

Perioperative Stroke in Noncardiac, Nonneurosurgical Surgery

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ABSTRACT

Perioperative stroke after noncardiac, nonneurosurgical procedures is more common than generally acknowledged. It is reported to have an incidence of 0.05–7% of patients. Most are thrombotic in origin and are noted after discharge from the postanesthetic care unit. Common predisposing factors include age, a previous stroke, atrial fibrillation, and vascular and metabolic diseases. The mortality is more than two times greater than in strokes occurring outside the hospital. Delayed diagnosis and a synergistic interaction between the inflammatory changes normally associated with stroke, and those normally occurring after surgery, may explain this increase.

Intraoperative hypotension is an infrequent direct cause of stroke. Hypotension will augment the injury produced by embolism or other causes, and this may be especially important

in the postoperative period, during which monitoring is not nearly as attentive as in the operating room. Increased awareness and management of predisposing risk factors with early detection should result in improved outcomes.

STROKE is an important cause of morbidity and mortality, particularly in patients more than 65 yr old. In cardiac, neurologic, and carotid surgery, the incidence is known to be high (2.2–5.2%).¹ However, little is known regarding perioperative stroke following other types of surgery including general, urologic, orthopedic, thoracic, and gynecologic procedures. The aims of this article are to review the incidence, pathophysiology, risk factors, and outcomes associated with perioperative stroke following noncardiac, nonneurologic, and vascular surgery. Suggestions regarding the timing of elective surgery after stroke and ways in which one can reduce the incidence and improve outcomes are also outlined.

Definition

The World Health Organization definition of stroke is a “focal or global neurologic deficit of cerebrovascular cause that persists beyond 24 h or is interrupted by death within 24 h.” Transient ischemic attack is acute loss of focal cerebral or ocular function with symptoms lasting less than 24 h and is usually presumed to be embolic or thrombotic in origin. In addition, a third type of cerebrovascular event has recently attracted much attention in the nonsurgical setting. Covert stroke is an asymptomatic ischemic event usually only detected by advanced neuroimaging techniques, such as diffusion-weighted magnetic resonance imaging sequences.² Although the diagnosis is often missed at the time of the event, covert stroke has been associated with an adverse effect on cognitive function and quality of life. Currently other than in cardiac and carotid artery surgery, there is no study evaluating the incidence, impact, and risk factors of covert stroke in the general surgical population.³ This review therefore concentrates on periopera-

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Table 1. Incidence of Perioperative Stroke after Noncardiac Surgery

First Author	Period of Analysis	Study Design	Patient Population	Strokes, n	Patients, n	Risk of Stroke (%)	Length of Follow-up	Diagnostic Criteria	Mechanisms of Stroke
Knapp ⁴	1959–1962	Retrospective	Male patients older than 50 yr undergoing all types of surgery	34	8,984	0.4	Unclear. Less than 3 yr	Neurologic examination	Not reported
Cooperman ⁵	1978	Retrospective	Vascular surgery	4	566	0.7	Hospital discharge	Unclear	Not reported
Turnipseed ⁶	1977–1979	Prospective	Peripheral vascular surgery	7 (2 had TIA)	160	4.4	Hospital discharge	Unclear	Thrombosis: 43% Hypoperfusion: 0% Embolism: 57% Hemorrhagic: 0%
Hart ⁷	1975–1982	Retrospective	Adult patients undergoing noncarotid and noncardiac surgery	12	24,500	0.05	Hospital discharge	CT	Thrombosis: 8% Hypoperfusion: 17% Embolism: 50% Hemorrhagic: 0% Unclear: 25%
Larsen ⁸	1981–1983	Prospective	Patients older than 40 yr, undergoing noncardiac, noncarotid artery surgery	9 (3 had TIA)	2,463	0.4	Hospital discharge	Neurologic examination	Thrombosis: 0% Hypoperfusion: 44% Embolism: 33% Hemorrhagic: 0% Unclear: 23%
Landercaasper ⁹	1980–1988	Retrospective	Patients with a history of cerebrovascular disease undergoing noncardiac, noncarotid artery surgery	5	173	2.9	Hospital discharge	CT	Thrombosis: 0% Hypoperfusion: 0% Embolism: 20% Hemorrhagic: 60% Unclear: 20%
Parikh ¹⁰	1987–1992	Retrospective	Noncardiac, noncarotid artery surgery	19	24,641	0.08	Hospital discharge	CT	Thrombosis: 37% Hypoperfusion: 5% Embolism: 47% Hemorrhagic: 5% Unclear: 6%
Limburg ¹¹	1986–1996	Retrospective	Selected patients at risk of perioperative stroke	70	2,002	3.5	Hospital discharge	CT/MRI	Thrombosis: 51% Hypoperfusion: 19% Embolism: 27% Hemorrhagic: 3%
*Kikura ¹²	1991–2002	Prospective	Consecutive adult patients undergoing general orthopedic, vascular, and thoracic surgery	97	21,903	0.4	30 days after surgery	CT/MRI	Include ischemic stroke only
Parvizi ¹³	2004–2005	Prospective	Patients undergoing hip or knee arthroplasties	6 (include TIA)	1,636	0.4	6 weeks after surgery	Unclear	Not reported
*Kikura ¹⁴	1991–2006	Retrospective	Patients undergoing noncardiac, noncarotid surgery	126	36,634	0.34	30 days after surgery	CT/MRI	Not reported
Popa ¹⁵	1998–2002	Retrospective	Patients older than 65 yr, undergoing major hip surgery	76	1,886	4.0	1 yr after surgery	CT/MRI	Thrombosis: 88% Hemorrhagic: 12%
Bateman ¹⁶	2002–2004	Retrospective	Patients older than 18 yr undergoing: Hemicolectomy Hip replacement Lung resection	— 939 420 242	— 131,067 201,235 39,339	— 0.7 0.2 0.6	Hospital discharge	CT/MRI	Include ischemic stroke only
Huang ¹⁷	2002–2007	Retrospective	Cesarean section undergoing regional or general anesthesia	151	303,862	0.05	Hospital discharge	Not reported	Not reported

* Patient population overlapped in these two reports.

CT = computer tomography; MRI = magnetic resonance imaging; TIA = transient ischemic attack.

tive overt stroke that is commonly defined as one that occurs during and up to 30 days after surgery.

Incidence, Morbidity, and Mortality of Perioperative Stroke in Noncardiac and Nonneurosurgical Procedures

The reported incidence of stroke following procedures other than cardiac, neurosurgical, and carotid artery surgery ranges

between 0.05 and 7.4% (table 1).^{4–17} Differences in patient population, changing clinical practice over 40 yr (1967–2009), study design, diagnostic tests, and duration of follow up may account for the large variance in reported preoperative stroke rates. The majority of the older and current studies are retrospective reviews of administrative databases. Although most major strokes are usually revealed in these databases,¹⁸ it is likely that minor strokes, covert strokes, and

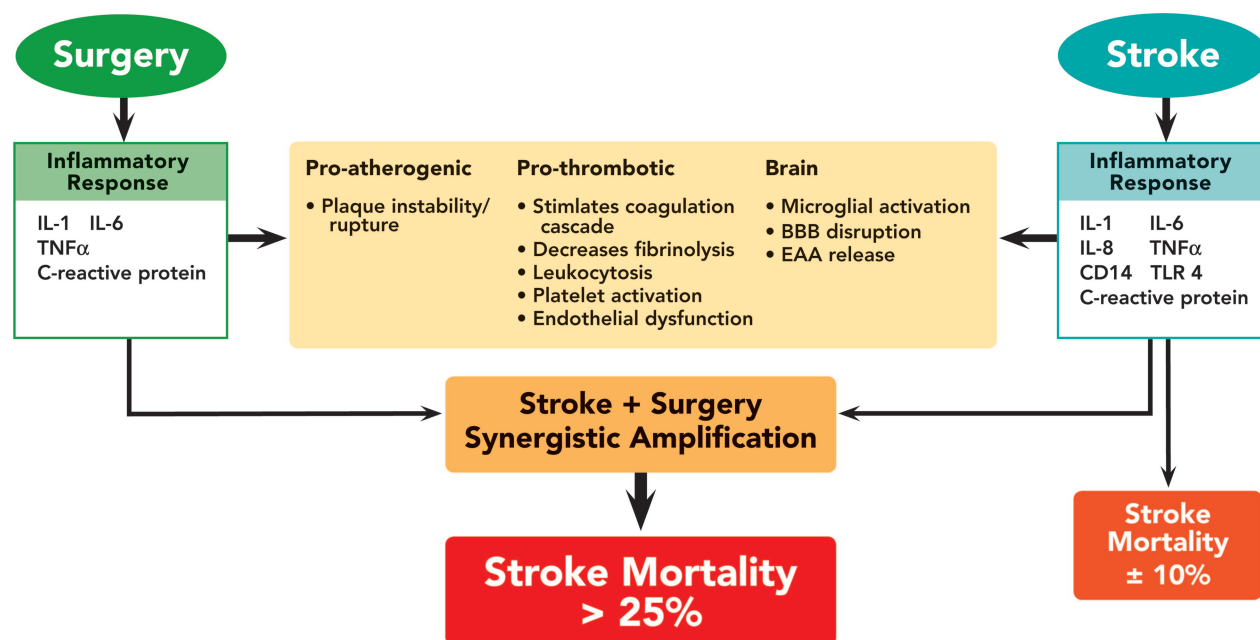


Fig. 1. Pathophysiology of perioperative stroke. BBB = blood brain barrier; CD = cluster of differentiation; EAA = excitatory amino acids; IL = interleukin; TLR = Toll-like receptor; TNF α = tumor necrosis factor α .

transient ischemic attacks are missed because they are not noted by the caregivers or the clinical notes are not correctly interpreted by the coding officers.

Outcome after perioperative stroke is usually devastating.¹⁶ In contrast to the 12.6% mortality rate associated with strokes in the nonsurgical setting,¹⁹ mortality from perioperative stroke ranges from 26% after general surgery¹⁰ to 87% in patients who have had a previous stroke.^{9,16} Early mortality from major stroke may result from delayed recognition and diagnosis on surgical services, cerebral edema, and intracranial hypertension, whereas late mortality may be caused by aspiration, pneumonia, metabolic derangement, sepsis, or myocardial infarction.⁷

Extensive evidence implicates inflammation in multiple phases of stroke pathophysiology, and there is increasing awareness that inflammatory events outside the brain have an important impact on stroke susceptibility and outcome, perhaps by amplification of those pathways activated in stroke (fig. 1).^{20,21} It is probable that the acute systemic inflammatory response triggered by surgery initiates or exacerbates ischemic cerebral injury. Laboratory studies using sepsis models in conjunction with neurologic injury^{22,23} and clinical studies demonstrate more severe neurologic deficits, especially when preceded by respiratory and urologic infections.^{24–29} Various cytokines have been implicated in the postoperative inflammatory response including interleukin-1, interleukin-6, and tumor necrosis factor α ,³⁰ and an increased C-reactive protein level.³¹ Interleukin-6 appears to be the major mediator of the stress response after surgery. Interestingly, the peak plasma concentration of interleukin-6 correlates significantly with computed tomography brain infarct volume and clinical outcome assessed by modified

Rankin scale score at 3 months in patients who suffer an acute ischemic stroke. A peak plasma interleukin-6 concentration greater than 30 pg/ml was associated with increased mortality at 12 months.³² The association between interleukin-6 measured on admission and in-hospital mortality in patients with acute ischemic stroke has been demonstrated in another study, which found that a 1-unit increase in interleukin-6 predicted an 18% higher risk of dying during hospitalization for acute ischemic stroke.³³

Pathophysiology

Strokes are either ischemic or hemorrhagic. Ischemic stroke may be classified according to presenting symptoms and signs, using the Oxfordshire Community Stroke Project categories, or etiologically, according to the definition in the Trial of Org 10172 in Acute Stroke Treatment.^{34,35} The latter identifies the pathophysiologic mechanism of vessel occlusion, including large artery thrombosis, artery to artery embolism, cardioembolic, and small vessel (lacunar) occlusion. Watershed infarction is another important mechanism of ischemic stroke. Cortical and internal (white matter, centrum ovale) watershed areas occur at the junction of the distal fields of two or more nonanastomosing arterial systems and are vulnerable to ischemia because of their position, where perfusion pressure is the lowest.³⁶ The pathophysiology of watershed infarcts is controversial, with substantial evidence supporting both low flow and multiple microembolic mechanisms.³⁷ An embolic component is most frequent with cortical watershed infarcts, especially when associated with atherosclerotic stenosis of inflow vessels. Hemodynamic factors seem most important for internal watershed infarcts or in-

farcts associated with complete occlusion of inflow vessels. It has been postulated that hypoperfusion, or hypotension, and embolism play a synergistic role: the decreased perfusion reduces clearance of microemboli, and the blocked vessels extend the hypoperfused area.³⁸

The majority of perioperative strokes occur after the second postoperative day.^{7,10} Of all the studies that reported the details of stroke, only 5.8% (14 of 242) of cases were thought to have occurred during surgery,^{4–11,13,15} suggesting that postoperative events rather than intraoperative mechanisms are important.^{7,11} It is estimated that more than 60% of strokes in the cardiothoracic population have an embolic origin; about 12–15% are ischemic because of hypoperfusion, lacunar infarction, and thrombosis; 1% are hemorrhagic; 10% have multiple etiologies; and 15% have unknown etiology.³⁹ The pathophysiology of perioperative stroke occurring in patients undergoing noncardiac, nonneurosurgical procedures is less well defined. Currently only nine studies have reported the mechanisms of stroke after noncardiac and nonneurologic surgery (301 strokes, table 1).^{6–12,15} In contrast to the cardiothoracic patients, the majority, or 68%, of strokes were because of cerebrovascular thrombosis. About 16% of strokes were thought to be embolic in nature. Another 5% of strokes were because of intracerebral hemorrhage.

It is unclear why patients would have higher incidences of thrombotic strokes after noncardiac and nonneurosurgical procedures. However, postoperative endothelial dysfunction may be a major contributory factor. In this regard, the vascular endothelium is important in the regulation of vascular tone, thrombosis, and inflammation through the release of nitric oxide, prostacyclin, and a series of endothelial-derived hyperpolarizing factors.^{40,41} Vessels with endothelial dysfunction are prone to plaque rupture, reactive vasospasm, and thrombus formation. General anesthetics, in particular nitrous oxide, impair endothelial function.^{42,43} In conjunction with the neuroendocrine, or “stress,” response after surgery, it is plausible that endothelial dysfunction predisposes patients to cerebrovascular thrombosis although there is no clinical evidence currently to support this. In addition, withholding antiplatelet agents or anticoagulants in the perioperative period may aggravate surgery-induced hypercoagulability and increase the risk of stroke.^{44–47} The lower incidence and mortality in hip arthroplasty patients found by Bateman *et al.* may reflect the early anticoagulation of these patients.¹⁶ Fourteen percent of strokes after general surgery are associated with atrial fibrillation, again highlighting the importance of embolism and the hypercoagulable state.^{7–9}

Who Is at Risk?

Comorbidities

The risk factors most consistently linked to perioperative ischemic stroke are shown in table 2. Age, a previous history of stroke, and atrial fibrillation are among the most important. There are conflicting data regarding whether stroke occurs more frequently in men than in women.^{48,49}

The role of extracranial carotid artery stenosis on perioperative stroke remains controversial.^{16,49} Carotid bruit does not correlate with the severity of the underlying carotid artery stenosis, *per se*, and has not been shown to increase the risk of perioperative stroke.^{7,50} Even in patients with significant carotid artery stenosis who are undergoing cardiac surgery, strokes are often contralateral to the affected carotid artery and therefore cannot be attributed to the stenosis alone.^{51,52} However, similar data in noncardiac, nonneurosurgical patients are currently lacking. The risk of perioperative stroke in patients with intracranial cerebral artery stenosis is unknown, but these patients carry a much higher risk (15% each yr) of stroke in the nonsurgical setting, and therefore possibly in the perioperative period, too.⁵³

Type of Surgery

The nature of surgery also has some bearing on perioperative stroke.^{1,16,49} For example, hip arthroplasty and peripheral vascular surgery are associated with a higher incidence than knee arthroplasty or general surgery.^{1,16,49} Head and neck surgery increases the risk for stroke to 0.2–5%.^{54–57} Patients undergoing neck dissection for cancer typically present with multiple medical comorbidities that already increase their risk for stroke. In addition, external beam radiation accelerates atheromatous changes in arteries.⁵⁸ It is therefore not surprising that manipulation of these diseased vascular structures could result in plaque rupture, embolism, and vasospasm.^{59–61}

Other procedures that potentially compromise cerebral perfusion may also increase the risk of stroke. Pohl and Cullen reported four cases of strokes and ischemic spinal cord injury in patients after shoulder surgery in the beach-chair (nearly 90 degrees upright) position.⁶² Two patients had posterior fossa infarcts, one had disseminated cerebral and temporal infarcts, and one had a unilateral watershed infarct. The authors could only speculate on mechanisms and suggested that postural hypotension and extreme rotation, or hyperflexion of the neck, resulted in a decrease in cerebral blood flow and potentially aggravated thromboembolic mechanisms.^{62–64} A study measuring cerebral oximetry in the sitting position found a high incidence, 80% of patients, with a more than 20% decrease in saturation, but no adverse neurologic consequences. This may reflect the small sample size and the need for cerebral saturation to be reduced for a relatively long time, perhaps up to 50 min at less than 50% saturation to produce an adverse outcome.⁶⁵ Despite studies using surrogate endpoints, the risk of stroke after shoulder surgery in beach-chair position remains undefined.⁶⁴

β -Blockers and Hypotension

A meta-analysis by Bangalore *et al.* found an increased risk of nonfatal stroke, hypotension, and bradycardia with the use of β -blockers in patients undergoing noncardiac surgery.⁶⁶ The recent PeriOperative Ischemic Evaluation trial (POISE) car-

Table 2. Risk Factors for Stroke

First Author	Period of Study	Patient Population	Risk Factors	Odds Ratio (95% CI)	P Value
*Parikh ¹⁰	1987–1992	Noncardiac, noncarotid artery	Hypertension	—	0.025
			Smokers		0.09
			Prior stroke		0.02
			Arrhythmia		0.04
Limburg ¹¹	1986–1996	Selected patients at risk of perioperative stroke	Prior stroke	14.3 (3.3–63)	0.0004
			Chronic obstructive pulmonary disease	8.8 (2.5–30.5)	0.0006
			Peripheral vascular disease	8.0 (2.3–28.4)	0.001
			Higher blood urea	2.9 (1.1–7.4)	0.01
			Hypertension on admission	1.04 (1.0–1.1)	0.01
†Kikura ¹²	2005	General surgery patients	Age older than 70 yr	20.2 (7.3–56)	<0.001
			Age 50–69 yr	3.7 (1.2–11)	0.02
			Hyperuricemia	3.5 (1.2–9.8)	0.01
			Prior ischemic stroke	2.4 (1.4–4.1)	0.002
			Cancer	1.6 (1.0–2.5)	0.03
Parvizi ¹³	2004–2005	Patients undergoing hip or knee arthroplasties	Age	1.2 (1.0201.2)	0.0001
			Body mass index (per every kg/m ²)	1.0 (1.0–1.1)	0.002
†Kikura ¹⁴	1991–2006	Patients undergoing noncardiac, noncarotid surgery	Age equal to or older than 70 yr	23.6 (9.6–58.1)	<0.0001
			High risk surgery	1.5 (1.1–2.2)	0.02
			Diabetes mellitus	2.2 (1.4–3.3)	0.006
			Coronary artery disease	2.3 (1.3–4.1)	0.003
			Prior congestive heart failure	1.7 (1.1–2.7)	0.03
			History of atrial fibrillation	5.5 (2.8–10.9)	<0.0001
			Prior stroke	7.1 (4.6–11)	<0.0001
‡Popa ¹⁵	1998–2002	Patients older than 65 yr undergoing major hip surgery	History of atrial fibrillation	2.2 (1.3–3.7)	0.005
			Hip fracture	3.8 (1.9–7.4)	<0.001
			Age older than 75 yr	2.2 (1.2–4.2)	0.02
			Aspirin use	1.8 (1.1–3.1)	0.01
			Prior stroke	4.2 (2.6–6.7)	<0.001
Bateman ¹⁶	2002–2004	Patients older than 18 yr undergoing hemicolectomy, hip replacement, or lung surgery	Renal impairment	3.0 (2.5–3.5)	<0.001
			History or current atrial fibrillation	2.0 (1.7–2.3)	<0.001
			Prior stroke	1.6 (1.3–2.1)	<0.001
			Valvular heart disease	1.5 (1.3–1.9)	<0.001
			Current congestive heart failure	1.4 (1.2–1.7)	<0.001
			Diabetes mellitus	1.2 (1.0–1.4)	0.038

* Odds ratios not calculated in this study. † Patient population overlapped in these two reports. ‡ Hazard ratios calculated. CI = confidence intervals.

ried the greatest weight in the analysis.⁶⁷ Although there is an association among β -blocker use, hypotension, and stroke, this cannot be assumed to be a direct cause and effect.⁶⁶ Many aspects remain unclear. There are substantial variations in drug choice, drug dose, and regimen; definitions of outcomes including definition of hypotension; and patients' surgical and medical risks. Previous studies have shown that hypotension may not increase the risk of perioperative stroke even in patients with extracranial carotid artery stenosis.^{7,51,68} Importantly, it is unclear in studies, including POISE, whether the hypotension occurred immediately before the stroke or after. POISE reports "clinically significant hypotension," defined as a systolic blood pressure of less than 100 mmHg for an unspecified time, as an "intraoperative and postoperative predictor" of stroke (see table 4), but the results do not state the temporal relationship between hypotension and the stroke, and also fail to specify if the hypotension was

intraoperative or postoperative.⁶⁷ Postoperative hypotension occurring on the ward is likely to be prolonged and therefore potentially more detrimental than intraoperative hypotension, which is usually easily detected. There is consensus that patients chronically on β -blockers should be kept on their drugs through the perioperative period, and that caution is needed when these agents are begun immediately before surgery.

It is unclear whether the stroke rate is increased with other antihypertensive or sympatholytic agents, such as clonidine and dexmedetomidine. The introduction of these drugs in the perioperative period could increase vulnerability to cerebral ischemia, as the compensatory mechanisms to cope with hypotension are attenuated because of hypovolemia and blood loss. Clinical trials will be needed to address this. The POISE 2 trial, which is expected to be completed in 2014, includes a clonidine arm and more detailed reporting on intra- and postoperative blood pressure (personal communication,

April 2010, P. J. Devereaux, M.D., Ph.D., Associate Professor, McMaster University, Hamilton, Ontario, Canada).

Stroke Prevention – Risk Modification

Timing Elective Surgery after a Recent Stroke

Acute stroke impairs cerebral autoregulation so that cerebral blood flow becomes passively dependent on perfusion pressure. The injured brain is therefore vulnerable to even modest hypotension.^{69,70} The impairment in cerebral autoregulation is not limited to the affected stroke hemisphere, but appears to be an overall phenomenon that occurs to the same extent after both anterior and posterior circulation strokes.⁷⁰ Failure of cerebral autoregulation and vasomotor response to carbon dioxide has been demonstrated within 8 h after ictus and lasting for 2–6 months.^{70–73} Ideally, enough time should be allowed for autoregulation to be restored before elective surgery, as well as abatement of the inflammatory response. Previous investigators have recommended delaying nonurgent surgery for 1–3 months after stroke.^{9,74} If surgery needs to take place sooner, blood pressure should be meticulously monitored, and one could make a reasonable argument for monitoring for cerebral ischemia using transcranial Doppler or neurophysiology (e.g., electroencephalography and evoked potentials).

Preoperative Carotid Artery Revascularization

In patients with high-grade (more than 70% stenosis) symptomatic carotid artery stenosis, revascularization in the form of carotid artery stenting or endarterectomy should be offered before nonurgent elective surgery. However, in accordance with the 2009 European Society for Vascular Surgery guideline, carotid endarterectomy is contraindicated for patients with less than 50% stenosis.⁷⁵ Revascularization for patients with asymptomatic carotid artery stenosis is much more controversial. Some evidence suggests that intensive medical therapy offers superior secondary stroke prevention compared with carotid endarterectomy or stenting.⁷⁶ This includes smoking cessation, blood pressure control, anticoagulation for atrial fibrillation, and administration of lipid lowering and antiplatelet therapy. In contrast, the recently published 10-yr follow-up of the European Asymptomatic Carotid Surgery Trial found a benefit favoring surgery in asymptomatic patients with more than 60% stenosis. The implications for preoperative carotid endarterectomy were not addressed.⁷⁷

Perioperative Management of Atrial Fibrillation

Patients with preexisting atrial fibrillation who have received antiarrhythmic or rate-controlling agents should continue therapy throughout the perioperative period. Intravenous formulations should be used if necessary. Correction of postoperative electrolyte imbalances and fluid volume is important, as electrolyte disturbances and dehydration increase atrial activity and predispose the arrhythmia.⁴⁹ Although no

randomized controlled trial is available to specifically address the problem of anticoagulation for postoperative atrial fibrillation, the American College of Chest Physicians recommends that heparin therapy be considered for high-risk patients or those with a previous history of stroke or transient ischemic attack, and to continue anticoagulation therapy for 30 days after the return of normal sinus rhythm.⁷⁸ The Effectiveness of Bridging Anticoagulation for Surgery study, which compares dalteparin with a placebo, is expected to be completed by 2013. For patients with new onset atrial fibrillation, echocardiography and cardioversion are appropriate.

Perioperative Management of Patients on Oral Anticoagulant Therapy

Patients who are on oral anticoagulant therapy pose a common and challenging perioperative problem. There is a need to balance the risk of a thromboembolic event during interruption of oral anticoagulant therapy against the risk of bleeding. However, there is a paucity of data to inform decisions regarding perioperative antithrombotic therapy.⁷⁹ Consequently, there is little consensus on the optimal management strategy. Nevertheless, three approaches to oral anticoagulation management have been suggested: (1) to continue warfarin therapy, (2) to withhold warfarin therapy for some time before and after the procedure, or (3) to temporarily withhold warfarin therapy while also providing a short acting, or bridging, anticoagulant during the perioperative period.⁸⁰

For procedures that carry a low risk of bleeding, continuation of warfarin therapy is probably safe.⁷⁹ However, in patients undergoing major surgery or invasive procedures, interruption of antithrombotic therapy is typically required to avoid bleeding.^{81–83} The risk stratification and bridging anticoagulant approaches adopted by the 2008 guidelines of the American College of Chest Physicians should advise clinical practice (table 3).

Perioperative Management of Patients on Antiplatelet Drugs

Withdrawing antiplatelet therapy given for secondary prevention of stroke exposes patients to an increased risk of recurrent ischemic stroke. This may be related to the rebound or prothrombotic effect associated with antiplatelet withdrawal in addition to the prothrombotic effect of surgery.^{84,85} On the other hand, continuing antiplatelet therapy may increase the risk of major bleeding. Unfortunately, there are currently no data to guide the management, and clinical practice has been variable. The situation is more problematic when antiplatelet drugs are given for previous placement of intracranial stents. Withholding antiplatelet in these patients may confer higher risks of stroke. The POISE 2 trial, a large randomized control trial evaluating the risks and benefits of continuing antiplatelet therapy, has recently started recruiting patients, and should be completed by 2014. This study

Table 3. Perioperative Management of Patients on Oral Anticoagulation Therapy⁷⁸

Risk Stratum	Indication for Oral Anticoagulation		Management during Temporary Disruption of Oral Anticoagulation
	Mechanical Heart Valve	Atrial Fibrillation	—
High	Mitral valve prosthesis older aortic valve prosthesis †Stroke or TIA within 6 mo	*CHADS ₂ score of 5 or 6 Rheumatic valvular heart disease Stroke or TIA within 3 mo	Bridge with therapeutic dose Subcutaneous LMWH
Moderate	Bileaflet aortic valve prosthesis and one other risk factor for stroke	*CHADS ₂ score 3 or 4	Bridge with either therapeutic dose or low dose subcutaneous LMWH
Low	Bileaflet aortic valve prosthesis No other risk factors for stroke	CHADS ₂ score 0–2 No prior stroke or TIA	No bridging anticoagulation or low dose subcutaneous LMWH

* CHADS₂ score: One point for each of congestive heart failure, hypertension, and age older than 75 yr. Two points for previous stroke or transient ischemic attack. † Ball and cage or tilting disc.

LMWH = low molecular weight heparin; TIA = transient ischemic attack.

may provide important guidelines for patients taking aspirin in the perioperative period.

Intraoperative Blood Pressure Management

Hypotension in the presence of severe internal carotid artery stenosis, occlusion, and/or an incompetent circle of Willis, the circulus arteriosus cerebri, are risk factors for watershed infarcts (see Pathophysiology).^{38,86} Only 45–50% of the population has the typical complete or normal polygon configuration of the circle of Willis.⁸⁷ Maintenance of an adequate cerebral perfusion pressure is thus important, especially in patients with these risk factors. Patients who suffer a cerebral embolic event are also dependent on cerebral perfusion to maintain collateral flow to reduce infarct size. Unfortunately, there are few data to inform on optimal intraoperative blood pressure targets, and this is compounded by the lack of a standardized definition of hypotension.⁸⁸ Below the cerebral blood flow penumbra threshold, which is approximately a 50% reduction in cerebral blood flow, neuronal function is impaired, and the tissue is at risk of injury.⁸⁹ It is unknown whether prolonged reductions in cerebral blood flow above the penumbral threshold may also result in injury.^{86,90} Studies in healthy, awake individuals suggest that the average lower limit of autoregulation is approximately 70 mmHg, *i.e.*, higher than usually stated in textbooks. It is commonly assumed that one should be safe keeping blood pressure within the individual's autoregulatory range.⁹¹ There is, however, enormous individual variation in the lower limit of autoregulation, 41–113 mmHg, to the extent that it is inappropriate to assume that any one target arterial pressure may apply to a broad population of patients.⁹¹ In addition, the lower limit of autoregulation is not static, being increased by hypertension; returned to “normal” with treatment of hypertension; and rapidly shifting with changes in sympathetic tone.⁹² The latter presumably accommodates the 20% or more decrease in blood pressure that occurs during nonrapid eye movement sleep.⁹³

Given such complexity, the absence of outcome data defining a blood pressure threshold for stroke in general surgical patients, and the relative infrequency of purely hemodynamic strokes, it is not surprising that there is no consensus on appropriate perioperative blood pressure targets.⁸⁸ A common practice is to maintain mean or systolic blood pressures within 20% of baseline, which is usually the blood pressure measured immediately before entry to the operating room.^{88,94} This reference value is above the patient's usual awake blood pressure and even further increased above their sleep values.^{94,95} Such a relatively conservative approach to intraoperative blood pressure management is justifiable in patients at high risk for perioperative strokes. In healthy patients, blood pressures that approximate sleep levels are likely quite acceptable, *i.e.*, 25–35% decrease from immediate preoperative baseline.⁹⁵

Other Contributing Factors

Beyond avoidance of severe hyperglycemia and hypoglycemia, both of which are detrimental,^{96,97} there is no consensus on the perioperative target glucose values to enhance clinical outcomes. Although an earlier study of patients in the surgical intensive care unit found a survival benefit following strict glucose control, or glucose concentrations 4.4–6.1 mM, compared with traditional management, or glucose concentrations 10–11.1 mM,⁹⁸ evidence from recent randomized controlled trials⁹⁹ and meta-analyses suggest that there is no benefit to overall mortality with strict glycemic control compared with traditional management.^{100,101} In fact, an increased incidence of stroke was found with strict intraoperative glucose control in cardiac surgery patients.⁹⁹ The American Diabetes Association and the American Association of Clinical Endocrinologists have published a joint consensus statement defining a target range of 7.8–10 mM among critically ill patients. Pending results from prospective trials in patients undergoing major surgery, this seems a reasonable aim for all surgical patients.¹⁰²

Table 4. Issues Concerning Prevention and Early Management of Perioperative Stroke

Issues	Management
Recent stroke	Defer elective surgery for longer than 3 mo, risk factor modification. For urgent surgery, meticulous blood pressure monitoring and maintenance. Consider monitoring for cerebral ischemia with transcranial doppler or neurophysiological monitoring.
Carotid stenosis	For symptomatic, high grade (more than 70% stenosis), revascularization recommended prior to elective surgery. Revascularization is contraindicated for less than 50%, symptomatic stenosis. There is still controversy about the best management of asymptomatic stenosis, but more than 60% stenosis is increasingly being operated on.
Atrial fibrillation	Continue antiarrhythmic therapy perioperatively, correct electrolyte disturbances and dehydration. For postoperative atrial fibrillation in patients at high risk of stroke, consider heparin therapy and continue heparin for 30 days after return of sinus rhythm.
Patients on oral anticoagulation	See guidelines outlined in Table 3.
Patients on antiplatelets	No good evidence to guide practice. Maintain on aspirin if possible.
Hyperglycemia	Maintain blood glucose within normal range.
Hypertension	Intraoperative blood pressure targets on awake resting range.
Perioperative stroke	Early diagnosis aided by noncontrast computed tomography of the brain, consider thrombolysis on a case-by-case basis. Correct postoperative hypotension and fever; transfer to an acute stroke unit for general supportive care and prevention of complications.

Patients with previous stroke are often taking statin and other lipid-lowering drugs for secondary stroke prevention. Discontinuation of statin therapy can be harmful and may acutely impair vascular function. Statin withdrawal in patients with acute stroke was associated with an 8.7-fold increase in the risk for early neurologic deterioration.¹⁰³ Thus, statin therapy should be continued throughout the perioperative period in at-risk patients. Instituting statins *de novo* preoperatively or immediately at stroke onset has yet to be convincingly shown in randomized trials to be of benefit.¹⁰⁴

Genetic predisposition to perioperative stroke is not well understood or studied. A limited number of studies in cardiac surgery have found that a few genetic polymorphisms, including apolipoprotein E4 allele, glycoprotein Ib, and C-reactive protein contributed to worse cognitive outcome and poorer recovery after stroke in cardiac surgery.^{105,106} Similar data in noncardiac surgery are currently lacking. Despite the advances in genomic research, currently no single locus has been identified in genome-wide association studies.

With regard to local or regional as compared with general anesthesia, there is no significant difference in the risk of stroke between the two anesthetic techniques.^{107,108}

Early Management of a Perioperative Stroke

Important elements in early management are identifying at-risk patients and early diagnosis (table 4). Nursing staff initially detect the vast majority of perioperative strokes, as most strokes are not acute intraoperative events but are diagnosed during the postoperative period and later hospital stay.¹⁰⁹ However, routine surgical nursing care does not include a

useful neurologic examination. There is extensive research and clinical experience with the use of the National Institutes of Health Stroke Scale and the Canadian Neurologic Scale.¹¹⁰ These do not take long to do, but require some training, making it unlikely that they would be widely adopted. Wide integration of simpler scales would be a step in the direction of earlier detection.¹¹¹ There is also a need to shorten the time from nursing diagnosis to neurologist's assessment, without waiting for the surgical team to complete the day's operating room activities.¹¹² An increasing number of medium- to large-sized medical centers have an "Acute Stroke Team" that is managed by neurologists and who respond rapidly if a stroke is suspected. Emergency noncontrast scanning of the brain is the primary diagnostic brain-imaging study for evaluation of patients with suspected stroke, and the goal is to complete the computer tomography examination within 25 min of the provisional diagnosis being made.¹¹³ Noncontrast computer tomography accurately discriminates ischemic stroke from intracranial hemorrhage and nonvascular causes of neurologic symptoms, such as tumors. It is, however, relatively insensitive in detecting acute and small cortical or subcortical infarctions, especially in the posterior fossa.¹¹⁴ Multimodal computer tomography and magnetic resonance imaging may provide additional information that will improve diagnosis of ischemic stroke. However, emergency treatment of stroke should not be delayed to obtain multimodal imaging studies.¹¹³

General supportive care and prevention of complications are also important to patients with perioperative stroke. This may be best achieved by moving the surgical patient to an Acute Stroke Unit, where management is coordinated by stroke neurologists. Partial airway obstruction, hypoventila-

tion, aspiration pneumonia, and atelectasis are common causes of hypoxia that may worsen the brain injury. Both hypertension and hypotension are associated with poor outcome after stroke. Urgent correction of common postoperative causes of hypotension, including volume depletion, blood loss, myocardial ischemia, or arrhythmias, may improve neurologic outcomes. Although there are data from small clinical trials suggesting that drug-induced hypertension could be used for the treatment of selected patients with acute ischemic stroke, there are no data from large clinical trials, and current consensus does not recommend this treatment.¹¹³ Intentional hemodilution does not improve functional outcome and is not recommended for the treatment of acute stroke.¹¹³ The source of any fever should be ascertained and treated, as fever is associated with poor neurologic outcome after acute stroke.^{115,116} Both myocardial ischemia and cardiac arrhythmias are potential complications, and the current American Heart Association guidelines recommend that patients with acute ischemic stroke should have cardiac monitoring for at least the first 24 h and that any serious arrhythmia should be actively treated.¹¹³

Unfortunately, much of the emergency advanced treatment of acute stroke, such as pharmacologic thrombolysis, mechanical recanalization of occluded arteries, and heparin administration, are not suitable for patients after surgery. The current American Heart Association guidelines consider major surgery within 14 days of stroke a contraindication to intravenous thrombolysis. However, given the benefit to be gained, on a case-by-case basis, patients who suffer a perioperative ischemic stroke may be eligible for intravenous thrombolysis. Intraarterial thrombolysis is another option for treatment, either alone or in conjunction with intravenous thrombolysis, and may be safely administered to patients within 6 h of symptom onset. Currently, aspirin is the only oral antiplatelet agent that has been found beneficial in the treatment of acute ischemic stroke, and should be used in the perioperative period whenever deemed safe.¹¹³

In conclusion, perioperative stroke is more common than generally acknowledged. Increased awareness and management of predisposing risk factors with early detection should result in improved outcomes. Prospective studies of overt and covert stroke in the perioperative period are needed in order to inform incidence, pathophysiology, prevention, and treatment.

References

- Wong GY, Warner DO, Schroeder DR, Offord KP, Warner MA, Maxson PM, Whisnant JP: Risk of surgery and anesthesia for ischemic stroke. *ANESTHESIOLOGY* 2000; 92:425-32
- Debette S, Markus HS: The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: Systematic review and meta-analysis. *BMJ* 2010; 341: c3666
- Barber PA, Hach S, Tippet 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
- Knapp RB, Topkins MJ, Artusio JF, Jr: The cerebrovascular accident and coronary occlusion in anesthesia. *JAMA* 1962; 182:332-4
- Cooperman M, Pflug B, Martin EW, Jr., Evans WE: Cardiovascular risk factors in patients with peripheral vascular disease. *Surgery* 1978; 84:505-9
- Turnipseed WD, Berkoff HA, Belzer FO: Postoperative stroke in cardiac and peripheral vascular disease. *Ann Surg* 1980; 192:365-8
- Hart R, Hindman B: Mechanisms of perioperative cerebral infarction. *Stroke* 1982; 13:766-73
- Larsen SF, Zaric D, Boysen G: Postoperative cerebrovascular accidents in general surgery. *Acta Anaesthesiol Scand* 1988; 32:698-701
- Landercasper J, Merz BJ, Cogbill TH, Strutt PJ, Cochrane RH, Olson RA, Hutter RD: Perioperative stroke risk in 173 consecutive patients with a past history of stroke. *Arch Surg* 1990; 125:986-9
- Parikh S, Cohen JR: Perioperative stroke after general surgical procedures. *N Y State J Med* 1993; 93:162-5
- Limburg M, Wijdeveld EF, Li H: Ischemic stroke after surgical procedures: Clinical features, neuroimaging, and risk factors. *Neurology* 1998; 50:895-901
- Kikura M, Takada T, Sato S: Preexisting morbidity as an independent risk factor for perioperative acute thromboembolism syndrome. *Arch Surg* 2005; 140:1210-7
- Parvizi J, Mui A, Purtill JJ, Sharkey PF, Hozack WJ, Rothman RH: Total joint arthroplasty: When do fatal or near-fatal complications occur? *J Bone Joint Surg Am* 2007; 89:27-32
- Kikura M, Oikawa F, Yamamoto K, Iwamoto T, Tanaka KA, Sato S, Landesberg G: Myocardial infarction and cerebrovascular accident following non-cardiac surgery: Differences in postoperative temporal distribution and risk factors. *J Thromb Haemost* 2008; 6:742-8
- Popa AS, Rabinstein AA, Huddleston PM, Larson DR, Gulerud RE, Huddleston JM: Predictors of ischemic stroke after hip operation: A population-based study. *J Hosp Med* 2009; 4:298-303
- Bateman BT, Schumacher HC, Wang S, Shaefi S, Berman MF: Perioperative acute ischemic stroke in noncardiac and non-vascular surgery: Incidence, risk factors, and outcomes. *ANESTHESIOLOGY* 2009; 110:231-8
- Huang CJ, Fan YC, Tsai PS: Differential impacts of modes of anesthesia on the risk of stroke among preeclamptic women who undergo Caesarean delivery: A population-based study. *Br J Anaesth* 2010; 105:818-26
- Kokotailo RA, Hill MD: Coding of stroke and stroke risk factors using international classification of diseases, revisions 9 and 10. *Stroke* 2005; 36:1776-81
- El-Saed A, Kuller LH, Newman AB, Lopez O, Costantino J, McTigue K, Cushman M, Kronmal R: Geographic variations in stroke incidence and mortality among older populations in four US communities. *Stroke* 2006; 37:1975-9
- Elkind MS: Inflammatory mechanisms of stroke. *Stroke* 2010; 41:S3-8
- McColl BW, Allan SM, Rothwell NJ: Systemic infection, inflammation and acute ischemic stroke. *Neuroscience* 2009; 158:1049-61
- McColl BW, Rothwell NJ, Allan SM: Systemic inflammatory stimulus potentiates the acute phase and CXC chemokine responses to experimental stroke and exacerbates brain damage *via* interleukin-1 and neutrophil-dependent mechanisms. *J Neurosci* 2007; 27:4403-12
- Utagawa A, Truettner JS, Dietrich WD, Bramlett HM: Systemic inflammation exacerbates behavioral and histopathologic consequences of isolated traumatic brain injury in rats. *Exp Neurol* 2008; 211:283-91
- Smith CJ, Emsley HC, Vail A, Georgiou RF, Rothwell NJ, Tyrrell PJ, Hopkins SJ: Variability of the systemic acute

- phase response after ischemic stroke. *J Neurol Sci* 2006; 251:77-81
25. Zeller JA, Lenz A, Eschenfelder CC, Zunker P, Deuschl G: Platelet-leukocyte interaction and platelet activation in acute stroke with and without preceding infection. *Arterioscler Thromb Vasc Biol* 2005; 25:1519-23
26. Palasik W, Fiszer U, Lechowicz W, Czartoryska B, Krzesiewicz M, Lugowska A: Assessment of relations between clinical outcome of ischemic stroke and activity of inflammatory processes in the acute phase based on examination of selected parameters. *Eur Neurol* 2005; 53:188-93
27. Clayton TC, Thompson M, Meade TW: Recent respiratory infection and risk of cardiovascular disease: Case-control study through a general practice database. *Eur Heart J* 2008; 29:96-103
28. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P: Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med* 2004; 351:2611-8
29. Grau AJ, Buggle F, Heindl S, Steichen-Wiehn C, Banerjee T, Maiwald M, Rohlfis M, Suhr H, Fiehn W, Becher H, Werner H: Recent infection as a risk factor for cerebrovascular ischemia. *Stroke* 1995; 26:373-9
30. Bastian D, Tamburstuen MV, Lyngstadaas SP, Reikerås O: Systemic and local cytokine kinetics after total hip replacement surgery. *Eur Surg Res* 2008; 41:334-40
31. Riché F, Dosquet C, Panis Y, Valleur P, Laisne MJ, Briard C, Wautier JL: Levels of portal and systemic blood cytokines after colectomy in patients with carcinoma or Crohn's disease. *J Am Coll Surg* 1995; 180:718-24
32. Smith CJ, Emsley HC, Gavin CM, Georgiou RF, Vail A, Barberan EM, del Zoppo GJ, Hallenbeck JM, Rothwell NJ, Hopkins SJ, Tyrrell PJ: Peak plasma interleukin-6 and other peripheral markers of inflammation in the first week of ischaemic stroke correlate with brain infarct volume, stroke severity and long-term outcome. *BMC Neurol* 2004; 4:2
33. Rallidis LS, Vekelis M, Panagiotakos DB, Rizos I, Zolindaki MG, Kaliva K, Kremastinos DT: Inflammatory markers and in-hospital mortality in acute ischaemic stroke. *Atherosclerosis* 2006; 189:193-7
34. 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
35. 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
36. Mohr JP: Distal field infarction. *Neurology* 1969; 19:279
37. Momjian-Mayor I, Baron JC: The pathophysiology of watershed infarction in internal carotid artery disease: Review of cerebral perfusion studies. *Stroke* 2005; 36:567-77
38. Caplan LR, Hennerici M: Impaired clearance of emboli (washout) is an important link between hypoperfusion, embolism, and ischemic stroke. *Arch Neurol* 1998; 55:1475-82
39. Likosky DS, Marrin CA, Caplan LR, Baribeau YR, Morton JR, Weintraub RM, Hartman GS, Hernandez F, Jr., Braff SP, Charlesworth DC, Malenka DJ, Ross CS, O'Connor GT, Northern New England Cardiovascular Disease Study Group: Determination of etiologic mechanisms of strokes secondary to coronary artery bypass graft surgery. *Stroke* 2003; 34:2830-4
40. Abrams J: Role of endothelial dysfunction in coronary artery disease. *Am J Cardiol* 1997; 79:2-9
41. Devereaux PJ, Chan MTV, Eikelboom J: Major vascular complications in patients undergoing non-cardiac surgery: Magnitude of the problem, risk prediction, surveillance, and prevention. Evidence based Cardiology, 3rd edition. Edited by Yusuf S, Cairns JA, Camm AJ, Fallen EL, Gersh BJ. West Sussex, UK; Wiley-Blackwell, 2010, pp 47-62
42. Myles PS, Chan MTV, 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
43. Myles PS, Chan MTV, Kaye DM, McIlroy DR, Lau CW, Symons JA, Chen SH: Effect of nitrous oxide anesthesia on plasma homocysteine and endothelial dysfunction. *ANESTHESIOLOGY* 2008; 109:657-63
44. Collins GJ, Jr., Barber JA, Zajtcuk R, Vanek D, Malogne LA: The effects of operative stress on the coagulation profile. *Am J Surg* 1977; 133:612-6
45. Kluft C, Cooper P, Jie AF, Lowe GD, Forbes CD, Blamey SL, van de Putte LB: Evaluation of euglobulin methods for the study of blood fibrinolytic activity: Results for patients with rheumatoid arthritis and in the postoperative period. *Haemostasis* 1985; 15:144-50
46. Dixon B, Santamaria J, Campbell D: Coagulation activation and organ dysfunction following cardiac surgery. *Chest* 2005; 128:229-36
47. Hinterhuber G, Bohler K, Kittler H, Quehenberger P: Extended monitoring of hemostatic activation after varicose vein surgery under general anesthesia. *Dermatol Surg* 2006; 32:632-9
48. Vagnerova K, Koerner IP, Hurn PD: Gender and the injured brain. *Anesth Analg* 2008; 107:201-14
49. Selim M: Perioperative stroke. *N Engl J Med* 2007; 356:706-13
50. Ropper AH, Wechsler LR, Wilson LS: Carotid bruit and the risk of stroke in elective surgery. *N Engl J Med* 1982; 307:1388-90
51. Naylor AR, Mehta Z, Rothwell PM, Bell PR: Carotid artery disease and stroke during coronary artery bypass: A critical review of the literature. *Eur J Vasc Endovasc Surg* 2002; 23:283-94
52. Li Y, Walicki D, Mathiesen C, Jenny D, Li Q, Isayev Y, Reed JF, 3rd, Castaldo JE: Strokes after cardiac surgery and relationship to carotid stenosis. *Arch Neurol* 2009; 66:1091-6
53. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, Levine SR, Chaturvedi S, Kasner SE, Benesch CG, Sila CA, Jovin TG, Romano JG: Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med* 2005; 352:1305-16
54. Thompson SK, Southern DA, McKinnon JG, Dort JC, Ghali WA: Incidence of perioperative stroke after neck dissection for head and neck cancer: A regional outcome analysis. *Ann Surg* 2004; 239:428-31
55. Rechtweg J, Wax MK, Shah R, Granke K, Jarmuz T: Neck dissection with simultaneous carotid endarterectomy. *Laryngoscope* 1998; 108:1150-3
56. Nosan DK, Gomez CR, Maves MD: Perioperative stroke in patients undergoing head and neck surgery. *Ann Otol Rhinol Laryngol* 1993; 102:717-23
57. Haynes JC, Machtay M, Weber RS, Weinstein GS, Chalian AA, Rosenthal DI: Relative risk of stroke in head and neck carcinoma patients treated with external cervical irradiation. *Laryngoscope* 2002; 112:1883-7
58. Abayomi OK: Neck irradiation, carotid injury and its consequences. *Oral Oncol* 2004; 40:872-8
59. Lewis AF, Mullis TC, Wein RO, Eby TL: Postoperative carotid spasm in the setting of head and neck surgery. *Am J Otolaryngol* 2008; 29:291-4
60. Osguthorpe JD, Adkins WY: Carotid arteriospasm. *Laryngoscope* 1985; 95:942-4
61. Smith PG, Killeen TE: Carotid artery vasospasm complicating extensive skull base surgery: Cause, prevention, and management. *Otolaryngol Head Neck Surg* 1987; 97:1-7
62. Pohl A, Cullen DJ: Cerebral ischemia during shoulder sur-

- gery in the upright position: A case series. *J Clin Anesth* 2005; 17:463-9
63. Tissington Tatlow WF, Bammer HG: Syndrome of vertebral artery compression. *Neurology* 1957; 7:331-40
 64. Friedman DJ, Parnes NZ, Zimmer Z, Higgins LD, Warner JJ: Prevalence of cerebrovascular events during shoulder surgery and association with patient position. *Orthopedics* 2009; 32:256
 65. Slater JP, Guarino T, Stack J, Vinod K, Bustami RT, Brown JM III, Rodriguez AL, Magovern CJ, Zaubler T, Freundlich K, Parr GV: Cerebral oxygen desaturation predicts cognitive decline and longer hospital stay after cardiac surgery. *Ann Thorac Surg* 2009; 87:36-44
 66. Bangalore S, Wetterlev J, Pranesh S, Sawhney S, Glud C, Messerli FH: Perioperative beta blockers in patients having non-cardiac surgery: A meta-analysis. *Lancet* 2008; 372:1962-76
 67. 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
 68. Ballotta E, Renon L, Da Giau G, Barbon B, De Rossi A, Baracchini C: Prospective randomized study on asymptomatic severe carotid stenosis and perioperative stroke risk in patients undergoing major vascular surgery: Prophylactic or deferred carotid endarterectomy? *Ann Vasc Surg* 2005; 19:876-81
 69. Agnoli A, Fieschi C, Bozzao L, Battistini N, Prencipe M: Autoregulation of cerebral blood flow. Studies during drug-induced hypertension in normal subjects and in patients with cerebral vascular diseases. *Circulation* 1968; 38:800-12
 70. Dawson SL, Blake MJ, Panerai RB, Potter JF: Dynamic but not static cerebral autoregulation is impaired in acute ischaemic stroke. *Cerebrovasc Dis* 2000; 10:126-32
 71. Rubin G, Levy EI, Scarrow AM, Firlik AD, Karakus A, Wechsler L, Jungreis CA, Yonas H: Remote effects of acute ischemic stroke: A xenon CT cerebral blood flow study. *Cerebrovasc Dis* 2000; 10:221-8
 72. Dawson SL, Panerai RB, Potter JF: Serial changes in static and dynamic cerebral autoregulation after acute ischaemic stroke. *Cerebrovasc Dis* 2003; 16:69-75
 73. Aries MJ, Elting JW, De Keyser J, Kremer BP, Vroomen PC: Cerebral autoregulation in stroke: A review of transcranial Doppler studies. *Stroke* 2010; 41:2697-704
 74. Blacker DJ, Flemming KD, Link MJ, Brown RD, Jr: The preoperative cerebrovascular consultation: Common cerebrovascular questions before general or cardiac surgery. *Mayo Clin Proc* 2004; 79:223-9
 75. Liapis CD, Bell PR, Mikhailidis D, Sivenius J, Nicolaides A, Fernandes e Fernandes J, Biasi G, Norgren L: ESVS guidelines. Invasive treatment for carotid stenosis: Indications, techniques. *Eur J Vasc Endovasc Surg* 2009; 37:1-19
 76. Spence JD: Secondary stroke prevention. *Nat Rev Neurol* 2010; 6:477-86
 77. Halliday A, Harrison M, Hayter E, Kong X, Mansfield A, Marro J, Pan H, Peto R, Potter J, Rahimi K, Rau A, Robertson S, Streifler J, Thomas D; Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group: 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): A multicentre randomised trial. *Lancet* 2010; 376:1074-84
 78. Epstein AE, Alexander JC, Gutterman DD, Maisel W, Wharton JM: Anticoagulation: American College of Chest Physicians guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery. *Chest* 2005; 128:248-75
 79. Douketis JD, Berger PB, Dunn AS, Jaffer AK, Spyropoulos AC, Becker RC, Ansell J: The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133:299S-339S
 80. Garcia DA, Regan S, Henault LE, Upadhyay A, Baker J, Othman M, Hylek EM: Risk of thromboembolism with short-term interruption of warfarin therapy. *Arch Intern Med* 2008; 168:63-9
 81. McKenna R: Abnormal coagulation in the postoperative period contributing to excessive bleeding. *Med Clin North Am* 2001; 85:1277-310
 82. Torn M, Rosendaal FR: Oral anticoagulation in surgical procedures: Risks and recommendations. *Br J Haematol* 2003; 123:676-82
 83. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet* 2000; 355:1295-302
 84. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Ramirez C, Sabate M, Jimenez-Quevedo P, Hernandez R, Moreno R, Escaned J, Alfonso F, Banuelos C, Costa MA, Bass TA, Macaya C: Clopidogrel withdrawal is associated with pro-inflammatory and prothrombotic effects in patients with diabetes and coronary artery disease. *Diabetes* 2006; 55:780-4
 85. O'Riordan JM, Margey RJ, Blake G, O'Connell PR: Antiplatelet agents in the perioperative period. *Arch Surg* 2009; 144:69-76
 86. Momjian-Mayor I, Barron J-C: The pathophysiology of watershed infarcts. *Stroke* 2005; 36:567-77
 87. Kapoor K, Singh B, Dewan LI: Variations in the configuration of the circle of Willis. *Anat Sci Int* 2008; 83:96-106
 88. Bijker JB, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KG, Kalkman CJ: Incidence of intraoperative hypotension as a function of the chosen definition: Literature definitions applied to a retrospective cohort using automated data collection. *ANESTHESIOLOGY* 2007; 107:213-20
 89. Bandera E, Botteri M, Minelli C, Sutton A, Abrams KR, Latronico N: Cerebral blood flow threshold of ischemic penumbra and infarct core in acute ischemic stroke: A systematic review. *Stroke* 2006; 37:1334-9
 90. Blacker DJ, Flemming KD, Wijdicks EF: Risk of ischemic stroke in patients with symptomatic vertebrobasilar stenosis undergoing surgical procedures. *Stroke* 2003; 34:2659-63
 91. Larsen FS, Olsen KS, Hansen BA, Paulson OB, Knudsen GM: Transcranial Doppler is valid for determination of the lower limit of cerebral blood flow autoregulation. *Stroke* 1994; 25:1985-8
 92. Chillon J-M, Baumbach GL: Autoregulation: Arterial and Intracranial pressure, Cerebral Blood Flow and Metabolism, 2nd edition. Edited by Edvinsson L, Krause DN. Philadelphia, Lippincott Williams & Wilkins, 2002, pp395-412
 93. Millar-Craig MW, Bishop CN, Raftery EB: Circadian variation of blood-pressure. *Lancet* 1978; 1:795-7
 94. Howell SJ, Sear JW, Foëx P: Hypertension, hypertensive heart disease and perioperative cardiac risk. *Br J Anaesth* 2004; 92:570-83
 95. Soo JC, Lacey S, Kluger R, Silbert BS: Defining intra-operative hypotension—a pilot comparison of blood pressure during sleep and general anaesthesia. *Anaesthesia* 2011; 66:354-60
 96. Lipshutz AK, Gropper MA: Perioperative glycemic control: An evidence-based review. *ANESTHESIOLOGY* 2009; 110:408-21
 97. Duning T, Ellger B: Is hypoglycaemia dangerous? *Best Pract Res Clin Anaesthesiol* 2009; 23:473-85
 98. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lau-

- wers P, Bouillon R: Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001; 345:1359-67
99. Gandhi GY, Nuttall GA, Abel MD, Mullany CJ, Schaff HV, O'Brien PC, Johnson MG, Williams AR, Cutshall SM, Mundy LM, Rizza RA, McMahon MM: Intensive intraoperative insulin therapy *versus* conventional glucose management during cardiac surgery: A randomized trial. *Ann Intern Med* 2007; 146:233-43
100. Griesdale DE, de Souza RJ, van Dam RM, Heyland DK, Cook DJ, Malhotra A, Dhaliwal R, Henderson WR, Chittock DR, Finfer S, Talmor D: Intensive insulin therapy and mortality among critically ill patients: A meta-analysis including NICE-SUGAR study data. *CMAJ* 2009; 180:821-7
101. Marik PE, Preiser JC: Toward understanding tight glycemic control in the ICU: A systematic review and metaanalysis. *Chest* 2010; 137:544-51
102. Moghissi ES, Korytkowski MT, DiNardo M, Einhorn D, Hellman R, Hirsch IB, Inzucchi SE, Ismail-Beigi F, Kirkman MS, Umpierrez GE; American Association of Clinical Endocrinologists; American Diabetes Association: American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Diabetes Care* 2009; 32:1119-31
103. Blanco M, Nombela F, Castellanos M, Rodriguez-Yanez M, Garcia-Gil M, Leira R, Lizasoain I, Serena J, Vivancos J, Moro MA, Davalos A, Castillo J: Statin treatment withdrawal in ischemic stroke: A controlled randomized study. *Neurology* 2007; 69:904-10
104. Ní Chroínín D, Callaly EL, Duggan J, Merwick A, Hannon N, Sheehan O, Marnane M, Horgan G, Williams EB, Harris D, Kyne L, McCormack PM, Moroney J, Grant T, Williams D, Daly L, Kelly PJ: Association between acute statin therapy, survival, and improved functional outcome after ischemic stroke: The north Dublin population stroke study. *Stroke* 2011; 42:1021-9
105. Grocott HP, White WD, Morris RW, Podgoreanu MV, Mathew JP, Nielsen DM, Schwinn DA, Newman MF: Genetic polymorphisms and the risk of stroke after cardiac surgery. *Stroke* 2005; 36:1854-8
106. Lanktree MB, Dichgans M, Hegele RA: Advances in genomic analysis of stroke: What have we learned and where are we headed? *Stroke*; 2010; 41:825-32
107. Rodgers A, Walker N, Schug S, McKee A, Kehlet H, van Zundert A, Sage D, Futter M, Saville G, Clark T, MacMahon S: Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: Results from overview of randomised trials. *BMJ* 2000; 321:1493
108. Rerkasem K, Rothwell PM: Local *versus* general anesthetic for carotid endarterectomy. *Stroke* 2009; 40:e584-5
109. Alberts MJ, Brass LM, Perry A, Webb D, Dawson DV: Evaluation times for patients with in-hospital strokes. *Stroke* 1993; 24:1817-22
110. Nilanont Y, Komoltri C, Saposnik G, Cote R, Di Legge S, Jin Y, Prayoonwiwat N, Pongvarin N, Hachinski V: The Canadian Neurological Scale and the NIHSS: Development and validation of a simple conversion model. *Cerebrovasc Dis* 2010; 30:120-6
111. Whiteley WN, Wardlaw JM, Dennis MS, Sandercock PA: Clinical scores for the identification of stroke and transient ischaemic attack in the emergency department: A cross-sectional study. *J Neurol Neurosurg Psychiatry* 2011; 82:1006-10
112. Byrne B, O'Halloran P, Cardwell C: Accuracy of stroke diagnosis by registered nurses using the ROSIER tool compared to doctors using neurological assessment on a stroke unit: A prospective audit. *Int J Nurs Stud* 2011; 48:979-85
113. Adams HP, Jr., del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, Grubb RL, Higashida RT, Jauch EC, Kidwell C, Lyden PD, Morgenstern LB, Qureshi AI, Rosenwasser RH, Scott PA, Wijdicks EF: Guidelines for the early management of adults with ischemic stroke: A guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists *Stroke* 2007; 38:1655-711
114. Mullins ME, Schaefer PW, Sorensen AG, Halpern EF, Ay H, He J, Koroshetz WJ, Gonzalez RG: CT and conventional and diffusion-weighted MR imaging in acute stroke: Study in 691 patients at presentation to the emergency department. *Radiology* 2002; 224:353-60
115. Azzimondi G, Bassein L, Nonino F, Fiorani L, Vignatelli L, Re G, D'Alessandro R: Fever in acute stroke worsens prognosis. A prospective study. *Stroke* 1995; 26:2040-3
116. Reith J, Jorgensen HS, Pedersen PM, Nakayama H, Raaschou HO, Jeppesen LL, Olsen TS: Body temperature in acute stroke: Relation to stroke severity, infarct size, mortality, and outcome. *Lancet* 1996; 347:422-5