Perioperative Stroke Risk in Nonvascular Surgery

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Key Words

Perioperative stroke · General surgery · Risk factors · Antithrombotic therapy

Abstract

Background: Perioperative stroke is an ischemic or hemorrhagic cerebrovascular accident that can arise intraoperatively or from 3 to 30 days after surgery. This relatively rare complication deserves attention because of its high mortality and serious disability, the latter of which can lead to prolonged hospital stay as well as discharge to long-term care facilities. The aim of this article was to review the literature on perioperative stroke in general surgery, excluding carotid and cardiac surgeries because these have already been thoroughly investigated in previous papers. **Methods:** A search strategy was designed to identify all relevant studies on perioperative stroke in the English language. This search was restricted to papers published up to December 5, 2011. Studies were initially identified from the Medline/PubMed database, EMBASE and the Cochrane Database using the search terms 'surgery', 'perioperative stroke', 'risk factors', 'anticoagulation treatment' and 'antiplatelet treatment'. **Results:** The incidence of perioperative stroke among patients who undergo nonvascular surgery is reported to be about 0.08–0.7%. This depends on the type and complexity of the surgical procedure along with patient risk factors. The reported perioperative mortality is 18–26%. One of the main issues is the man-

agement of patients taking anticoagulant or antiplatelet drugs, as the risk of bleeding has to be counterbalanced with the risk of arterial thrombosis due to discontinuation. Additionally, the presence of symptomatic carotid stenosis should be taken into account in the risk evaluation. **Conclusions:** To date, current guidelines are incomplete regarding the management of patients with vascular disease undergoing nonvascular surgery. It is recommended to stop oral anticoagulation approximately 5 days before major surgery to adequately allow the INR to normalize, and at the same time subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin should be started. Regarding new anticoagulants, dabigatran does not need to be withheld for minor procedures. Currently, there are no clear recommendations on the use of rivaroxaban and apixaban. Data concerning the management of patients undergoing antiplatelet therapy are lacking. To date, neurologists discourage the perioperative withdrawal of aspirin (acetylsalicylic acid, ASA) especially in patients in secondary prevention. The 'Antiplatelet Agents in the Perioperative Management of Patients Trial' is ongoing to assess the safety and determine the optimal use of ASA in the perioperative management of patients undergoing general and abdominal surgery. In the meantime an individualized, accurate, multidisciplinary (surgical, neurological, cardiological and anesthesiological) risk/benefit assessment remains the best basis for treatment decision.

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Introduction

Perioperative stroke is an ischemic or hemorrhagic cerebrovascular accident that can arise intraoperatively or from 3 to 30 days after surgery [1]. It is a relatively rare complication of surgical interventions which deserves attention because of its high mortality and serious disability that can lead to both prolonged hospital stay as well as discharge to long-term care facilities [2, 3]. Furthermore, the real incidence is most likely underestimated as the neurological deficits may be mild, transient or misdiagnosed because sedatives and narcotics often hinder neurological assessment [1, 4].

The aim of this article was to review the literature on perioperative stroke in general surgery, excluding carotid and cardiac surgeries because these have already been thoroughly investigated in previous papers [2, 5–14].

Materials and Methods

A search strategy was designed to identify all relevant studies on perioperative stroke in the English language. This search was restricted to papers published up to December 5, 2011. Studies were initially identified from the Medline/PubMed database, EMBASE and the Cochrane Database using the search terms ‘surgery’, ‘perioperative stroke’, ‘risk factors’, ‘anticoagulation treatment’ and ‘antiplatelet treatment’. One of the researchers (F.M.) read all of the abstracts in order to choose pertinent papers for this review. If any doubt was raised on the pertinence of an article, a second opinion was requested from another author (V.C.).

Results

Of the 3,352 papers found during the literature search only 57 (33 studies and 24 reviews) have been considered relevant for the purpose of this review.

Incidence

The incidence of perioperative stroke among patients who undergo noncardiovascular surgery is reported to be about 0.08–0.7% (0.3–0.4% symptomatic) [3, 4, 15, 16]. The incidence increases with age: 0.1–0.2% for age <65 years, 0.5% for age 65–74 years and 1.0% for age ≥75 years [3, 4, 17]. Perioperative mortality is remarkably high at 18–26% [3, 4, 15, 16].

Timing

The postoperative period is generally defined as 3–30 days after surgery, while most perioperative strokes are identified within the first days after surgery [1, 4–6].

Type of Surgery

The incidence of perioperative stroke depends on the type of the surgical procedure: 0.08–0.7% general surgery, 0.2–0.9% orthopedic surgery and 0.6–0.9% lung operations [3, 17–20]. Neck and head surgery have been associated with a high rate of perioperative stroke: 4.8% [21] (table 1). This high risk might be due to hyperextension and rotation leading to overstretching and compression of the neck’s major arteries that trigger intimal dissection, thrombus formation and vascular occlusion [1, 21]. Furthermore, this incidence is most likely underestimated as these patients typically have a tracheostomy in place; thus, communication is compromised and a neurological evaluation, especially in the presence of slight changes, is difficult to perform and the neurological deficit may easily be missed.

Causes and Pathophysiology

The main reported causes of perioperative ischemic stroke include cerebral atherothrombosis, lacunar stroke, cardioembolism due to atrial fibrillation (AF), dehydration, hypotension and perioperative systemic hypercoagulability [1, 4, 7, 22]. Other less common causes have been reported to be air, fat or paradoxical embolism and arterial dissection of neck arteries [18] (table 1). Perioperative strokes are predominantly ischemic and embolic rather than hemorrhagic [9, 10, 16]. New-onset AF is the comorbid diagnosis in 27.6% of postoperative stroke cases [3], leading to cardioembolism or cerebral hypoperfusion in those cases that develop a rapid ventricular response. Another cardiac source of emboli are diseased valves that can be favorable places for a thrombus to flourish because of alterations in blood flow coupled with perioperative hypercoagulability, hemodynamic changes and anticoagulation withholding [3].

Risk Factors

Patient-related risk factors include the following: age >70, female sex, previous stroke or transient ischemic attack, history of hypertension, diabetes mellitus, renal insufficiency, dialysis, smoking, chronic obstructive pulmonary disease, peripheral vascular disease, cardiac disease (history of myocardial infarction within 6 months prior to surgery, AF, valvular cardiopathy), carotid stenosis, atherosclerosis of the ascending aorta and the discontinuation of antithrombotic therapy before surgery. Procedure-related factors include timing of surgery (urgent vs. elective), type and duration of procedure, type of anesthesia (general vs. regional), intraoperative complications such as arrhythmia or heart rate alterations [23],

hyperglycemia, dehydration and blood loss [18] (table 1). Particular attention is needed for those patients who have had previous stroke because they are at higher risk for perioperative cerebrovascular accidents [1, 2, 5–7, 11, 12, 19–21, 24–26]. In fact, general surgery has a low stroke risk of about 0.2% [19], but it increases to 2.9% in patients with precedent stroke [24] and rises to 3.6% in patients with carotid stenosis and prior symptoms [27]. If neurological symptoms are related to a basilar or intracranial vertebral artery stenosis, the perioperative stroke risk has been reported to be 6.0% with prolonged intraoperative hypotension acting as a precipitating factor [28]. The relation between asymptomatic carotid stenosis of any grade and the incidence of perioperative stroke in general elective surgery has not yet been determined [29].

Anticoagulation Therapy before Surgery

The management of patients taking oral anticoagulant (OAC) therapy is challenging because the risk of a thromboembolic event needs to be counterbalanced with the risk of bleeding. In a review of 31 reports on the perioperative treatment of patients receiving OAC, arterial thromboembolism and stroke rates were reported to be 1.6 and 0.4%, respectively, for all patients and 0.6 and 0.3%, respectively, for patients who had been taking warfarin therapy withheld without the administration of intravenous heparin or subcutaneous low-molecular-weight heparin (LMWH) [30]. On the other hand, an increase in major bleeding over the first 2 postoperative days has been reported to be approximately 2–4% for major surgery and 0–2% for invasive procedures [30]. Regarding new OAC agents, the risk of severe bleeding with dabigatran has been reported to be similar to that of patients using LMWH in orthopedic surgery, and the same as or lower than patients with well-controlled AF on warfarin (3.11 vs. 3.36%, respectively) [31]. Despite the clinical indication, patients with AF are frequently not put back on anticoagulation after surgery.

Antiplatelet Withdrawal before Surgery

Due to the high incidence of cardiovascular disease, antiplatelets are widely prescribed to up to 25% of the elderly population under aspirin (acetylsalicylic acid, ASA) treatment [32]. Antiplatelet drugs are effective in preventing arterial thrombosis both in primary [33, 34] and secondary [35] prevention but their continuation could lead to bleeding in the operative setting. This risk depends on the type of therapy (one, two or more antiplatelet drugs), surgical procedure (hip arthroplasty, tonsillectomy and transurethral resection of the prostate tend to bleed more; neurosurgery, ophthalmology and otorhinolaryngology

Table 1. Main causes and risk factors for perioperative stroke

<i>Causes</i> [1, 4, 7, 18, 22]	
Cerebral atherothrombosis	
Atrial fibrillation	
Lacunar stroke	
Dehydration	
Hypotension	
Perioperative systemic hypercoagulability	
Paradoxical embolism	
Arterial dissection	
<i>Risk factors with odds ratios</i> [3, 4, 17, 18, 23]	
Age >70	23.6 (9.6–58.1) [17]
Previous stroke or transient ischemic attack	2.18 (1.75–2.72) [3] 7.1 (4.6–11) [17]
Diabetes mellitus	2.2 (1.4–3.3) [17] 1.42 (1.25–1.62) [3]
Renal insufficiency and dialysis	5.36 (4.68–6.13) [3]
Chronic obstructive pulmonary disease	1.61 (1.44–1.81) [3]
Peripheral vascular disease	2.20 (1.77–2.74) [3]
Cardiac disease	
AF	3.98 (3.57–4.45) [3] 5.5 (2.8–10.9) [17]
Congestive heart failure	3.71 (3.26–4.22) [3]
Valvular disease	2.51 (2.10–2.99) [3]
Ischemic heart disease	1.75 (1.56–1.97) [3] 2.3 (1.3–4.1) [17]
Angina pectoris	2.5 (1.4–4.4)
Other risk factors	
Female sex	
Hypertension	
Smoking	
Carotid stenosis	
Atherosclerosis of the ascending aorta	
Discontinuation of antithrombotic therapy before surgery	
Timing of surgery (urgent vs. elective)	
Type and duration of procedure	
Type of anaesthesia (general vs. regional)	
Intraoperative complications (arrhythmia or heart rate alterations)	
Hyperglycemia	
Dehydration	
Blood loss	
<i>Type of surgery</i> [3, 17–21, 26, 57]	
General (0.08–0.7%)	[3, 26]
Orthopedic (0.2–0.9%)	[3, 20]
Lung (0.6–0.9%)	[3, 17]
Peripheral vascular (0.3–3%)	[18, 20]
Neck and head (3.2 ^a –4.8%)	[21, 57]

For risk factors, values in parentheses are 95% confidence intervals; for type of surgery, percent incidence is given in parentheses; the incidence is expressed as a range using the minimum and the maximum values described in the literature.

^a Neck dissection and simultaneous carotid endarterectomy.

Table 2. Management of patients with vascular disease undergoing noncardiovascular surgery

Antiplatelet therapy

ASA (primary prevention): stop 5 days prior to surgery and resume 24 h after surgery [40]

ASA (secondary prevention): do not withdraw [40]

Clopidogrel: stop 5 days before surgery and resume 24 h after surgery [39]

ASA + clopidogrel: continue both antiplatelets in the perioperative period; if bleeding risk reduction is required:

stop clopidogrel 5 days prior to surgery and continue ASA

consider 'bridging therapy' with short-acting intravenous glycoprotein IIb/IIIa inhibitors [52, 53]; bridging therapy with heparin not suggested [40]

resume clopidogrel 24 h after surgery [40]

Anticoagulant therapy [40]

Stop vitamin K antagonists and start subcutaneous LMWH or intravenous UFH 5 days before surgery

Stop subcutaneous LMWH 12 h (twice-daily regimen) or 24 h (once-daily regimen) prior to surgery

If UFH is used, stop it 4–6 h prior to surgery

Resume vitamin K antagonists + LMWH/UFH 12–24 h after surgery until INR therapeutic range is achieved

Dabigatran:

do not stop for minor procedures

stop 24 h to 5 days prior to major surgery (depending on renal function)

resume 1–4 h after the operation

consider bridging therapy with heparin if there is a high thrombotic risk

Carotid revascularization (carotid endarterectomy or carotid artery stenting)

Symptomatic carotid stenosis $\geq 70\%$ [47]

do not permit even minimal bleeding) and the sensitivity of patients to antiplatelet agents [36]. Patients taking ASA have a 1.5-fold higher risk of blood loss without any increase in bleeding-related surgical mortality or morbidity [37]. Thus, low-dose ASA increases bleeding only quantitatively and does not move the bleeding complications toward a higher risk quality [37]. In fact, for anatomical reasons, urological interventions and diagnostic procedures tend to have a high rate of bleeding. In addition, a randomized controlled study has reported that there was no difference in intraoperative hemorrhage, operation time and amount of tissue resected between patients taking ASA during transurethral resection of the prostate and those not taking ASA, even though there was a reported increase in postoperative blood loss of 51% (284 vs. 144 ml) [38]. Regarding clopidogrel, only a limited number of case reports and a small clinical series of visceral and vascular surgery have been published. However, a recent study has reported that patients receiving clopidogrel 5 days before lung resection had similar mortality, postoperative length of stay, rate of perioperative transfusion, reoperation for bleeding, myocardial infarction and stroke compared to controls sharing the same risk factors for both thrombosis and increased blood loss [39]. Thus, withdrawing clopidogrel only 5 days instead of 7–10 days [40] before major surgery seems to be safe and allows for adequate hemostasis. Clopidogrel plus

ASA increases surgical bleeding and the rate of transfusion by 50% without increasing morbidity, mortality or surgical outcome [41]. Nevertheless, this type of bleeding is rarely life threatening and can be managed like any other type and even prevented by using less invasive or advanced surgical approaches [42].

The abrupt discontinuation of antiplatelet agents, in fact, is associated with a rebound phenomenon that accentuates the problem and makes the thrombus formation more probable [43]. The time interval between discontinuation and acute cerebral events has been reported to be 14.3 ± 11.3 days [37]. Despite the high thrombotic risk, of 287 English urologists, 62% withdrew ASA prior to transurethral resection of the prostate without specifying any reason [44]. Additionally, an American survey of ophthalmologists found that 52% discontinued ASA prior to surgery, while a survey of gastroenterologists reported that 81% stopped ASA before colonoscopy, 79% before endoscopic retrograde cholangiopancreatography and 51% prior to upper endoscopy [45, 46].

Conclusions

Even if the incidence of perioperative stroke among patients who undergo noncardiovascular surgery is reported to be very low (0.3–0.4% symptomatic) [3, 4, 15,

16], it nonetheless remains a devastating disease with a high perioperative mortality (18–26%) [3, 4, 15, 16]. Management guidelines for patients with vascular disease undergoing surgery are insufficient and, therefore, surgeons generally make these decisions independently. On the basis of the findings of this review, the authors make the following recommendations (table 2).

Regarding symptomatic stenosis $\geq 70\%$, carotid revascularization by carotid endarterectomy or carotid artery stenting before general surgery is the standard care [47], while there is no evidence to date to support a prophylactic revascularization in asymptomatic patients that would expose them to a 2-fold higher risk of periprocedural stroke and myocardial infarction without significantly reducing the risk of stroke [48–50]. However, of these latter patients, those having hemodynamically significant bilateral carotid stenosis may benefit from revascularization [18].

The guidelines of the American College of Chest Physicians (ACCP) recommend stopping OACs approximately 5 days before major surgery to adequately allow the INR to normalize and, at the same time, to start the ‘bridging anticoagulation’ with subcutaneous LMWH or intravenous unfractionated heparin (UFH) at different dosages (therapeutic or prophylactic) and different timings depending on the individual thrombotic risk of the patient [40]. Specifically, as far as bridging therapy is concerned, the last dose of LMWH must be given no less than 12 h before the operation with a twice-daily regimen, or 24 h before the operation with a once-daily regimen to avoid the persistence of anticoagulant effect during surgery [51]. If intravenous UFH has been used, it should be stopped 4–6 h prior to surgery. OACs must be resumed 12–24 h after surgery together with heparin, as warfarin takes a few days to reach its full effect [40]. Regarding new anticoagulants, dabigatran does not need to be withheld for minor procedures, whereas for major surgery it has to be discontinued 24 h to 5 days prior to surgery depending on the risk of bleeding and on the renal function of the patient. Dabigatran can be resumed 1–4 h after surgery if the wound is stable, otherwise the resumption must be

delayed. If the patient has a high thrombotic risk a perioperative bridging therapy with heparin should be considered. Currently, there are no clear recommendations on the use of rivaroxaban and apixaban.

Data concerning the management of patients undergoing antiplatelet therapy are lacking. To date, the ACCP guidelines discourage the perioperative withdrawal of ASA, especially in patients in secondary prevention [40]. If the interruption is absolutely needed, resumption within 24 h after the procedure is suggested [40]. When clopidogrel withdrawal is required in order to reduce perioperative bleeding, bridging therapy, which includes short-acting intravenous glycoprotein IIb/IIIa inhibitors such as tirofiban or eptifibatide (until just before intervention in those patients with coronary stent recently implanted), can be administered [52, 53]. The ACCP guidelines suggest against the routine use of bridging therapy with UFH or LMWH because the efficacy and safety data on patients taking antiplatelet therapy are lacking [40]. In fact, heparin does not have antiplatelet properties and is not protective against stent thrombosis [54, 55]. Despite this, many surgeons substitute antiplatelet therapy with LMWH as an antithrombotic bridging therapy or, empirically, use the same doses of the venous thromboembolism prophylaxis.

The Antiplatelet Agents in the Perioperative Management of Patients Trial, an ongoing randomized controlled trial, has the aim of assessing the safety and determining the optimal use of ASA in the perioperative management of patients undergoing general and abdominal surgery. This is being done by comparing a group of low-risk patients, who were withdrawn from ASA 5 days prior to surgery and resumed taking it 5 days after the intervention, to controls who did not discontinue the antiplatelet agent [56].

While waiting upon the results of the above-mentioned and other trials, an individualized, accurate, multidisciplinary (surgical, neurological, cardiological and anesthesiological) risk/benefit assessment remains the best basis for treatment decision.

References

- 1 Kim J, Gelb AW: Predicting perioperative stroke. *J Neurosurg Anesthesiol* 1995;7:211–215.
- 2 McKhann GM, Grega MA, Borowicz LM Jr, Baumgartner WA, Selnes OA: Stroke and encephalopathy after cardiac surgery: an update. *Stroke* 2006;37:562–571.
- 3 Bateman BT, Schumacher HC, Wang S, Shae-fi S, Berman MF: Perioperative acute ischemic stroke in noncardiac and nonvascular surgery: incidence, risk factors, and outcomes. *Anesthesiology* 2009;110:231–238.
- 4 Kikura M, Bateman BT, Tanaka KA: Perioperative ischemic stroke in non-cardiovascular surgery patients. *J Anesth* 2010;24:733–738.

- 5 Bucerius J, Gummert JF, Borger MA, Walther T, Doll N, Onnasch JF, Metz S, Falk V, Mohr FW: Stroke after cardiac surgery: a risk factor analysis of 16,184 consecutive adult patients. *Ann Thorac Surg* 2003;75:472–478.
- 6 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: Determination of etiologic mechanisms of strokes secondary to coronary artery bypass graft surgery. *Stroke* 2003;34:2830–2834.
- 7 Likosky DS, Caplan LR, Weintraub RM, Hartman GS, Malenka DJ, Ross CS, Landis ES, Applebaum B, Braff SP, O'Connor GT: Intraoperative and postoperative variables associated with strokes following cardiac surgery. *Heart Surg Forum* 2004;7:E271–E276.
- 8 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;23:283–294.
- 9 Restrepo L, Wityk RJ, Grega MA, Borowicz L Jr, Barker PB, Jacobs MA, Beauchamp NJ, Hillis AE, McKhann GM: Diffusion- and perfusion-weighted magnetic resonance imaging of the brain before and after coronary artery bypass grafting surgery. *Stroke* 2002;33:2909–2915.
- 10 Brooker RF, Brown WR, Moody DM, Hammon JW Jr, Reboussin DM, Deal DD, Ghazi-Birry HS, Stump DA: Cardiomyotomy suction: a major source of brain lipid emboli during cardiopulmonary bypass. *Ann Thorac Surg* 1998;65:1651–1655.
- 11 Hogue CW Jr, Murphy SF, Schechtman KB, Davila-Roman VG: Risk factors for early or delayed stroke after cardiac surgery. *Circulation* 1999;100:642–647.
- 12 van Wermeskerken GK, Lardenoye JW, Hill SE, Grocott HP, Phillips-Bute B, Smith PK, Reves JG, Newman MF: Intraoperative physiologic variables and outcome in cardiac surgery. Part II. Neurologic outcome. *Ann Thorac Surg* 2000;69:1077–1083.
- 13 Jongen LM, Hendrikse J, Moll FL, Mali WP, van der Worp HB: Cerebral perfusion affects the risk of ischemia during carotid artery stenting. *Cerebrovasc Dis* 2010;29:538–545.
- 14 Korn-Lubetzki I, Steiner I, Oren A, Tauber R, Steiner-Birmann B, Bitran D: The possible risk for strokes complicating cardiac surgery in patients with intraoperative hypothermia. *Cerebrovasc Dis* 2010;30:602–605.
- 15 Parikh S, Cohen JR: Perioperative stroke after general surgical procedures. *NY State J Med* 1993;93:162–165.
- 16 Limburg M, Wijdevicks EF, Li H: Ischemic stroke after surgical procedures: clinical features, neuroimaging, and risk factors. *Neurology* 1998;50:895–901.
- 17 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;6:742–748.
- 18 Selim M: Perioperative stroke. *N Engl J Med* 2007;356:706–713.
- 19 Larsen SF, Zaric D, Boysen G: Postoperative cerebrovascular accidents in general surgery. *Acta Anaesthesiol Scand* 1988;32:698–701.
- 20 Wong GY, Warner DO, Schroeder DR, Oford KP, Warner MA, Maxson PM, Whisnant JP: Risk of surgery and anesthesia for ischemic stroke. *Anesthesiology* 2000;92:425–432.
- 21 Nosan DK, Gomez CR, Maves MD: Perioperative stroke in patients undergoing head and neck surgery. *Ann Otol Rhinol Laryngol* 1993;102:717–723.
- 22 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;79:223–229.
- 23 Mortazavi SM, Kakli H, Bican O, Moussoutas M, Parvizi J, Rothman RH: Perioperative stroke after total joint arthroplasty: prevalence, predictors, and outcome. *J Bone Joint Surg Am* 2010;92:2095–2101.
- 24 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;125:986–989.
- 25 Knapp RB, Topkins MJ, Artusio JF Jr: The cerebrovascular accident and coronary occlusion in anesthesia. *JAMA* 1962;182:332–334.
- 26 Kam PC, Calcroft RM: Peri-operative stroke in general surgical patients. *Anaesthesia* 1997;52:879–883.
- 27 Evans BA, Wijdevicks EF: High-grade carotid stenosis detected before general surgery: is endarterectomy indicated? *Neurology* 2001;57:1328–1330.
- 28 Blacker DJ, Flemming KD, Wijdevicks EF: Risk of ischemic stroke in patients with symptomatic vertebralbasilar stenosis undergoing surgical procedures. *Stroke* 2003;34:2659–2663.
- 29 Paciaroni M, Caso V, Acciarresi M, Baumgartner RW, Agnelli G: Management of asymptomatic carotid stenosis in patients undergoing general and vascular surgical procedures. *J Neurol Neurosurg Psychiatry* 2005;76:1332–1336.
- 30 Dunn AS, Turpie AG: Perioperative management of patients receiving oral anticoagulants: a systematic review. *Arch Intern Med* 2003;163:901–908.
- 31 Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L: Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139–1151.
- 32 Shahar E, Folsom AR, Romm FJ, Bisgard KM, Metcalf PA, Crum L, McGovern PG, Hutchinson RG, Heiss G: Patterns of aspirin use in middle-aged adults: the atherosclerosis risk in communities (ARIC) study. *Am Heart J* 1996;131:915–922.
- 33 Cannon CP: Elderly patients with acute coronary syndromes: higher risk and greater benefit from antiplatelet therapy and/or interventional therapies. *Am J Geriatr Cardiol* 2003;12:259–262.
- 34 Dornbrook-Lavender KA, Pieper JA, Roth MT: Primary prevention of coronary heart disease in the elderly. *Ann Pharmacother* 2003;37:1654–1663.
- 35 Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71–86.
- 36 Lecompte T, Hardy JF: Antiplatelet agents and perioperative bleeding. *Can J Anaesth* 2006;53:S103–S112.
- 37 Burger W, Chemnitz JM, Kneissl GD, Rucker G: Low-dose aspirin for secondary cardiovascular prevention – cardiovascular risks after its perioperative withdrawal versus bleeding risks with its continuation – review and meta-analysis. *J Intern Med* 2005;257:399–414.
- 38 Nielsen JD, Holm-Nielsen A, Jespersen J, Vinther CC, Settgast IW, Gram J: The effect of low-dose acetylsalicylic acid on bleeding after transurethral prostatectomy – a prospective, randomized, double-blind, placebo-controlled study. *Scand J Urol Nephrol* 2000;34:194–198.
- 39 Ceppa DP, Welsby IJ, Wang TY, Onaitis MW, Tong BC, Harpole DH, D'Amico TA, Berry MF: Perioperative management of patients on clopidogrel (Plavix) undergoing major lung resection. *Ann Thorac Surg* 2011;92:1971–1976.
- 40 Douketis JD, Berger PB, Dunn AS, Jaffer AK, Spyropoulos AC, Becker RC, Ansell J: The perioperative management of anti-thrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, ed 8. *Chest* 2008;133:299S–339S.
- 41 Di Minno MN, Prisco D, Ruocco AL, Mastronardi P, Massa S, Di Minno G: Perioperative handling of patients on antiplatelet therapy with need for surgery. *Intern Emerg Med* 2009;4:279–288.

- 42 Samama CM, Bastien O, Forestier F, Denninger MH, Isetta C, Juliard JM, Lasne D, Leys D, Mismetti P: Antiplatelet agents in the perioperative period: expert recommendations of the French Society Of Anesthesiology And Intensive Care (SFAR) 2001 – summary statement. *Can J Anaesth* 2002;49:S26–S35.
- 43 Beving H, Zhao C, Albage A, Ivert T: Abnormally high platelet activity after discontinuation of acetylsalicylic acid treatment. *Blood Coagul Fibrinolysis* 1996;7:80–84.
- 44 Enver MK, Hoh I, Chingwundoh FI: The management of aspirin in transurethral prostatectomy: current practice in the UK. *Ann R Coll Surg Engl* 2006;88:280–283.
- 45 Kadakia SC, Angueira CE, Ward JA, Moore M: Gastrointestinal endoscopy in patients taking antiplatelet agents and anticoagulants: survey of ASGE members. *American Society for Gastrointestinal Endoscopy. Gastrointest Endosc* 1996;44:309–316.
- 46 Stone LS, Kline OR Jr, Sklar C: Intraocular lenses and anticoagulation and antiplatelet therapy. *J Am Intraocul Implant Soc* 1985;11:165–168.
- 47 Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, Rankin RN, Claggett GP, Hachinski VC, Sackett DL, Thorpe KE, Meldrum HE, Spence JD: Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med* 1998;339:1415–1425.
- 48 Gerraty RP, Gates PC, Doyle JC: Carotid stenosis and perioperative stroke risk in symptomatic and asymptomatic patients undergoing vascular or coronary surgery. *Stroke* 1993;24:1115–1118.
- 49 Chaturvedi S, Bruno A, Feasby T, Holloway R, Benavente O, Cohen SN, Cote R, Hess D, Saver J, Spence JD, Stern B, Wilterdink J: Carotid endarterectomy – an evidence-based review: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2005;65:794–801.
- 50 Barnett HJ, Meldrum HE: Endarterectomy for carotid stenosis: new approaches in patient selection. *Cerebrovasc Dis* 2001;11(suppl 1):105–111.
- 51 Thachil J, Gatt A, Martlew V: Management of surgical patients receiving anticoagulation and antiplatelet agents. *Br J Surg* 2008;95:1437–1448.
- 52 Savonitto S, D’Urbano M, Caracciolo M, Barlocco F, Mariani G, Nichelatti M, Klugmann S, De Servi S: Urgent surgery in patients with a recently implanted coronary drug-eluting stent: A phase II study of ‘bridging’ antiplatelet therapy with tirofiban during temporary withdrawal of clopidogrel. *Br J Anaesth* 2010;104:285–291.
- 53 Savonitto S, Caracciolo M, Cattaneo M, De Servi S: Management of patients with recently implanted coronary stents on dual antiplatelet therapy who need to undergo major surgery. *J Thromb Haemost* 2011;9:2133–2142.
- 54 Collet JP, Montalescot G, Blanchet B, Tanguy ML, Golmard JL, Choussat R, Beygui F, Payot L, Vignolles N, Metzger JP, Thomas D: Impact of prior use or recent withdrawal of oral antiplatelet agents on acute coronary syndromes. *Circulation* 2004;110:2361–2367.
- 55 Batchelor WB, Mahaffey KW, Berger PB, Deutsch E, Meier S, Hasselblad V, Fry ET, Teirstein PS, Ross AM, Binanay CA, Zidar JP: A randomized, placebo-controlled trial of enoxaparin after high-risk coronary stenting: the ATLAST trial. *J Am Coll Cardiol* 2001;38:1608–1613.
- 56 Antolovic D, Reissfelder C, Rakow A, Contin P, Rahbari NN, Buchler MW, Weitz J, Koch M: A randomised controlled trial to evaluate and optimize the use of antiplatelet agents in the perioperative management in patients undergoing general and abdominal surgery – the APAP trial (ISRCTN45810007). *BMC Surg* 2011;11:7.
- 57 Rechtweg J, Wax MK, Shah R, Granke K, Jar-muz T: Neck dissection with simultaneous carotid endarterectomy. *Laryngoscope* 1998;108:1150–1153.