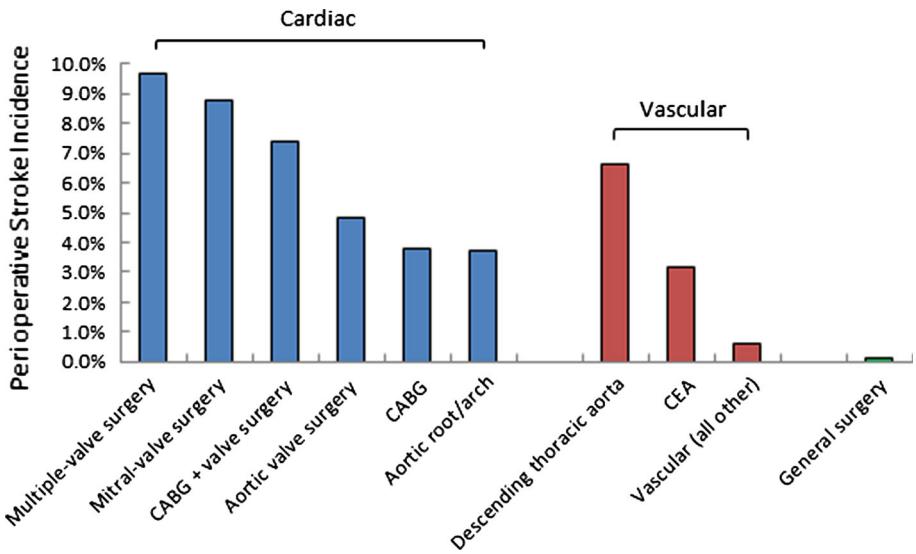

Figure Ischemic stroke risk as a function of surgical procedure. Stroke incidences are calculated composite averages derived from representative literature from cardiac,[5,96,97] vascular,[51,97-99] and general surgery.[6,7] CABG = coronary artery bypass graft; CEA = carotid endarterectomy

Recent stroke

In 2014, Jorgensen *et al.* presented observational cohort data regarding postoperative risk of major adverse cardiovascular events (MACE) after recent IS.[55] The data come from the Danish National Patient Register—a national registry of prospectively collected data from patients in the Danish healthcare system. In this study,

Table 2 Proposed perioperative modifiable risk factors

Candidate Modifiable Risk Factor	Possible Risk Reduction Strategy
Recent stroke[55]	Delay elective surgery ≥ 9 months after stroke
Intraoperative cerebral hypoxia[79,80]	Cerebral oxygenation protocol
Hypotension[83]	Avoid >30% decrease in MAP from baseline
High thromboembolism risk[a,93]	Evidence-based bridging protocol
GA, orthopedic joint replacement[81,82]	Consider neuraxial technique if possible
Beta-blockade[20]	Transfuse to Hgb ≥ 9 if patient on β-blockade

[a] Per the American College of Chest Physicians Guidelines;[95] GA = general anesthesia; Hgb = hemoglobin; MAP = mean arterial pressure

patients who had a recent history of IS also showed an increased risk of MACE and mortality within 30 days of the operation. Further, patients were also at risk for postoperative IS, and this risk progressively decreased the longer the duration of time between stroke and subsequent surgery: stroke < three months previously (odds ratio [OR], 67.6; 95% confidence interval [CI], 52.27 to 87.42), stroke three to < six months previously (OR, 24.02; 95% CI, 15.03 to 38.39), and stroke six to < 12 months previously (OR, 10.39; 95% CI, 6.18 to 17.44). The increased risk of perioperative stroke appeared to return to that of patients with a remote history of stroke in the preceding nine to 12 months. One criticism was the lack of a non-surgery control group.[59] Indeed, an increased risk of stroke recurrence has been shown within 12 months of incident stroke without surgery.[60,61] Nonetheless, probing for history of recent stroke seems reasonable. As time from the onset of stroke symptoms to intervention is critical, any conditions that obscure the ability to evaluate for stroke symptoms (e.g., recovery from general anesthesia) may place patients at higher risk. As such, elective cases should be delayed and a risk/benefit analysis should be conducted in these scenarios given 1) the challenges present with the diagnosis and management of stroke after surgery and anesthesia and 2) the eightfold increase in mortality with perioperative stroke.[7] Further investigation into the optimal timing of surgery after stroke is certainly warranted.

Perioperative beta-blockade

Evidence shows a reduced risk of MACE with perioperative beta-blockade, though this may come at the expense of an increased risk of stroke in non-cardiac surgery patients.[54,62] In the 2014 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines, the authors recommend a risk-benefit analysis for perioperative beta-blockade on a case-by-case basis.[62] Specifically, the suggestion is made to weigh the risk of MACE against the risk of perioperative stroke to guide the decision-making with regard to management of perioperative beta-blockade. In cases where the risk of MACE may be higher than that of perioperative stroke, perioperative beta-blockade may be beneficial, whereas in cases where the risk of stroke is higher than that of MACE, a strategy involving aggressive beta-blockade may be harmful. This distinction is certainly not always easy to delineate clinically. An initial step may be to identify patients on beta-blockade who are at high risk for cerebrovascular ischemia based on patient- and surgery-specific risk factors. For example, as mentioned above, the combination of anemia and beta-blockade may place patients at risk for stroke. As such, patients on preoperative beta-blockade presenting for surgery with a high risk of major hemorrhage may be at increased risk. Further investigation may be informative.

Anticoagulant and antiplatelet therapy

In general, the risk of excessive perioperative bleeding is weighed against the risk of thromboembolism, though a clear diametric clinical distinction is not always present. For patients on anticoagulation for conditions such as atrial fibrillation, the ACC/AHA Guidelines recommend discontinuation of anticoagulation for ≥ 48 hr for major surgery.[62] The American College of Chest Physicians recommends continued perioperative anticoagulation for patients at high risk for venous thromboembolism.[63] At this point, it is unclear if aggressive perioperative anticoagulation would reduce the risk of postoperative stroke,[39] and further investigation would be of benefit for clinical decision-making. With regard to antiplatelet therapy, both observational and interventional data have shown a cerebroprotective effect of acetylsalicylic acid in cardiac surgery patients.[64,65] In non-cardiac surgery patients, the POISE-2 trial showed a reduced incidence of stroke in patients who started acetylsalicylic acid therapy during the course of the study,[66] though this benefit was not seen in patients who had already been on acetylsalicylic acid therapy. Further, the authors reported that this was likely a spurious subgroup effect in the initiation stratum due to the combination of small sample size, an unexpectedly large benefit of acetylsalicylic acid,

benefits not previously shown in other studies, and a hypothesized direction opposite to the observed finding.[66,67]

Intraoperative management

From the perspective of the anesthesiologist, an evidence-based intraoperative strategy to minimize the risk of stroke may indeed sound appealing. To that end, different intraoperative anesthetic techniques and pharmacologic and physiologic strategies have been studied with the intent of minimizing postoperative risk of stroke. Below, we review some of the major studies examining intraoperative considerations that may impact the risk of perioperative stroke.

Anesthetic and monitoring techniques

Various anesthetic and neuromonitoring techniques have been studied in patients undergoing surgical procedures associated with a high risk of stroke, e.g., carotid endarterectomy (CEA). In over 3,000 patients presenting for CEA, the GALA trial randomized patients to general anesthesia (GA) *vs* local anesthesia in a multicentre randomized controlled format.[68] The trial could not show any definitive difference in stroke outcomes between those two groups. A secondary analysis of this trial did not show an increased risk of stroke in patients exposed to nitrous oxide[69] despite the known increase in plasma homocysteine levels associated with its use.[70] This finding was reaffirmed in patients undergoing major non-cardiac surgery, where the use of nitrous oxide did not confer an increased risk of stroke.[71] In patients who are indeed undergoing high-risk procedures like CEA under GA, neuromonitoring techniques, such as electroencephalography and somatosensory-evoked potential monitoring (SSEP), allow detection of intraoperative ischemia.[72,73] Electroencephalography, however, may allow for faster and more sensitive detection of ischemia than SSEP in these cases.[72,74] A review of these techniques as well as a discussion of their respective benefits and drawbacks can be found elsewhere.[74-76] Assessment of regional cerebral oxygenation (rSO_2) is an additional intraoperative neuromonitoring technique where near-infrared spectroscopy is used to measure cerebral tissue oxygenation indirectly.[77,78] In cardiac surgery patients, preliminary data indicate that intraoperative rSO_2 monitoring may reduce the risk of perioperative stroke,[79,80] though further studies are needed to confirm or refute these findings.

Lastly, investigators have recently assessed rates of perioperative stroke in orthopedic surgery patients receiving either general or neuraxial anesthesia for various joint arthroplasty procedures.[81,82] In both studies, general anesthesia was associated with a higher risk of perioperative stroke. Based on study design—a large retrospective database study[82] and a prospective observational cohort study[81]—no inferences regarding causality can be drawn. Nonetheless, the notion that anesthetic technique may modulate the risk of perioperative stroke in certain patient populations certainly deserves further investigative consideration.

Physiologic management

Optimal intraoperative physiologic management may play a role in stroke prevention. Maintaining blood pressure near preoperative baseline values may help lower the risk of stroke, though supporting evidence is limited. Two large retrospective database studies were carried out to examine the relationship between intraoperative blood pressure and postoperative stroke.[16,83] Bijker *et al.* showed an association between intraoperative hypotension and postoperative stroke when mean arterial pressure (MAP) was reduced by 30% (per minute) compared with baseline (OR, 1.01; 99.9% CI, 1.00 to 1.03).[83] This OR expresses the increase in the risk of stroke per minute of defined intraoperative hypotension (i.e., a 30% MAP reduction). In a subsequent retrospective database study, Mashour *et al.* found associations between postoperative stroke and intraoperative hypotension 20% below baseline for both systolic blood pressure (SBP) and MAP (median values measured over ten-minute intervals).[16] Reasons for the discrepancy between these studies are unclear, but they might relate to differences in the definition of baseline blood pressure as well as the duration of hypotension. Indeed, definitions of intraoperative hypotension and baseline blood pressure vary widely in the literature, as does the studied duration of perioperative hypotension.[84] As an additional consideration, Bijker *et al.* also noted significant variance in the intervals used to record postoperative blood pressure and lack of a detailed characterization of the severity of postoperative hypotension.[83] For these reasons, data regarding postoperative blood pressure were excluded from their analysis. Studying the effects of the outcomes of hypotension and perioperative stroke thus becomes difficult when considering the rarity of stroke, the lack of standardized definitions for baseline blood pressure and intraoperative hypotension, and the time period during which hypotension may be most deleterious (i.e., intraoperative *vs* postoperative).

Avoiding extremes in plasma glucose concentration may also help reduce the risk of stroke. Ghandi *et al.* found an increased risk of postoperative stroke with tight intraoperative glucose control in cardiac surgery patients.[85] Conversely, Doenst *et al.* showed an increased risk of composite adverse events—including stroke—with hyperglycemia during cardiac surgery.[86] At present, few data are otherwise available to guide intraoperative glucose management, especially in the non-cardiac surgery literature.

Intraoperative beta-blockade

As discussed previously, the findings of the POISE trial led many to rethink the approach to perioperative beta-blockade. At the time, few data existed relating risk of perioperative stroke to specific beta-blockers, dosing regimens, and, notably, effects of *intraoperative* beta-blockade. In a retrospective investigation of 57,218 patients, Mashour *et al.*[16] found a 3.3-fold (95% CI, 1.4 to 7.8; $P = 0.003$) unadjusted increased risk of perioperative stroke in patients who received intraoperative metoprolol. This finding was not shown with other beta-blockers studied. Postulated mechanisms for this association include impaired cerebral tissue oxygen delivery via decreased cerebral vasodilation and impaired CO in the setting of hemodilution.[46-48] At present, few other data exist regarding intraoperative beta-blockade and cerebrovascular outcomes. Decisions regarding intraoperative beta-blockade may be made on a case-by-case basis depending on the patient, type of surgical intervention, and ongoing physiologic considerations as previously described.

Postoperative management

In general, only approximately 5-15% of perioperative strokes occur intraoperatively or in the immediate (i.e., apparent in the postanesthesia care unit) postoperative setting.[16,51] Indeed, most postoperative strokes present at least 24 hr after surgery.[16,51] Given this timeline, continued clinical vigilance for stroke symptoms along with timely neurology consultation is paramount for successful diagnosis and management of postoperative stroke. Emergent neuroimaging should be obtained in parallel with activation of the stroke rapid response team, if available. A multidisciplinary discussion involving neurology and the primary surgical service should ensue with input from interventional neuroradiology and anesthesiology as needed. Providers should seek expeditious evaluation and mobilization of resources, as in-hospital stroke may be associated with worse outcomes compared with community-onset stroke.[57] Indeed, Saltman *et al.* reported delayed recognition of symptoms, delayed neuroimaging, lower rates of thrombolysis, and exceptionally severe stroke with in-hospital stroke patients compared with those with community-onset stroke.[57] Surgical patients represented nearly 50% of all in-hospital strokes in this study. Thus, timely and optimal management of perioperative stroke may be crucial in these high-risk patients. Glucose should be checked, as both hypo- and hyperglycemia have been associated with worse stroke outcomes.[85,87] Acetylsalicylic acid should be considered prior to discharge if surgically feasible, given improved outcomes when used for secondary prevention.[88] A proposed management checklist for perioperative stroke is outlined in Table 3.

Treatment for postoperative stroke remains a source of ongoing active discussion. According to the 2013 AHA/ASA Guidelines, patients who have undergone recent major surgery may be candidates for intravenous fibrinolysis, though a careful risk-benefit analysis should first be conducted.[89] These guidelines also speculate that selective intra-arterial thrombolysis may be warranted in a select group of surgical patients who may be at high risk

Table 3 Perioperative ischemic stroke management

Perioperative Ischemic Stroke Checklist
☑ Monitoring, supplemental oxygen, adequate intravenous access
☑ Activate stroke team. Concurrently:
☐ Notify surgical team, neuro-interventional team
☐ Establish time last known well
☐ Neurologic exam, stroke scale (i.e., NIHSS)
☐ Check glucose, troponins
☐ Check electrolytes, complete blood count, coagulation parameters
☐ 12-lead EKG
☐ Emergent neuroimaging (CT *vs* MRI)
☑ Candidate for rtPA? Endovascular retrieval?
☐ Yes - maintain BP < 185/110 mmHg, no ASA or anticoagulation
☐ No - maintain BP < 220/120 mmHg, consider ASA
☑ Multidisciplinary management

ASA = acetylsalicylic acid (aspirin); BP = blood pressure; CT = computed tomography; EKG = electrocardiogram; MRI = magnetic resonance imaging; NIHSS = National Institutes of Health Stroke Scale; rtPA = recombinant tissue plasminogen activator

for systemic hemorrhage. Several case series have shown a favourable safety profile of intra-arterial intervention across diverse surgical populations.[90-92] Catheter-based mechanical interventions may also be appropriate in these select populations, especially given recent data showing improved functional outcomes and reduction in mortality among select patients.[93] Ultimately, further investigation is warranted.

In terms of blood pressure management in IS patients, the 2013 AHA/ASA Guidelines recommend permissive hypertension up to 220/120 mmHg if *not* being considered for thrombolytic reperfusion therapy and if not contraindicated by coexisting medical conditions (i.e., acute aortic dissection, acute myocardial infarction, etc.).[89] If intravenous thrombolytic therapy is being considered, however, recommendations are for controlled blood pressure reduction to $< 185/110$ mmHg.[89] Since the release of these Guidelines, the results of the China Antihypertensive Trial in Acute Ischemic Stroke (CATIS) have been released. From a starting mean [standard deviation (SD)] SBP of 166.7 (17.3) mmHg, there was no clinical benefit in reducing blood pressure to 144.7 (15.0) mmHg at 24 hr or to 137.3 (11.8) mmHg at seven days.[56] Thus, at present, a SBP goal of approximately 140-185 mmHg may be reasonable. Certainly, avoiding extremes of blood pressure may help avoid further neurologic insult, as has been observed in patients after receiving thrombolysis.[94]

Conclusions

Perioperative stroke has attracted renewed attention over the past few years, as associated morbidity and mortality remain high and potentially modifiable risk factors have been identified. Significant investigative work remains to be done in the areas of perioperative beta-blockade, anticoagulation, antiplatelet management, and intraoperative management. The SNACC Consensus Statement represents a succinct yet thorough review of the current literature supporting preventative and management approaches to perioperative stroke.

Funding source Department of Anesthesiology, University of Michigan Health System.

Conflicts of interest None declared.

References

1. *Mendis S*, *Puska P*, *Norrving B*. Global Atlas on Cardiovascular Disease Prevention and Control. Geneva: World Health Organization Publications; 2011 .
2. *Mathers CD*, *Loncar D*. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006; 3: e442.
3. *Wong GY*, *Warner DO*, *Schroeder DR*, *et al*. Risk of surgery and anesthesia for ischemic stroke. Anesthesiology 2000; 92: 425-32.
4. *Etzioni DA*, *Liu JH*, *Maggard MA*, *Ko CY*. The aging population and its impact on the surgery workforce. Ann Surg 2003; 238: 170-7.
5. *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: 472-8.
6. *Bateman BT*, *Schumacher HC*, *Wang S*, *Shaefi S*, *Berman MF*. Perioperative acute ischemic stroke in noncardiac and nonvascular surgery: incidence, risk factors, and outcomes. Anesthesiology 2009; 110: 231-8.
7. *Mashour GA*, *Shanks AM*, *Kheterpal S*. Perioperative stroke and associated mortality after noncardiac, nonneurologic surgery. Anesthesiology 2011; 114: 1289-96.
8. *Mrkobrada M, Hill MD, Chan MT, et al.* The neurovision pilot study: non-cardiac surgery carries a significant risk of acute covert stroke. Stroke 2013; 44: T MP9 (abstract).
9. *Barber PA*, *Hach S*, *Tippett LJ*, *Ross L*, *Merry AF*, *Milsom P*. Cerebral ischemic lesions on diffusion-weighted imaging are associated with neurocognitive decline after cardiac surgery. Stroke 2008; 39: 1427-33.
10. *Parikh S*, *Cohen JR*. Perioperative stroke after general surgical procedures. N Y State J Med 1993; 93: 162-5.
11. *Landercasper J*, *Merz BJ*, *Cogbill TH*, *et al*. Perioperative stroke risk in 173 consecutive patients with a past history of stroke. Arch Surg 1990; 125: 986-9.
12. *Biteker M*, *Kayatas K*, *Turkmen FM*, *Misirli CH*. Impact of perioperative acute ischemic stroke on the outcomes of noncardiac and nonvascular surgery: a single centre prospective study. Can J Surg 2014; 57: E55-61.
13. *Mashour GA*, *Moore LE*, *Lele AV*, *Robicsek SA*, *Gelb AW*. Perioperative care of patients at high risk for stroke during or after non-cardiac, non-neurologic surgery: consensus statement from the Society for Neuroscience in Anesthesiology and Critical Care. J Neurosurg Anesthesiol 2014; 26: 273-85.
14. *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.
15. *Likosky DS*, *Marrin CA*, *Caplan LR*, *et al*. Determination of etiologic mechanisms of strokes secondary to coronary artery bypass graft surgery. Stroke 2003; 34: 2830-4.
16. *Mashour GA*, *Sharifpour M*, *Freundlich RE*, *et al*. Perioperative metoprolol and risk of stroke after noncardiac surgery. Anesthesiology 2013; 119: 1340-6.
17. *Ng JL*, *Chan MT*, *Gelb AW*. Perioperative stroke in noncardiac, nonneurosurgical surgery. Anesthesiology 2011; 115: 879-90.
18. *Popa AS*, *Rabinstein AA*, *Huddleston PM*, *Larson DR*, *Gullerud RE*, *Huddleston JM*. Predictors of ischemic stroke after hip operation: a population-based study. J Hosp Med 2009; 4: 298-303.
19. *Limburg M*, *Wijdicks EF*, *Li H*. Ischemic stroke after surgical procedures: clinical features, neuroimaging, and risk factors. Neurology 1998; 50: 895-901.
20. *Ashes C*, *Judelman S*, *Wijeysundera DN*, *et al*. Selective beta1-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: 777-87.
21. *POISE Study Group; 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: 1839-47.

22. *Schietroma M*, *Carlei F*, *Mownah A*, *et al*. Changes in the blood coagulation, fibrinolysis, and cytokine profile during laparoscopic and open cholecystectomy. Surg Endosc 2004; 18: 1090-6.
23. *Khafagy HF*, *Hussein NA*, *Madkour ME*, *et al*. Perioperative effects of anesthesia and surgery on inflammation-coagulation interaction. Life Sci J 2014; 11: 900-6.
24. *Collins GJ Jr*, *Barber JA*, *Zajtchuk R*, *Vanek D*, *Malogne LA*. The effects of operative stress on the coagulation profile. Am J Surg 1977; 133: 612-6.
25. *Cundiff DK*. Clinical evidence for rebound hypercoagulability after discontinuing oral anticoagulants for venous thromboembolism. Medscape J Med 2008; 10: 258.
26. *Broderick JP*, *Bonomo JB*, *Kissela BM*, *et al*. Withdrawal of antithrombotic agents and its impact on ischemic stroke occurrence. Stroke 2011; 42: 2509-14.
27. *Stouthard JM*, *Levi M*, *Hack CE*, *et al*. Interleukin-6 stimulates coagulation, not fibrinolysis, in humans. Thromb Haemost 1996; 76: 738-42.
28. *Rost NS*, *Wolf PA*, *Kase CS*, *et al*. Plasma concentration of C-reactive protein and risk of ischemic stroke and transient ischemic attack: the Framingham study. Stroke 2001; 32: 2575-9.
29. *Everett BM*, *Kurth T*, *Buring JE*, *Ridker PM*. The relative strength of C-reactive protein and lipid levels as determinants of ischemic stroke compared with coronary heart disease in women. J Am Coll Cardiol 2006; 48: 2235-42.
30. *Ridker PM*, *Cushman M*, *Stampfer MJ*, *Tracy RP*, *Hennekens CH*. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997; 336: 973-9.
31. *Kuhn EW*, *Liakopoulos OJ*, *Stange S*, *et al*. Preoperative statin therapy in cardiac surgery: a meta-analysis of 90,000 patients. Eur J Cardiothorac Surg 2014; 45: 17-26.
32. *Antoniou GA, Hajibandeh S, Hajibandeh S, Vallabhaneni SR, Brennan JA, Torella F*. Meta-analysis of the effects of statins on perioperative outcomes in vascular and endovascular surgery. J Vasc Surg 2015; 61: 519-32e1.
33. *Everett BM*, *Glynn RJ*, *MacFadyen JG*, *Ridker PM*. Rosuvastatin in the prevention of stroke among men and women with elevated levels of C-reactive protein: Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER). Circulation 2010; 121: 143-50.
34. *Engstrom G*, *Lind P*, *Hedblad B*, *Stavenow L*, *Janzon L*, *Lindgarde F*. Effects of cholesterol and inflammation-sensitive plasma proteins on incidence of myocardial infarction and stroke in men. Circulation 2002; 105: 2632-7.
35. *Ridker PM*, *Rifai N*, *Clearfield M*, *et al*. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. N Engl J Med 2001; 344: 1959-65.
36. *Liakopoulos OJ*, *Choi YH*, *Haldenwang PL*, *et al*. Impact of preoperative statin therapy on adverse postoperative outcomes in patients undergoing cardiac surgery: a meta-analysis of over 30,000 patients. Eur Heart J 2008; 29: 1548-59.
37. *McGirt MJ, Perler BA, Brooke BS, et al.* 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors reduce the risk of perioperative stroke and mortality after carotid endarterectomy. J Vasc Surg 2005; 42: 829-36; discussion 836-7.
38. *Likosky DS*, *Caplan LR*, *Weintraub RM*, *et al.; Northern New England Cardiovascular Disease Study Group*. Intraoperative and postoperative variables associated with strokes following cardiac surgery. Heart Surg Forum 2004; 7: E271-6.
39. *Kaatz S*, *Douketis JD*, *Zhou H*, *Gage BF*, *White RH*. Risk of stroke after surgery in patients with and without chronic atrial fibrillation. J Thromb Haemost 2010; 8: 884-90.
40. *McLaren AT*, *Marsden PA*, *Mazer CD*, *et al*. Increased expression of HIF-1alpha, nNOS, and VEGF in the cerebral cortex of anemic rats. Am J Physiol Regul Integr Comp Physiol 2007; 292: R403-14.
41. *Brannon ES*, *Merrill AJ*, *Warren JV*, *Stead EA*. The cardiac output in patients with chronic anemia as measured by the technique of right atrial catheterization. J Clin Invest 1945; 24: 332-6.
42. *Duke M*, *Abelmann WH*. The hemodynamic response to chronic anemia. Circulation 1969; 39: 503-15.
43. *Tu YK*, *Liu HM*. Effects of isovolemic hemodilution on hemodynamics, cerebral perfusion, and cerebral vascular reactivity. Stroke 1996; 27: 441-5.
44. *Korosue K*, *Ishida K*, *Matsuoka H*, *Nagao T*, *Tamaki N*, *Matsumoto S*. Clinical, hemodynamic, and hemorheological effects of isovolemic hemodilution in acute cerebral infarction. Neurosurgery 1988; 23: 148-53.
45. *Korosue K, Heros RC*. Mechanism of cerebral blood flow augmentation by hemodilution in rabbits. Stroke 1992; 23: 1487-92; discussion 1492-3.
46. *Ragoonanan TE*, *Beattie WS*, *Mazer CD*, *et al*. Metoprolol reduces cerebral tissue oxygen tension after acute hemodilution in rats. Anesthesiology 2009; 111: 988-1000.
47. *Hare GM*, *Worrall JM*, *Baker AJ*, *Liu E*, *Sikich N*, *Mazer CD*. Beta2 adrenergic antagonist inhibits cerebral cortical oxygen delivery after severe haemodilution in rats. Br J Anaesth 2006; 97: 617-23.
48. *El Beheiry MH*, *Heximer SP*, *Voigtlaender-Bolz J*, *et al*. Metoprolol impairs resistance artery function in mice. J Appl Physiol 1985; 2011(111): 1125-33.
49. *Hu T*, *Beattie WS*, *Mazer CD*, *et al*. Treatment with a highly selective beta(1) antagonist causes dose-dependent impairment of cerebral perfusion after hemodilution in rats. Anesth Analg 2013; 116: 649-62.
50. *Sacco RL, Kasner SE, Broderick JP, et al.; 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 Metabolis.* 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
51. *Sharifpour M*, *Moore LE*, *Shanks AM*, *Didier TJ*, *Kheterpal S*, *Mashour GA*. Incidence, predictors, and outcomes of perioperative stroke in noncarotid major vascular surgery. Anesth Analg 2013; 116: 424-34.
52. *Goodney PP*, *Likosky DS*, *Cronenwett JL*, *Vascular Study Group of Northern New England*. Factors associated with stroke or death after carotid endarterectomy in Northern New England. J Vasc Surg 2008; 48: 1139-45.
53. *Gialdini G*, *Nearing K*, *Bhave PD*, *et al*. Perioperative atrial fibrillation and the long-term risk of ischemic stroke. JAMA 2014; 312: 616-22.
54. *Blessberger H, Kammler J, Domanovits H, et al.* Perioperative beta-blockers for preventing surgery-related mortality and morbidity. Cochrane Database Syst Rev 2014; 9: CD004476.
55. *Jorgensen 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: 269-77.
56. *He J*, *Zhang Y*, *Xu T*, *CATIS Investigators*, *et al*. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: the CATIS randomized clinical trial. JAMA 2014; 311: 479-89.
57. *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.
58. *Maatz W*, *Kohler J*, *Botsios S*, *John V*, *Walterbusch G*. Risk of stroke for carotid endarterectomy patients with contralateral carotid occlusion. Ann Vasc Surg 2008; 22: 45-51.

59. *Powers WJ*. Time since stroke and risk of adverse outcomes after surgery. JAMA 2014; 312: 1930.
60. *Dhamoon MS*, *Sciacca RR*, *Rundek T*, *Sacco RL*, *Elkind MS*. Recurrent stroke and cardiac risks after first ischemic stroke: the Northern Manhattan Study. Neurology 2006; 66: 641-6.
61. *Brown DL*, *Lisabeth LD*, *Roychoudhury C*, *Ye Y*, *Morgenstern LB*. Recurrent stroke risk is higher than cardiac event risk after initial stroke/transient ischemic attack. Stroke 2005; 36: 1285-7.
62. *Fleisher LA, Fleischmann KE, Auerbach AD, et al.; American College of Cardiology, American Heart Association.* 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. J Am Coll Cardiol 2014; 64: e77-137.
63. *Guyatt GH*, *Akl EA*, *Crowther M*, *Gutterman DD*, *Schuunemann HJ*, *American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel*. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141: 7S-47S.
64. *Cao L*, *Silvestry S*, *Zhao N*, *Diehl J*, *Sun J*. Effects of preoperative aspirin on cardiocerebral and renal complications in non-emergent cardiac surgery patients: a sub-group and cohort study. PLoS One 2012; 7: e30094.
65. *Mangano DT*, *Multicenter Study of Perioperative Ischemia Research Group*. Aspirin and mortality from coronary bypass surgery. N Engl J Med 2002; 347: 1309-17.
66. *Devereaux PJ*, *Mrkobrada M*, *Sessler DI*, *POISE-2 Investigators*, *et al*. Aspirin in patients undergoing noncardiac surgery. N Engl J Med 2014; 370: 1494-503.
67. *Sun X*, *Briel M*, *Walter SD*, *Guyatt GH*. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ 2010; 340: c117.
68. *GALA Trial Collaborative Group GTC, Lewis SC, Warlow CP, Bodenham AR, et al.* General anaesthesia versus local anaesthesia for carotid surgery (GALA): a multicentre, randomised controlled trial. Lancet 2008; 372: 2132-42.
69. *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: 361-7.
70. *Myles PS*, *Chan MT*, *Leslie K*, *Peyton P*, *Paech M*, *Forbes A*. Effect of nitrous oxide on plasma homocysteine and folate in patients undergoing major surgery. Br J Anaesth 2008; 100: 780-6.
71. *Myles PS, Leslie K, Chan MT, et al.; ANZCA Trials Group for the ENIGMA-II Investigators.* The safety of addition of nitrous oxide to general anaesthesia in at-risk patients having major non-cardiac surgery (ENIGMA-II): a randomised, single-blind trial. Lancet 2014; 384: 1446-54.
72. *Pinkerton JA Jr*. EEG as a criterion for shunt need in carotid endarterectomy. Ann Vasc Surg 2002; 16: 756-61.
73. *Manninen P*, *Sarjeant R*, *Joshi M*. Posterior tibial nerve and median nerve somatosensory evoked potential monitoring during carotid endarterectomy. Can J Anesth 2004; 51: 937-41.
74. *Fielmuth S*, *Uhlig T*. The role of somatosensory evoked potentials in detecting cerebral ischaemia during carotid endarterectomy. Eur J Anaesthesiol 2008; 25: 648-56.
75. *Pennekamp CW*, *Moll FL*, *de Borst GJ*. The potential benefits and the role of cerebral monitoring in carotid endarterectomy. Curr Opin Anaesthesiol 2011; 24: 693-7.
76. *Moritz S*, *Kasprzak P*, *Arlt M*, *Taeger K*, *Metz C*. Accuracy of cerebral monitoring in detecting cerebral ischemia during carotid endarterectomy: a comparison of transcranial Doppler sonography, near-infrared spectroscopy, stump pressure, and somatosensory evoked potentials. Anesthesiology 2007; 107: 563-9.
77. *Wahr JA*, *Tremper KK*, *Samra S*, *Delpy DT*. Near-infrared spectroscopy: theory and applications. J Cardiothorac Vasc Anesth 1996; 10: 406-18.
78. *Jobsis FF*. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. Science 1977; 198: 1264-7.
79. *Murkin JM*, *Adams SJ*, *Novick RJ*, *et al*. Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study. Anesth Analg 2007; 104: 51-8.
80. *Goldman S*, *Sutter F*, *Ferdinand F*, *Trace C*. Optimizing intraoperative cerebral oxygen delivery using noninvasive cerebral oximetry decreases the incidence of stroke for cardiac surgical patients. Heart Surg Forum 2004; 7: E376-81.
81. *Mortazavi SM*, *Kakli H*, *Bican O*, *Moussouttas M*, *Parvizi J*, *Rothman RH*. Perioperative stroke after total joint arthroplasty: prevalence, predictors, and outcome. J Bone Joint Surg Am 2010; 92: 2095-101.
82. *Memtsoudis SG*, *Sun X*, *Chiu YL*, *et al*. Perioperative comparative effectiveness of anesthetic technique in orthopedic patients. Anesthesiology 2013; 118: 1046-58.
83. *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: 658-64.
84. *Bijker JB*, *Gelb AW*. Review article: the role of hypotension in perioperative stroke. Can J Anesth 2013; 60: 159-67.
85. *Gandhi GY*, *Nuttall GA*, *Abel MD*, *et al*. Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: a randomized trial. Ann Intern Med 2007; 146: 233-43.
86. *Doenst T*, *Wijeysundera D*, *Karkouti K*, *et al*. Hyperglycemia during cardiopulmonary bypass is an independent risk factor for mortality in patients undergoing cardiac surgery. J Thorac Cardiovasc Surg 2005; 130: 1144.
87. *McGirt MJ*, *Woodworth GF*, *Brooke BS*, *et al*. Hyperglycemia independently increases the risk of perioperative stroke, myocardial infarction, and death after carotid endarterectomy. Neurosurgery 2006; 58: 1066-73.
88. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. CAST (Chinese Acute Stroke Trial) Collaborative Group. Lancet 1997; 349: 1641-9.
89. *Jauch EC, Saver JL, Adams HP Jr, et al.; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Clinical Cardiology.* Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013; 44: 870-947.
90. *Chalela JA*, *Katzan I*, *Liebeskind DS*, *et al*. Safety of intra-arterial thrombolysis in the postoperative period. Stroke 2001; 32: 1365-9.
91. *Moazami N, Smedira NG, McCarthy PM, et al.* Safety and efficacy of intraarterial thrombolysis for perioperative stroke after cardiac operation. Ann Thorac Surg 2001; 72: 1933-7; discussion 1937-9.
92. *Katzan IL*, *Masaryk TJ*, *Furlan AJ*, *et al.* Intra-arterial thrombolysis for perioperative stroke after open heart surgery. Neurology 1999; 52: 1081-4.
93. *Goyal M, Demchuk AM, Menon BK, et al.; ESCAPE Trial Investigators.* Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015; 372: 1019-30.

94. *Ahmed N, Wahlgren N, Brainin M, et al.; SITS Investigators.* Relationship of blood pressure, antihypertensive therapy, and outcome in ischemic stroke treated with intravenous thrombolysis: retrospective analysis from Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR). Stroke 2009; 40: 2442-9.
95. *Epstein AE*, *Alexander JC*, *Gutterman DD*, *Maisel W*, *Wharton JM*, *American College of Chest Physicians*. Anticoagulation: American College of Chest Physicians guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery. Chest 2005; 128: 24S-7S.
96. *Anyanwu AC*, *Filsoufi F*, *Salzberg SP*, *Bronster DJ*, *Adams DH*. Epidemiology of stroke after cardiac surgery in the current era. J Thorac Cardiovasc Surg 2007; 134: 1121-7.
97. *Higgins J*, *Lee MK*, *Co C*, *Janusz MT*. Long-term outcomes after thoracic aortic surgery: a population-based study. J Thorac Cardiovasc Surg 2014; 148: 47-52.
98. *Axelrod DA*, *Stanley JC*, *Upchurch GR Jr*, *et al*. Risk for stroke after elective noncarotid vascular surgery. J Vasc Surg 2004; 39: 67-72.
99. *Bonati LH, Dobson J, Featherstone RL, et al.; International Carotid Stenting Study Investigators.* Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the International Carotid Stenting Study (ICSS) randomised trial. Lancet 2015; 385: 529-38.