Raising the Alarm on Brain Attacks in Surgical Patients

Are We Doing Enough to Prevent and Treat Postoperative Strokes?

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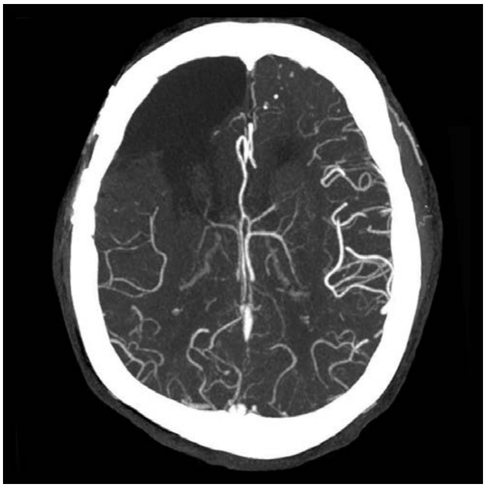

"The time is right…[to update] existing clinical practice guidelines…[on the] management of patients at high risk for perioperative acute ischemic stroke."

THE incidence of postoperative strokes in patients undergoing noncardiac, nonneurologic surgery is between 0.1 and 0.7%.[1,2] Previous studies reported that patients with a history of ischemic stroke are two to three times more likely to experience a postoperative stroke.[1,2] In this issue of Anesthesiology, Christiansen *et al.*[3] report that a history of stroke within 3 months of emergency noncardiac, nonintracranial surgery is associated with a significantly increased risk of a recurrent postoperative stroke using data on 146,694 acute surgeries from the Danish National Patient Registry (DNRP). Specifically, 10% of patients with a history of ischemic stroke within 3 months had a postoperative stroke compared with 2 to 3% of patients with a history of stroke more than 3 months ago and 0.3% in patients with no previous stroke.[3] In a previous study reported in the *Journal of the American Medical Association*, based on 481,183 elective surgeries in the DNRP, this same group reported similar time effects on the risk of postoperative stroke in patients undergoing elective noncardiac surgery: 12.0% in patients with stroke within 3 months, 4.5% in patients with stroke between 3 and 6 months, 1.0 to 2.0% if more than 6 months, and 0.1% in patients with no previous stroke.[4] Unlike the Danish database, previous studies in the United States that reported a much lower risk of recurrent strokes were based on databases (the Nationwide Inpatient Sample and the American College of Surgeons National Surgical Quality Improvement Program database) that grouped all previous strokes together.[1,2] These databases did not include information on how much time had elapsed between previous strokes and surgery.

The studies by Christiansen and colleagues[3,4] have important limitations. It is well known that patients with an ischemic stroke are at the highest risk for recurrent stroke soon after the event and that this risk declines over time. The magnitude of postoperative risk found in these studies, however, was considerably greater than that found in a comparable cohort who did not undergo surgery (12.0 *vs.* 3.5%).[5,6] Second, although the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision ischemic stroke diagnoses have been validated in the DNRP,[7] there are no data on whether these diagnoses in the postoperative period accurately reflect recurrent or new infarcts. Preexisting stroke symptoms often worsen in the setting of systemic stress (often called an *anamnestic* response, or bringing out an old memory), and it is possible that symptoms of a recent stroke may transiently worsen in the setting of surgery without acutely infarcted tissue. Third, the impact of increased magnetic resonance imaging use in the detection of small strokes, and even silent stroke, is increasingly recognized.[8] Fourth, the DNRP provides no information on the presumed underlying etiology of the recurrent stroke (*e.g.*, hypoperfusion, atheroembolic, proinflammatory, anesthetic effects, and cerebrovascular dysregulation). Finally, these studies are retrospective and used administrative data from one nation.

These authors[3,4] are to be commended for highlighting an important area that has received little attention in the literature. Perhaps the most important takeaway is the need for additional research to confirm and refine these estimates using different approaches in more diverse populations. In addition, more research is needed to better understand the

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Accepted for publication March 27, 2017. From the Departments of Anesthesiology (L.G.G.), Public Health Sciences (L.G.G., R.G.H.), and Neurology (R.G.H.), University of Rochester School of Medicine, Rochester, New York; and RAND Health, RAND, Boston, Massachusetts (L.G.G.).

<zdoi;10.1097/ALN.0000000000001686>

pathomechanisms of postoperative strokes, as well as the various antiischemic strategies (*e.g.*, molecular, antiinflammatory, and cell based) to minimize neuronal injury. Until then, however, we recommend the following:

First, the Society for Neuroscience in Anesthesiology and Critical Care recently published a consensus statement, supported but not endorsed by the American Society of Anesthesiologists, on the prevention and management of postoperative strokes.[9] They suggest that surgeons consider delaying elective surgery for 1 month in patients after a stroke. According to this consensus statement, the recommendation to delay elective surgery in patients with recent strokes is supported only by "opinion-based evidence."[9] The data by Christiansen and colleagues[3,4] suggest that the recommended delay for elective surgery might need to be longer, possibly up to at least 3 months after an acute stroke. In addition, in those stroke patients who are recommended for surgery, particular attention should be paid to baseline neurologic deficits so that new postoperative deficits can be identified.

Second, perioperative and surgical teams should have a heightened sense of awareness to new neurologic deficits and clear procedures to engage stroke teams.[10] Although major surgery within the past 14 days is a relative contraindication to fibrinolytic therapy,[11] existing guidelines state that the use of fibrinolytic therapy may be considered in the absence of intracranial or intraspinal surgery (class IIb recommendation).[9,11] However, many surgeons and anesthesiologists are likely to be hesitant to use fibrinolytic therapy in the immediate postoperative period due to the risk of major bleeding at the operative site. For many surgical patients, endovascular thrombectomy may be the only practical approach to restoring perfusion after a stroke caused by proximal artery occlusion. Existing guidelines specify that endovascular therapy is reasonable and can be useful in patients with contraindications to fibrinolytic therapy (class IIa recommendations).[12] Endovascular therapies with mechanical thrombectomy have been described as the second quantum leap in stroke care.[12,13] Not only is endovascular thrombectomy less likely to lead to bleeding complications in surgical patients, it is more likely to lead to better neurologic outcomes. At 90 days, patients with acute ischemic strokes undergoing endovascular therapy are more than 50% more likely to have reduced disability compared with standard lytic therapy.[14] Endovascular thrombectomy may represent a new frontier in the therapy of acute postoperative strokes.

Third, we believe that the care of high-risk patients whose elective surgery cannot be delayed (*e.g.*, cancer surgery) should be regionalized to comprehensive stroke centers with advanced neuroimaging capabilities and neuroendovascular specialists, resources that are not available in most hospitals and primary stroke centers.[15] In 2017 there are 121 comprehensive stroke centers in the United States.[16] For the many patients where this may not be practical (*e.g.*, location is remote from a comprehensive stroke center), however, a clear plan should be in place to manage such patients *via* a telestroke consultation.[17]

Fourth, the American Stroke Association has published clinical practice guidelines on the prevention and early management of patients with acute ischemic strokes.[11,12,18] These clinical practice guidelines do not discuss the management of patients with a recent stroke undergoing surgery or the approach to patients if a new stroke occurs after surgery. In particular, they do not address delaying elective surgery after a recent stroke. The only currently available guideline addressing this issue is from the Society for Neuroscience in Anesthesiology and Critical Care.[12] These guidelines, however, have not been widely disseminated; they have been cited only 20 times since publication in 2014, compared with 868 citations for the American Stroke Association guidelines, also published in 2014. The timing is right to convene a group of neurologists, anesthesiologists, and surgeons to review the literature and write a focused update of existing clinical practice guidelines focusing on the perioperative management of patients at high risk for perioperative acute ischemic stroke.

Many patients fear disabling strokes more than death.[19] We need to do much more than we are doing to better understand, prevent, and treat strokes in high-risk surgical patients.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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Risks of Cardiovascular Adverse Events and Death in Patients with Previous Stroke Undergoing Emergency Noncardiac, Nonintracranial Surgery

The Importance of Operative Timing

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ABSTRACT

Background: The outcomes of emergent noncardiac, nonintracranial surgery in patients with previous stroke remain unknown.

Methods: All emergency surgeries performed in Denmark (2005 to 2011) were analyzed according to time elapsed between previous ischemic stroke and surgery. The risks of 30-day mortality and major adverse cardiovascular events were estimated as odds ratios (ORs) and 95% CIs using adjusted logistic regression models in *a priori* defined groups (reference was no previous stroke). In patients undergoing surgery immediately (within 1 to 3 days) or early after stroke (within 4 to 14 days), propensity-score matching was performed.

Results: Of 146,694 nonvascular surgeries (composing 98% of all emergency surgeries), 5.3% had previous stroke (mean age, 75 yr [SD = 13]; 53% women, 50% major orthopedic surgery). Antithrombotic treatment and atrial fibrillation were more frequent and general anesthesia less frequent in patients with previous stroke (all $P < 0.001$). Risks of major adverse cardiovascular events and mortality were high for patients with stroke less than 3 months (20.7 and 16.4% events; OR = 4.71 [95% CI, 4.18 to 5.32] and 1.65 [95% CI, 1.45 to 1.88]), and remained increased for stroke within 3 to 9 months (10.3 and 12.3%; OR = 1.93 [95% CI, 1.55 to 2.40] and 1.20 [95% CI, 0.98 to 1.47]) and stroke more than 9 months (8.8 and 11.7%; OR = 1.62 [95% CI, 1.43 to 1.84] and 1.20 [95% CI, 1.08 to 1.34]) compared with no previous stroke (2.3 and 4.8% events). Major adverse cardiovascular events were significantly lower in 323 patients undergoing immediate surgery (21%) compared with 323 successfully propensity-matched early surgery patients (29%; $P = 0.029$).

Conclusions: Adverse cardiovascular outcomes and mortality were greatly increased among patients with recent stroke. However, events were higher 4 to 14 days after stroke compared with 1 to 3 days after stroke. **(ANESTHESIOLOGY 2017; 127:9-19)**

What We Already Know about This Topic

- There is a steep decline and stabilization of risks within the first 9 months after stroke among patients undergoing elective surgery, but risks after emergency surgery are unknown

What This Article Tells Us That Is New

- After emergency noncardiac, nonintracranial surgery, risks of 30-day major adverse cardiovascular events (acute myocardial infarction, ischemic stroke, or cardiovascular death) were high for patients with stroke less than 3 months before surgery (odds ratio [OR] = 4.7), 3 to 9 months (OR = 1.9) and more than 9 months (OR = 1.6) compared with no previous stroke
- Risks of death (1.6, 1.2, and 1.2) in the same period were also increased
- Risk of major adverse cardiovascular events was significantly lower after immediate (1 to 3 days after stroke) compared with early surgery (4 to 14 days)
- These patterns were similar to that observed in poststroke patients having elective surgery

EMERGENCY surgery is one of the most high-risk situations encountered in clinical practice, and risks become especially pronounced in patients with weighty comorbidities, such as cerebrovascular disease.[1] Because time is an important factor in the clinical setting, detailed information on perioperative risks is important to guide decision-making and to inform the patient and relatives about realistic perioperative expectations. More than 800,000 patients experience a stroke in the United States every year, with the majority being ischemic strokes,[2] and the World Health Organization estimates that incidence rates of stroke in Europe will increase by approximately 1.5 million per year from 2000 to 2025.[3] Emergency surgeries in patients with previous stroke are becoming more frequent due to advances in treatment and an increased willingness to treat older and more fragile patients. Stroke has been included in widely used preoperative risk evaluation schemes, such as the revised cardiac risk index by Lee

This article is featured in “This Month in Anesthesiology,” page 1A. Corresponding article on page 3. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal’s Web site (www.anesthesiology.org). This article has an audio podcast.

<zdoi;10.1097/ALN.0000000000001685>

et al.,[4] but the importance of time elapsed between stroke and emergency surgery has not previously been reported and is not considered in current perioperative guidelines.[5,6] A recent study demonstrated a steep decline and stabilization of risks within the first 9 months after stroke among patients undergoing elective surgery.[7] In patients with previous myocardial infarction, a similar decrease in risks followed by stabilization at 6 months has been demonstrated, and perioperative guidelines do address the importance of time between stenting and noncardiac surgery.[8,9] The mechanism for increased risks in patients with recent stroke are thought to be at least partly mediated by deteriorating cerebral autoregulation within the first 5 days after stroke and impaired autoregulation for up to 3 months.[10,11] This condition renders patients vulnerable to secondary neuronal injury during anesthesia, surgical stress, and perioperative care. Indeed, a recent strategy to improve outcomes from emergency surgery includes very early operation, and a recent guideline presented several arguments in favor of surgical repair of hip fractures within 48 h, but does not provide specific guidance on whether this is appropriate in patients with very recent strokes.[12] Herein we hypothesized that very early or more delayed surgery would be associated with better outcomes than surgery conducted at an intermediate time point when autoregulation may be maximally dysregulated.

We investigated the association between time elapsed after ischemic stroke and the risk of adverse events after emergency noncardiac surgery. Although we recognize that postponing emergency surgeries is rarely an option, choosing to operate earlier is sometimes a possibility. Furthermore, our results may provide additional guidance for clinical decision-making and lead to a better understanding of expected perioperative outcomes in this growing and critically ill patient population.

Materials and Methods

Ethics

This study was approved by the Danish Data Protection Agency, Copenhagen, Denmark (reference No. GEH-2014–019 and I-Suite No. 02737). Register-based studies using depersonalized data do not require ethics committee approval or patient consent in Denmark.

Data Sources

In Denmark, all of the citizens have a unique personal identification number, which enables identification and linkage of individual patients across several Danish registers. For this study, we retrieved information on diagnoses at hospital discharge and surgical procedures from the Danish National Patient Register, complete since 1977.[13] All of the information is coded according to international standards including the International Classification of Diseases, Tenth Revision (ICD-10) and the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures.[14] From the Danish Anesthesia Database, complete since 2005, we retrieved information on whether a surgery was elective or emergent, as well as information on body mass index, type of anesthesia, and duration of anesthesia, which was collected as part of the daily clinical work. Information on pharmacotherapy before surgery was retrieved from the Danish Register of Medicinal Product Statistics, which holds information on all claimed prescriptions from Danish pharmacies. The specific drug, coded according to the Anatomical Therapeutic Chemical classification system, and the date of dispense were available. The register is linked to government reimbursement and has proven to be accurate.[15] The Central Population Register provided information on date of birth and sex. The National Causes of Death Register provided information on cause of death and death date.

Study Population

Our study population included all emergency noncardiac and nonintracranial surgeries from 2005 to 2011 for patients more than 20 yr of age. As several procedures were closely linked to a preceding stroke, we excluded cardiac surgeries, surgeries to the carotid arteries, gastrostomies, tracheostomies, and surgical procedures to the arteries of the aortic arch, as done previously.[16] Patients with repeat surgery within the 30-day follow-up period were only included at first surgery. Surgeries beyond a completed 30-day follow-up period were eligible for analyses. See figure 1, Supplemental Digital Content (http://links.lww.com/ALN/B461), for a flow diagram of the inclusion and exclusion criteria for the study population.

We undertook two analytic approaches. Patients with stroke 14 days or less before surgery were stratified as immediate surgery (1 to 3 days between stroke and surgery) and early surgery (4 to 14 days between stroke and surgery) and underwent propensity score–matched analysis and restricted cubic splines analysis to investigate the short-term relationship between time interval to surgery and perioperative outcomes. Longer time intervals were analyzed by logistic regression and restricted cubic spline analyses with patients, also stratified by time between stroke and surgery as patients with no previous stroke, patients with stroke less than 3 months before surgery (stroke less than 3 months), patients with stroke 3 to 9 months before surgery (stroke 3 to 9 months), and patients with stroke more than 9 months before surgery (stroke more than 9 months). Previous ischemic strokes

Submitted for publication June 20, 2016. Accepted for publication March 13, 2017. From The Cardiovascular Research Center, Herlev-Gentofte Hospital, University of Copenhagen, Hellerup, Denmark (M.N.C., C.A., G.H.G., M.E.J.); Department of Cardiology, Glostrup Hospital, University of Copenhagen, Glostrup, Denmark (C.A.); Department of Health Science and Technology, Aalborg University, Aalborg, Denmark (C.T.-P.); Anesthesiology and Critical Care Trials and Interdisciplinary Outcome Network, Department of Anesthesiology, University of Wisconsin, Madison, Wisconsin (R.D.S.); and The Pain Clinic, Department of Anesthesiology, Næstved Hospital, Næstved, Denmark (P.F.J.).

were defined as cerebral infarction (ICD-10: I63) or unspecified stroke (ICD-10: I64) occurring within 5 yr of surgery, because the majority of unspecified strokes in the Danish National Patient Registry have been shown to be of ischemic origin.[17] Transient ischemic attacks and hemorrhagic strokes were not considered because the frequency is low, and the validity and pathophysiology of these diagnoses are different from those of ischemic strokes. Vascular and nonvascular surgeries were analyzed separately in the main analyses, and only nonvascular surgeries were included in sensitivity analyses due to low numbers of vascular surgeries. Vascular surgery was defined as surgery to both arterial and nonarterial vessels according to the NOMESCO classifications (see table 1, Supplemental Digital Content, http://links.lww.com/ALN/B461, which is a list of surgery types according to the NOMESCO classifications).

Study Variables and Outcomes

The uses of pharmacotherapy within 120 days before surgery were grouped according to the Anatomical Therapeutic Chemical classification system. These included lipid modifying agents (C10A), β-blocking agents (C07), agents acting on the renin–angiotensin system (C09), potassium-sparing agents (C03D), thiazides (C03A), calcium channel blockers (C08), digoxin (C01AA05), vitamin K antagonists (B01AA0), glucose-lowering agents (A10), loop diuretics (C03CA01), and antithrombotic therapy as low-dose acetylsalicylic acid (B01AC06), dipyridamole (B01AC07), clopidogrel (B01AC04), or a combination of acetylsalicylic acid and dipyridamole (B01AC30).

Based on ICD-10 coding, we identified previous comorbid conditions as myocardial infarction, chronic obstructive pulmonary disease, anemia, cancer with metastases, renal disease, rheumatic disease, peripheral artery disease, liver disease, diabetes mellitus, chronic heart failure, ischemic heart disease, and atrial fibrillation (coding details are available in table 1, Supplemental Digital Content, http://links.lww.com/ALN/B461). We only considered comorbidities diagnosed or treated within 5 yr before surgery. The diagnoses for comorbidities used in this study have been validated with excellent positive predictive values of 97 to 100% in the Danish National Patient Registry.[17]

Surgeries were divided into 16 categories in accordance with previously published work[14,18] (coding details are available in table 1, Supplemental Digital Content, http://links.lww.com/ALN/B461) and defined as low-, intermediate-, or high-risk surgery in agreement with the European Society of Cardiology perioperative guidelines.[5] Our primary outcomes were 30-day all-cause mortality and a combined endpoint of 30-day major adverse cardiovascular events (MACEs), which included nonfatal ischemic stroke, nonfatal myocardial infarction, and cardiovascular death (any cause of death with ICD-10 code I). Nonfatal ischemic stroke was evaluated separately as a secondary endpoint.

Statistical Analysis

Differences between groups at baseline for continuous and categorical variables were tested using the Student's *t* test and chi-square test. We used three analytical approaches to assess risks of adverse outcomes, including logistic regression models, spline analyses, and propensity-score matching.

Multivariate logistic regression models were used to estimate odds ratios (ORs) with 95% CIs, adjusted for sex, age, body mass index, comorbidities, pharmacotherapy, type of surgery, and surgery risk. Patients with no previous stroke served as the reference. Analyses were performed for the primary and secondary endpoints stratified by vascular and nonvascular surgery. A few patients with missing data on body mass index (approximately 3% were missing for the stroke patients and 2% for no-stroke patients) were included, but considering the very small amount, no attempts were made to impute or otherwise replace the missing data.

Restricted cubic spline regression models adjusted for sex and age were used to analyze time between stroke and surgery as a continuous variable. These analyses included all of the patients with previous stroke undergoing nonvascular surgery. The median time between stroke and surgery for all of the patients (353 days) and patients with stroke 14 days or less before surgery (2 days) served as the reference. Five knots were placed at the 10th, 25th, 50th, 75th, and 90th percentiles of time between stroke and surgery.[19]

Among patients undergoing nonvascular surgery we used propensity-score matching to estimate risks of MACEs in patients having immediate surgery (1 to 3 days after stroke) and early surgery (4 to 14 days after stroke). Propensity-score matching was carried out in two steps. First, a logistic regression model was used to estimate the propensity score for undergoing early surgery, based on all of the variables from table 1 (C statistic for this model was 0.681). Next, we used the gmatch-macro, based on a greedy matching algorithm,[20] to match patients undergoing early surgery in a 1:1 ratio with patients undergoing immediate surgery. Patients were matched on propensity score (maximum deviation = 0.01), sex, and type of surgery in three groups (abdominal, orthopedic, or other surgery). Differences in baseline characteristics between the propensity score–matched groups were assessed using standardized mean differences, with a value of less than 0.10 indicating minimal imbalance between the groups.

We estimated absolute risks of MACEs in clinically relevant patient subgroups undergoing nonvascular surgery, stratified by the presence of stroke, chronic obstructive pulmonary disease, atrial fibrillation, diabetes mellitus, kidney disease, ischemic heart disease, previous stroke, heart failure, sex, and age more than or less than 70 yr, without additional adjustment. In addition, as a sensitivity analysis, we also estimated absolute risks of a MACE for stroke patients, stratified according to the revised cardiac risk index.[4]

Several sensitivity analyses were performed in the group of patients undergoing nonvascular surgery and subsequently

Table 1. Baseline Characteristics: Nonvascular

	No Previous Stroke		Stroke < 3 Months		Stroke 3–9 Months		Stroke > 9 Months	
Characteristic	n	%	n	%	n	%	n	%
Total No.	135,689		2,289		1,090		4,117	
Age, mean (SD), yr	57 (21)		74 (13)		75 (13)		75 (13)	
Men	60,666	44.7	1,137	49.7	509	46.7	1,880	45.7
Body mass index, mean (SD)	25.3 (5.0)		24.2 (4.7)		23.7 (4.6)		24.5 (4.9)	
Missing data, body mass index	2,602	1.9	75	3.3	36	3.3	127	3.1
Medication								
Lipid-lowering agents	16,623	12.3	810	35.4	453	41.6	1,655	40.2
Antithrombotics*	20,884	15.4	1,440	62.9	762	69.9	2,830	68.7
β-blocking agents	14,866	11.0	543	23.7	275	25.2	982	23.9
Renin-angiotensin system inhibitors	22,619	16.7	752	32.9	387	35.5	1,452	35.3
Aldosterone antagonists	3,237	2.4	110	4.8	55	5.0	213	5.2
Glucose-lowering agents	9,730	7.2	328	14.3	148	13.6	633	15.4
Thiazides	11,914	8.8	392	17.1	174	16.0	701	17.0
Calcium channel blocking agents	13,789	10.2	482	21.1	232	21.3	919	22.3
Loop diuretics	13,262	9.8	527	23.0	276	25.3	1,081	26.3
Digoxin	3,672	2.7	186	8.1	90	8.3	335	8.1
Vitamin K antagonist	4,293	3.2	215	9.4	72	6.6	347	8.4
Comorbid diseases								
Myocardial infarction	2,719	2.0	158	6.9	65	6.0	275	6.7
Chronic obstructive pulmonary disease	5,617	4.1	265	11.6	133	12.2	442	10.7
Anemia	6,714	4.9	332	14.5	172	15.8	575	14.0
Metastatic cancer	3,479	2.6	88	3.8	34	3.1	125	3.0
Peptic ulcer	4,716	3.5	203	8.9	102	9.4	406	9.9
Renal disease	3,391	2.5	157	6.9	84	7.7	260	6.3
Rheumatologic disease	1,735	1.3	51	2.2	43	3.9	132	3.2
Peripheral artery disease	3,538	2.6	264	11.5	122	11.2	424	10.3
Liver disease	1,969	1.5	50	2.2	25	2.3	98	2.4
Chronic heart failure	15,210	11.2	661	28.9	323	29.6	1,277	31.0
Ischemic heart disease	7,604	5.6	420	18.3	224	20.6	823	20.0
Atrial fibrillation	6,616	4.9	427	18.7	206	18.9	696	16.9
Venous thromboembolism	2,561	1.9	95	4.2	53	4.9	178	4.3
Diabetes mellitus	10,804	8.0	391	17.1	193	17.7	749	18.2
Surgeries								
Ear/nose/throat	987	0.7	4	0.2	3	0.3	13	0.3
Orthopedic major	40,423	29.8	1,173	51.2	601	55.1	2,239	54.4
Orthopedic minor	22,959	16.9	153	6.7	104	9.5	456	11.1
Abdominal, nonbowel	26,445	19.5	279	12.2	94	8.6	417	10.1
Abdominal, bowel	9,905	7.3	273	11.9	93	8.5	348	8.5
Breast	692	0.5	0		0		11	0.3
Plastic	14,446	10.6	190	8.3	96	8.8	330	8.0
Endocrinology	92	0.1	0		0		0	
Eye	1,879	1.4	7	0.3	13	1.2	24	0.6
Female reproductive	9,213	6.8	23	1.0	16	1.5	38	0.9
Male reproductive	1,377	1.0	11	0.5	6	0.6	43	1.0
Neurologic	2,246	1.7	43	1.9	18	1.7	37	0.9
Thoracic/pulmonary	805	0.6	73	3.2	4	0.4	26	0.6
Urology	4,220	3.1	56	2.4	40	3.7	134	3.3
Surgical risk								
Low	17,869	13.2	206	9.0	113	10.4	373	9.1
Intermediate	117,820	86.8	2,083	91.0	977	89.6	3,744	90.9
High	0		0		0		0	

Results are n (%) if not otherwise mentioned.

*Antithrombotics included any combination of acetylsalicylic acid, dipyridamole, and clopidogrel.

Table 2. Outcomes by Stroke Subgroup

	No Previous Stroke (N = 135,689)		Stroke < 3 months (N = 2,289)		Stroke 3–9 months (N = 1,090)		Stroke > 9 months (N = 4,117)	
Incidence	n	%	n	%	n	%	n	%
30-day all-cause mortality	6,501	4.8	376	16.4	134	12.3	482	11.7
30-day MACE	3,187	2.3	473	20.7	112	10.3	363	8.8
Separately analyzed endpoints*								
Acute myocardial infarction	396	0.3	19	0.8	11	1.0	26	0.6
Ischemic stroke	353	0.3	227	9.9	30	2.8	95	2.3
Cardiovascular death	2,438	1.8	227	9.9	71	6.5	242	5.9

Major adverse cardiovascular events (MACE) included nonfatal myocardial infarction, nonfatal ischemic stroke, and any cardiovascular death.
*Constitute the components of the combined endpoint of MACEs.

repeated in a subgroup of patients undergoing minor or major orthopedic surgery. We estimated stroke-associated risks of 30-day MACEs stratified by anesthesia time (less than 120 min *vs.* 120 min or more), type of anesthesia (general *vs.* other, which included regional anesthesia and/or sedation), and regular *versus* odd operation hours (regular being 7:00 AM to 4:00 PM on weekdays).

Data management and statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, USA). Figures were compiled using R statistical software version 3.2.2 (https://www.r-project.org; accessed February 5, 2017).

Main analyses were decided on *a priori*, including patient selection, variables, outcomes, and statistical methods. Subanalyses and sensitivity analyses were decided on *post hoc* and after inputs from peer review. Throughout the study, efforts were made to comply with the Strengthening the Reporting of Observational Studies in Epidemiology guideline for reporting observational studies.[21]

Results

All Patients: Baseline

We identified 146,694 emergency surgeries with 7,861 patients (5.4%) having previous stroke. Only 3,509 (2.4%) were vascular surgeries, with 365 patients having previous stroke. Eleven percent of the patients had more than one eligible surgery within the study period.

For patients undergoing nonvascular surgery, more than half were women in all of the groups. Previous stroke patients were 7 to 8 yr older, on average, than patients with no previous stroke. All of the comorbidities were more prevalent in patients with previous stroke compared with no-stroke patients (all $P < 0.05$). Major orthopedic surgery accounted for 51 to 55% of surgeries in patients with previous stroke compared with only 30% in patients with no previous stroke (table 2, Supplemental Digital Content, http://links.lww.com/ALN/B461, which contains details on these surgeries and the proportion of surgeries related to fractures). Abdominal nonbowel surgery was more frequent in no-stroke patients (19%) compared with patients with previous stroke (8 to 12%). At baseline, patients with stroke less than 3 months before surgery were largely comparable with patients with stroke 3 to 9 months and more than 9 months before surgery (baseline characteristics are presented in table 1 for nonvascular surgery and in table 3, Supplemental Digital Content, http://links.lww.com/ALN/B461, for vascular surgery).

Long-term Interval between Stroke and Surgery in All Patients: Crude Events and Adjusted Models

The crude number of events for nonvascular surgeries is shown in table 2. Thirty-day MACEs occurred in 20.7% of patients with stroke less than 3 months before surgery and 8.8% of patients with stroke more than 9 months before surgery compared with only 2.3% of patients with no previous stroke. We observed low rates of myocardial infarctions in all of the patient subgroups (1% or less). Ischemic strokes were especially frequent in patients with stroke less than 3 months before surgery (9.9%) compared to patients with more distant stroke (2.3 to 2.8%). Cardiovascular death was the main contributor to the MACE endpoint for no-stroke patients (1.8%), as well as in patients with recent (9.9%) or more distant stroke (5.9%). All-cause mortality was significantly higher after surgery in stroke patients (11.7 to 16.4%) compared with no-stroke patients (4.8%). P value for the difference between the stroke groups was less than 0.001 for all of the endpoints.

Results from adjusted logistic regression models stratified by vascular and nonvascular surgery are presented in figure 1. Patients with stroke less than 3 months were at high risk of MACE for both nonvascular surgery (OR = 4.71 [95% CI, 4.18 to 5.32]) and vascular surgery (OR = 3.42 [95% CI, 2.02 to 5.78]) compared with no-stroke patients. Similar findings were seen for all-cause mortality. Patients with stroke more than 9 months before surgery undergoing nonvascular surgery remained at a significantly increased risk of MACE (OR = 1.62 [95% CI, 1.43 to 1.84]) and mortality (OR = 1.20 [95% CI, 1.08 to 1.34]) compared with no-stroke patients. We observed very high risks of repeat ischemic stroke in patients with stroke less than 3 months

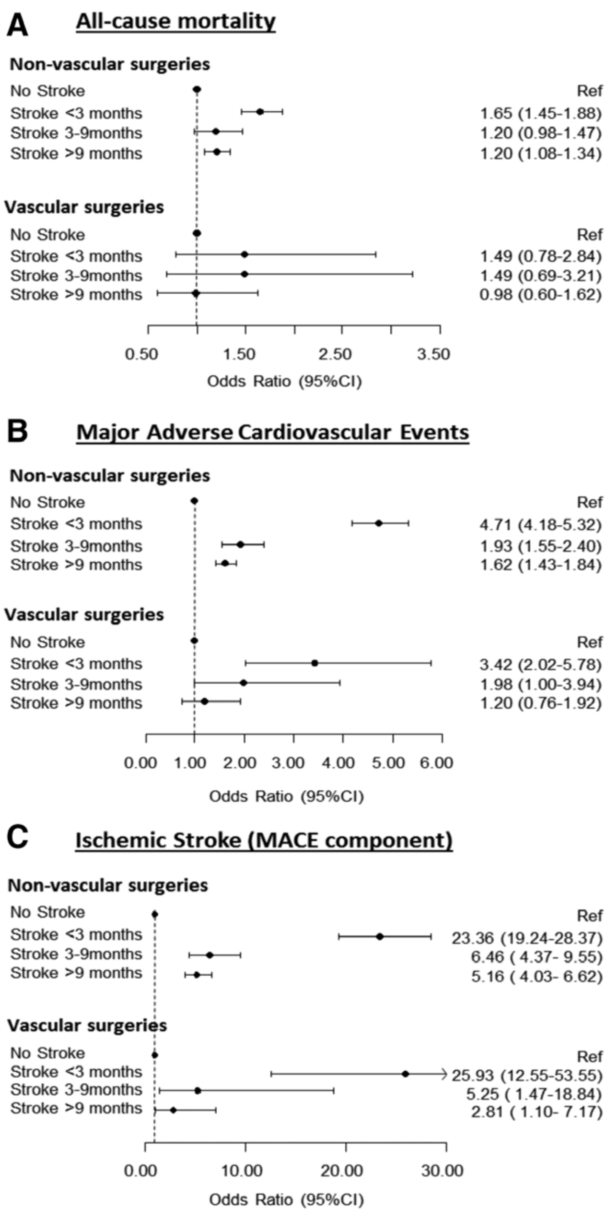

Fig. 1. Odds ratios for major adverse cardiovascular events and all-cause mortality. Data were adjusted for sex, age, body mass index, and all comorbidities, pharmacotherapy, surgery group, and surgery risk, as listed in table 1. MACE = major adverse cardiovascular events; Ref = reference.

before surgery undergoing nonvascular (OR = 23.36 [95% CI, 19.24 to 28.37]) and vascular surgery (OR = 25.93 [95% CI, 12.55 to 53.55]).

Time between stroke and surgery was analyzed as a continuous variable for nonvascular surgery in spline analyses (fig. 2A–C). As time between stroke and surgery increased, risks of MACE, death, and ischemic stroke declined. Patients undergoing surgery approximately 5 months after their index stroke were no longer at a significantly increased risk of MACE (OR = 1.21 [95% CI, 0.98 to 1.49]) or death (OR = 1.20 [95% CI, 0.98 to 1.45]) compared with patients undergoing surgery approximately 12 months after initial stroke (reference; fig. 2A–C).

Long-term Interval between Stroke and Surgery in All Patients: Absolute Risk by Comorbidity, Age, and Sex

The absolute risks of MACE in all patients undergoing nonvascular surgery are presented for a total of 36 clinically relevant patient subgroups, stratified by comorbidities, sex, and age (fig. 3). Risks of MACE in any male stroke patient more than 70 yr of age (16.2%) were lower than those of men more than 70 yr of age with concomitant stroke and chronic obstructive pulmonary disease (23.7%), stroke and myocardial infarction (27.7%), and stroke and kidney disease (22.7%). On the contrary, the impact of comorbidities in addition to previous stroke was less pronounced in women less than 70 yr of age where the absolute risks of MACE included any stroke patient (9.1%), stroke and chronic obstructive pulmonary disease (7.3%), stroke and myocardial infarction (12.1%), and stroke and kidney disease (12.5%). The sensitivity analysis of absolute risks of MACE stratified by the revised cardiac risk index is presented in table 4, Supplemental Digital Content (http://links.lww.com/ALN/B461).

Immediate and Early Surgery: Baseline

A large proportion of patients with previous stroke underwent surgery within 14 days of index stroke (see fig. 2, A and B, Supplemental Digital Content, http://links.lww.com/ALN/B461, which displays time between previous stroke and surgery). Using propensity-score matching, we matched 323 patients undergoing early surgery (4 to 14 days after stroke) with the same number of patients undergoing immediate surgery (1 to 3 days after stroke). Baseline characteristics before and after matching are shown in table 5, Supplemental Digital Content (http://links.lww.com/ALN/B461). After successful matching, standardized mean differences were less than 0.10, indicating minimal imbalance between the groups.

Immediate and Early Surgery: Crude Events and Adjusted Models

In the propensity score–matched population, risk of 30-day MACEs were significantly lower after immediate surgery (69 events) compared with early surgery (93 events; $P = 0.029$). No difference was observed for 30-day all-cause mortality ($P = 0.678$; table 3). In spline analyses, time between stroke and surgery up to 14 days was assessed as a continuous variable (fig. 2A–C). The point estimates indicated that risks of MACE and death after surgery increased within the first 7 and 3 days, respectively, after a stroke; however, 95% CIs were wide and the day-by-day differences not statistically significant.

Sensitivity Analyses: All Patients and Orthopedic Surgery Patients

Risks of MACE associated with each stroke subgroup were estimated in analyses stratified by time of surgery, anesthesia type, and duration of anesthesia, including all patients

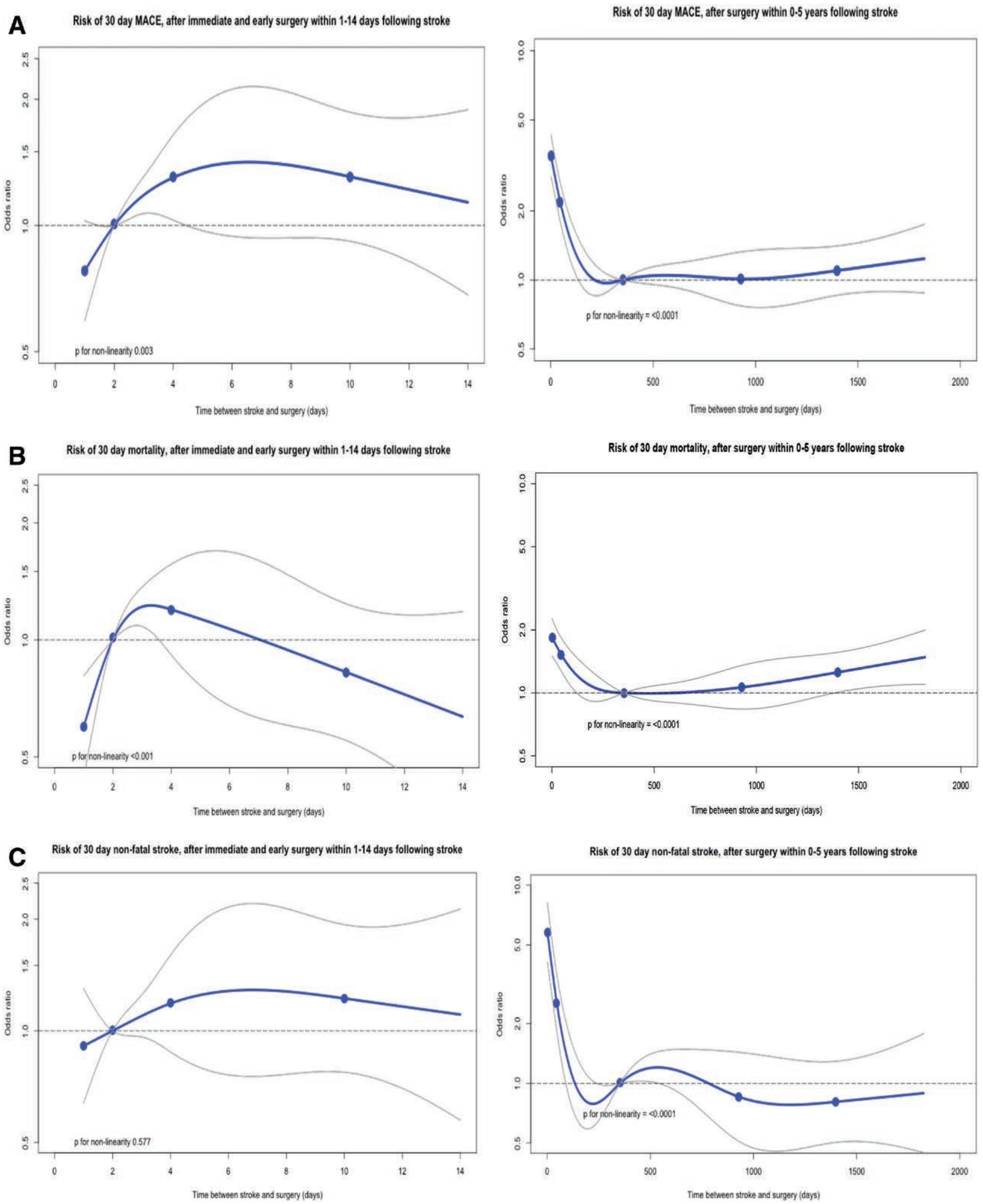

Fig. 2. Spline analyses. Data show the time between stroke and surgery and the risk of adverse outcomes. (*A*) Risk of 30-day major adverse cardiovascular events (MACE), including acute myocardial infarction, ischemic stroke, or cardiovascular death. (*B*) Risk of 30-day all-cause mortality. (*C*) Risk of 30-day nonfatal ischemic stroke. Time between stroke and surgery as a continuous variable were analyzed using a spline regression model adjusted for sex, age, and surgical category. Patients with 2 days between stroke and surgery were used as a reference for the spline analysis of the first 14 days and 353 days for the spline analysis of 0 to 5 yr.

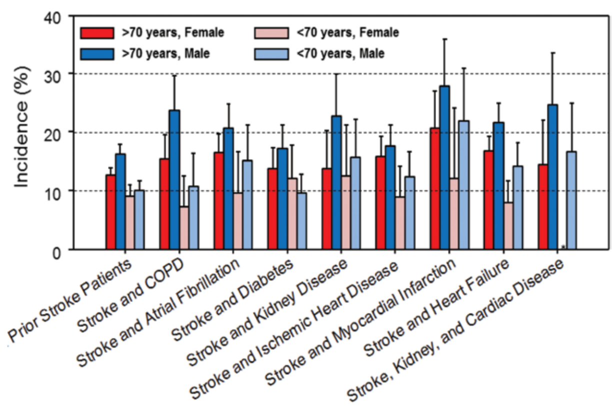

Fig. 3. Incidence of major adverse cardiovascular events (MACE), stratified by patient subgroup (stroke before surgery, specific comorbidities, sex, and age). Cardiac disease was defined as myocardial infarction, ischemic heart disease, or heart failure. *Error bars* represent 95% CIs. *The incidence was not calculated for this particular group due to an insufficient number of events. *P* was significant (less than 0.05) for all groups except for stroke and atrial fibrillation, stroke and kidney disease, stroke and myocardial infarction, and stroke and kidney and cardiac disease ($P > 0.05$). COPD = chronic obstructive pulmonary disease.

undergoing nonvascular surgery (see table 6, Supplemental Digital Content [http://links.lww.com/ALN/B461], which display the sensitivity analysis for the full study cohort). Patients with stroke less than 3 months were at significantly higher risks of MACE with duration of anesthesia less than 120 min (OR = 6.69 [95% CI, 5.44 to 8.23]) compared with duration of anesthesia at 120 min or more (OR = 3.93 [95% CI, 3.39 to 4.56]), with an overall *P* for interaction of less than 0.001. Risks of MACE varied with time of surgery at regular and odd hours, although the estimates for patients with stroke less than 3 months were very similar (surgery performed in regular hours, OR = 5.51 [95% CI, 4.58 to 6.63], and odd hours, OR = 4.25 [95% CI, 3.62 to 4.99]; *P* for interaction = 0.012). Risks of MACE did not differ by type of anesthesia stratified as general anesthesia and other types (*P* for interaction = 0.175). We repeated our main analyses in the subgroup of patients undergoing minor or major orthopedic surgery (46% of the study cohort). Unadjusted absolute risks and ORs for patients with stroke less than 3 months were largely comparable with our main findings, including risks of MACE (OR = 4.25 [95% CI, 3.62 to 5.00]), all-cause mortality (OR = 1.54 [95% CI, 1.29 to 1.84]), and ischemic stroke (OR = 22.28 [95% CI, 17.43 to 28.49]). (See table 7, Supplemental Digital Content [http://links.lww.com/ALN/B461], which shows the main analysis only for the cohort of orthopedic surgery). In the subgroup of orthopedic surgery, we also performed analyses stratified by time of surgery, anesthesia type, and anesthesia duration (see table 8, Supplemental Digital Content [http://links.lww.com/ALN/B461], for variable characteristics and full results). Risks of MACEs did not differ by anesthesia type (*P* for interaction = 0.827) or regular *versus* odd hours of operation (*P* for interaction = 0.101). Risks of MACE were significantly higher in orthopedic surgery patients if duration of anesthesia was less than 120 min *versus* duration of anesthesia more than 120 min (*P* for interaction < 0.001). In the group of patients undergoing orthopedic surgery, 818 patients underwent surgery during the first 14 days after stroke. The majority of these early surgeries (635 surgeries) were on the hip or femoral bone, and, of these, 58% were fracture repairs and only 1% were due to infection of a prosthesis.

Discussion

This nationwide study of patients with and without previous stroke undergoing emergency noncardiac, nonintracranial surgery demonstrated a time-dependent increased risk of 30-day MACE and all-cause mortality associated with previous stroke. Noticeably, among patients with stroke 14 days or less before surgery, we found that undergoing surgery 4 to 14 days after stroke was associated with significantly increased risks of a MACE compared with undergoing surgery within 1 to 3 days of stroke. In a long-term perspective, patients with a stroke less than 3 months before surgery were at elevated risk, which plateaued as time between stroke and surgery exceeded 4 to 5 months. Elderly patients with additional comorbidities, such as kidney disease or previous myocardial infarction in addition to stroke were at an especially high risk of a perioperative MACE. In addition, we found that the risk of a MACE was largely dependent on the duration of anesthesia, whereas the type of anesthesia and surgery at regular *versus* odd hours did not significantly affect the risk of adverse events.

Existing Recommendations

The observed long-term time dependency between stroke and perioperative risks was similar to that observed in a previous study from our group examining previous stroke in patients having elective noncardiac and nonintracranial surgery.[7] The associations in time between stroke and surgery and risks of perioperative adverse events have not previously been investigated in a setting of emergency noncardiac surgery, and only a few studies have previously addressed these issues in an elective surgery setting.[22–25] In addition, this study is the first to look at perioperative risks in patients undergoing surgery 14 days or less after stroke.

The lack of guidance for patients with previous stroke undergoing surgery was addressed in a recent consensus statement from the Society for Neuroscience in Anesthesiology and Critical Care; they suggested that elective surgery should be delayed 1 to 3 months but did not include any guidance for emergency surgery.[26,27] They concluded that the ultimate decision should always be based on the balance between risks of perioperative stroke and the risks of delaying surgery, which must be assessed thoroughly for each patient

Table 3. Outcomes for Propensity-score Matching

Variable	Stroke 1–3 days (N = 323)		Stroke 4–14 days (N = 323)		
	n	%	n	%	*P* Value
30-day all-cause mortality	54	16.7	58	18.0	0.678
30-day MACE	69	21.4	93	28.8	0.029
Separately analyzed endpoints*					
Acute myocardial infarction	4	1.2	3	0.9	0.704
Ischemic stroke	39	12.1	49	15.2	0.251
Cardiovascular death	26	8.0	41	12.7	0.053

Outcomes for propensity score–matching analysis are displayed in n (%) of events and *P* value for difference. Major adverse cardiovascular event (MACE) included nonfatal myocardial infarction, nonfatal ischemic stroke, and any cardiovascular death.

*Data constitute the components of the combined endpoint of MACEs.

in need of emergency surgery. The observed increasing risk of adverse events within the first days after stroke and the long-term increased risk within the first 4 to 5 months may provide guidance for clinicians preparing patients with previous stroke for surgery.

Clinical Importance

Our data suggest that emergency surgery is associated with better outcomes if operations occur within 72h of the stroke; thereafter, a higher risk period ensues that coincides with dysregulated cerebral autoregulation (see following paragraph). Hence, we hypothesize that anesthesia and surgery may constitute a larger second hit in the poststroke phase when conducted between 4 to 14 days after the initial insult. Nonetheless, the results of this study are important for guiding perioperative decision-making and to inform the patient and relatives about realistic expectations of perioperative outcomes. For example, patients with stroke less than 3 months had a 16% absolute risk of 30-day mortality and a 21% risk of MACE, which is substantial. In addition, estimating absolute risks in clinically relevant subgroups of patients, we found that patient risks were also highly dependent on other comorbidities, sex, and age, as outlined in figure 3. Informing clinicians about expected outcomes in these high-risk patients according to comorbidities and demographics may improve individual preoperative evaluation, rigorous monitoring, and patient care. Medical diseases such as atrial fibrillation and renal disease may be stabilized even in the setting of emergency surgery, and antithrombotic strategies should be carefully considered. Because this study showed a high incidence of repeat ischemic strokes (10% in patients with stroke less than 3 months), increased attention toward perioperative stroke screening seems relevant. The straightforward Face Arm Speech test for identifying neurologic deficits has shown promise, and the routine use of this test in the postoperative setting may be warranted.[28]

Surgery, Anesthesia, and Cerebral Autoregulation

Interestingly, in propensity score–matched analyses, we found that immediate surgery within 1 to 3 days of the index stroke was associated with significantly fewer MACEs than early surgery within 4 to 14 days. Similarly, findings from spline analyses suggested that risks of adverse events and death increased over the first 3 to 7 days, followed by a decline in risks. A systematic review of 23 studies on autoregulation of cerebral blood flow has provided a possible explanation for the increasing risk of adverse events within the first days after stroke and the continuous decrease in risks for the following several months.[29] The review suggests that autoregulation deteriorates during the first 5 days after an ischemic stroke, followed by a recovery period of an estimated three months. These time intervals coincide with our periods of higher risk and hence support biologic plausibility. However, because we did not have information on important perioperative parameters, clinical variables, or the indication for surgery, we urge caution with this interpretation. Future prospective studies with more detailed perioperative data should seek to address these issues in detail.

In our study, subgroup analysis stratified by duration of anesthesia showed an unexpected increased risk of MACE with shorter duration of surgery. One explanation might be that longer anesthesia time is due to more thorough preparation and thus reduced perioperative risks. We estimated preparation time as the difference in anesthesia time and total procedure time, which showed that mean preparation time was in fact longer in patients with previous stroke compared with no-stroke patients (data not shown). We were, however, unable to investigate these associations in depth because surgery- and anesthesia-specific variables, beyond the type of anesthesia used, were not available in our registries.

We hypothesized that general anesthesia might exert more profound effects on the cardiovascular system and thus further aggravate the impaired autoregulation, increasing the risks of adverse outcomes. The analyses stratified by type of anesthesia showed only a nonsignificant association toward increased risks with general anesthesia (70 *vs.* 80% had general anesthesia for patients with and without stroke, respectively), whereas no difference was observed in the subgroup of patients undergoing orthopedic surgery. However, because we lack details of intraoperative care, we cannot be sure that the patients allocated regional anesthesia had nonanesthetic depth sedation[30] and different hemodynamics compared with the general anesthetic group.

Strengths and Limitations

Our study included a contemporary unselected nationwide cohort of patients undergoing emergency noncardiac surgery. The Danish universal healthcare system ensures equal access to healthcare services irrespective of socioeconomic status. The comprehensive and validated administrative registers and the possibility for linking individual records using a unique personal identifier made possible the adjustment for important confounders, such as demographics, comorbidities, drug use, and surgery-related variables. Despite these efforts, residual confounding cannot be ruled out. The register-based method reduced the risk of report and selection bias, as well as other imprecisions related to data collection. We found that 19% of all previous stroke patients underwent emergency surgery within 14 days of the index stroke. This suggests that the stroke episode and the need for surgery are somehow correlated, but whether the ischemic stroke caused the emergency surgical condition (*i.e.*, the stroke facilitated an injurious fall resulting in a hip fracture) or whether a surgical condition caused a subsequent stroke (*i.e.*, a severe trauma resulting in disseminated intravascular coagulation causing an ischemic stroke) cannot be made out from the data available. In addition, information on in-hospital distributed medications and perioperative care was not available, and changes in medication during hospital admission, including preoperative antithrombotic and anticoagulation therapy, could not be accounted for in our study. No information on periprocedural blood loss or blood transfusions was available. It was not possible to distinguish between thromboembolic and atherothrombotic strokes, which are known to be different in pathophysiology. We have shown previously that stroke patients not undergoing surgery experience a similar reduction in risks of repeat stroke over time but that these risks and reductions are much more pronounced in patients undergoing surgery, which suggests that surgery constitutes a significant risk factor for repeat stroke.[16] Previous literature from our Danish registers suggests an underestimation of myocardial infarction due to the lack of a systematic assessment of the myocardial infarction by troponins after surgery.[31] The use of continuous time variables, such as anesthesia time, may be problematic and dependent on the specific surgery.[32]

Conclusions

In this study, we demonstrated that patients with previous stroke are at high risk of perioperative death and MACE for several months after emergency noncardiac and nonintracranial surgery. Interestingly, for the first 3 to 7 days after stroke, risks seemed to increase as cerebral autoregulation may have deteriorated, suggesting that immediate surgery may be associated with lower risks. We observed that patients were at particularly high risk within the first 3 months of an ischemic stroke, whereas the rapid decrease in risks of adverse events leveled off after approximately 4 to 5 months. Stroke-associated risks were dependent on patient sex, age, and additional comorbidities. Although emergency surgeries might not be feasible to postpone until the risk period subsides, high risk of adverse events and death should be taken into account during the perioperative risk assessment and conveyed when informing the patient and relatives about realistic expectations.

Research Support

Support was provided solely from institutional and/or departmental sources.

Competing Interests

The authors declare no competing interests.

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