Original Investigation

Time Elapsed After Ischemic Stroke and Risk of Adverse Cardiovascular Events and Mortality Following Elective Noncardiac Surgery

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IMPORTANCE The timing of surgery in patients with recent ischemic stroke is an important and inadequately addressed issue.

OBJECTIVE To assess the safety and importance of time elapsed between stroke and surgery in the risk of perioperative cardiovascular events and mortality.

DESIGN, SETTING, AND PARTICIPANTS Danish nationwide cohort study (2005-2011) including all patients aged 20 years or older undergoing elective noncardiac surgeries (n=481 183 surgeries).

EXPOSURES Time elapsed between stroke and surgery in categories and as a continuous measure.

MAIN OUTCOMES AND MEASURES Risk of major adverse cardiovascular events (MACE; including ischemic stroke, acute myocardial infarction, and cardiovascular mortality) and all-cause mortality up to 30 days after surgery. Odds ratios (ORs) were calculated by multivariable logistic regression models.

RESULTS Crude incidence rates of MACE among patients with (n = 7137) and without (n = 474 046) prior stroke were 54.4 (95% CI, 49.1-59.9) vs 4.1 (95% CI, 3.9-4.2) per 1000 patients. Compared with patients without stroke, ORs for MACE were 14.23 (95% CI, 11.61-17.45) for stroke less than 3 months prior to surgery, 4.85 (95% CI, 3.32-7.08) for stroke 3 to less than 6 months prior, 3.04 (95% CI, 2.13-4.34) for stroke 6 to less than 12 months prior, and 2.47 (95% CI, 2.07-2.95) for stroke 12 months or more prior. MACE risks were at least as high for low-risk (OR, 9.96; 95% CI, 5.49-18.07 for stroke <3 months) and intermediate-risk (OR, 17.12; 95% CI, 13.68-21.42 for stroke <3 months) surgery compared with high-risk surgery (OR, 2.97; 95% CI, 0.98-9.01 for stroke <3 months) (P = .003 for interaction). Similar patterns were found for 30-day mortality: ORs were 3.07 (95% CI, 2.30-4.09) for stroke less than 3 months prior, 1.97 (95% CI, 1.22-3.19) for stroke 3 to less than 6 months prior, 1.45 (95% CI, 0.95-2.20) for stroke 6 to less than 12 months prior, and 1.46 (95% CI, 1.21-1.77) for stroke 12 months or more prior to surgery compared with patients without stroke. Cubic regression splines performed on the stroke subgroup supported that risk leveled off after 9 months.

CONCLUSIONS AND RELEVANCE A history of stroke was associated with adverse outcomes following surgery, in particular if time between stroke and surgery was less than 9 months. After 9 months, the associated risk appeared stable yet still increased compared with patients with no stroke. The time dependency of risk may warrant attention in future guidelines.

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Previous studies have identified stroke as a major risk factor for adverse outcomes in noncardiac surgery. Stroke is also a major component in integrated perioperative risk evaluation schemes, such as the widely used revised cardiac risk index by Lee et al.[1] Surgery is known to cause hemodynamic, endocrine, and inflammatory disturbances contributing to an increased overall risk of death and adverse cardiac events. These alterations are especially important for perioperative risks among patients with established cardiovascular disease, including cerebrovascular disease, and may pose a particular risk among individuals with unstable cardiovascular comorbidities.[2]

Noncardiac surgeries performed in patients with a recent myocardial infarction or stent implantation have been associated with increased risk of perioperative cardiac events, stent thrombosis, and bleeding compared with patients with more distant myocardial infarction or stent implantation.[3-7] Whether a similar time-dependent relationship exists for stroke is not known, and the recommendations on timing of surgery in patients with prior stroke in current perioperative guidelines are sparse.[8,9] Of specific concern, cerebral autoregulation has shown to be impaired following stroke, particularly during the first 3 months after occurrence.[10] This may or may not be of importance in surgery, where hemodynamic conditions are altered following bleeding, intravenous fluid administration, and anesthesia/relaxation. Because the prevalence of stroke and the need for noncardiac surgery increase rapidly with age, it is important to address this matter.[11] We therefore investigated the association between prior stroke (including time elapsed between stroke and surgery) and the risk of major adverse cardiovascular events (MACE) in a large and unselected cohort of patients undergoing noncardiac elective surgery.

Methods

Ethical approval of register-based studies is not warranted in Denmark. The authors had full access to encrypted raw data provided by Statistics Denmark (Central Authority on Danish Statistics). The study was approved by the Danish data protection agency.

Registers

In Denmark, medical care is tax-financed, free of personal charge, and equally available to all inhabitants. For administrative purposes, the government has kept nationwide registers on health care–related data for decades. Moreover, all citizens are given a unique and permanent identification number at birth or upon immigration, which enabled us to link nationwide administrative registers. Five registers were used to identify our population and retrieve information on different variables. The Danish National Patient Register holds information on all hospital admissions since 1977 and was used to identify all surgeries in Denmark in 2005-2011, including information regarding patients' medical history. Available data included admission and discharge dates and diagnoses coded according to the *International Statistical Classification of Diseases, Tenth Revision* (*ICD-10*) since 1994. Correct coding of surgeries and comorbidities is paramount for governmental reimbursement to the departments.[12] Information on several surgery-related variables, including whether the surgery was acute or elective, was retrieved from the Danish Anesthesia Register, in which all surgeries requiring anesthesia have been registered since mid-2004. The National Population Register and the National Causes of Death Register hold information on vital status, date of birth, and death, including causes of death. Information on all drugs prescribed to the population was obtained from the Danish Register of Medicinal Product Statistics, which collects all prescriptions in Denmark (according to the Anatomical Therapeutic Chemical Classification System). The register is directly linked to the government for reimbursement and has been proven to be accurate.[13]

Population

All elective noncardiac surgeries performed in patients aged 20 years or older during the period 2005-2011 were included in the present study. For patients having multiple surgeries performed during a 30-day period, only the first in each period was included. We identified patients with prior ischemic stroke using *ICD-10* codes I63 or I64. Patients with a diagnosis of transient ischemic attack or hemorrhagic stroke were not included in this definition. As with other comorbidities, the stroke diagnosis was considered obsolete if more than 5 years had passed between stroke and surgery.

Our population was a priori divided into 5 subgroups based on time elapsed between stroke and surgery: patients with no prior stroke, patients with a stroke within less than 3 months, patients with a stroke within 3 to less than 6 months, patients with a stroke within 6 to less than 12 months, and patients with a stroke 12 months or more prior to surgery. Use of these cutoff points was inspired by a clinical impression and previous documented relations of time elapsed after myocardial infarction or stenting with risk of adverse outcomes.[3-7]

Pharmacotherapy

Use of specific drugs was defined as at least 1 claimed prescription for the following agents during the preceding 120 days prior to surgery: statins (Anatomical Therapeutic Chemical Classification C10A), β-blockers (C07), angiotensin-converting enzyme inhibitors and angiotensin II antagonists (ie, renin-angiotensin system inhibitors) (C09), aldosterone blockers (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).

Comorbidities

Records of discharge diagnoses defined by *ICD-10* codes up to 5 years prior to surgery were used to identify the following co-

morbidities: acute myocardial infarction, chronic obstructive pulmonary disease, anemia, cancer with metastases, renal disease, rheumatic disease, peripheral artery disease, liver disease, diabetes, chronic heart failure, ischemic heart disease, and atrial fibrillation. In addition to *ICD-10* codes, use of glucose-lowering agents was used as a proxy for diabetes and use of loop diuretics as a proxy for heart failure, as has been done previously.[14,15] *ICD-10* codes used to define comorbidity are available in eTable 1 in the Supplement. Diagnoses based on *ICD-10* codes from the National Patient Register have been validated, with positive predictive values ranging from 82% to 100%.[16]

Surgeries

All surgeries were identified from codes based on the Nordic Medico-statistical Committee's Classification of Surgical Procedures[17] (eTable 2 in the Supplement). Frequency and proportion of 3-letter surgery codes stratified by time between stroke and surgery are shown in eTable 3 in the Supplement. Surgeries were divided into 16 categories based on prior work and clinical impression: ear/nose/throat, major orthopedic, minor orthopedic, abdominal (bowel), abdominal (nonbowel), breast, plastic, endocrine, eye, female reproductive, male reproductive, neurological, arterial vessels, nonarterial vessels, thoracic/pulmonary, and urology surgery, as specified in eTable 4 in the Supplement. As each category consisted of several types of surgery, absolute and relative risk estimates were calculated to ensure that no major discrepancies in risk were found between types of surgery within each category. This classification has also been used in previous work.[18] We excluded gastrostomies, tracheostomies, intracranial surgeries/lesions on spinal cord, and surgical procedures to the arteries of the aortic arch, as these were more commonly performed in the subgroup of stroke less than 3 months prior and might have been confounded by indication. As a sensitivity analysis, we manually reviewed all surgical categories and excluded those that might have been misclassified as elective instead of acute/emergent surgeries (eFigure 1 and eTable 5 in the Supplement). In this analysis we also excluded orthopedic surgeries that were preceded by a diagnosis of trauma to the surgical area, as well as abdominal surgeries preceded by a diagnosis of peptic ulcer and cholecystitis within 7 days prior to surgery (eFigure 1 and eTable 6 in the Supplement). Finally, to further strengthen the likelihood of a causal relationship between association of time elapsed between stroke and surgery and risk of MACE, we also performed a subgroup analysis including only primary hip and knee replacement surgeries among people without a concomitant "fracture surgery" code and without a trauma within up to 7 days preceding the surgery (eFigure 1 in the Supplement).

Risk Stratification

As suggested by Boersma et al[19] and as specified in the European Society of Cardiology guidelines,[9] surgeries were stratified into 3 groups: low-, intermediate-, and high-risk surgeries. Coding details and allocation of surgeries are available in eTable 4 in the Supplement.

Outcomes

Primary outcomes were all-cause mortality and MACE. MACE was a composite outcome of nonfatal acute myocardial infarction (*ICD-10* codes I21-22), nonfatal ischemic stroke (*ICD-10* codes I63-64), and cardiovascular death (*ICD-10* "I" diagnosis listed as cause of death). We also identified recurrent ischemic strokes (*ICD-10* codes I63-64) as a separate end point. The majority of perioperative strokes in noncardiac, nonneurological surgery has shown to be of ischemic etiology.[20,21] The ischemic stroke diagnosis (code I63) has been validated with positive predictive values exceeding 97% and unspecified stroke (code I64) has been validated with a positive predictive value of 75% to 80% for stroke, with the majority of strokes being of ischemic etiology.[22] The acute myocardial infarction diagnosis has a positive predictive value of 94%.[23] All outcomes were evaluated 30 days after surgery. Events during surgery and at day 30 were included in the respective end points.

Statistical Analysis

Multivariable logistic regression models were used to estimate odds ratios (ORs) with 95% confidence intervals for respective stroke groups. Fully adjusted models included sex, age, body mass index, and all comorbidities, pharmacotherapies, and surgical categories from **Table 1**, as well as surgery risk level as defined above. Patients with no prior stroke were used as a reference. Relevant interaction analyses were chosen a priori based on clinical relevance (atrial fibrillation, antithrombotic therapy, use of statins, calendar year, and sex). Dose-response splines adjusted for sex, age, and surgical category were created by restricted cubic spline functions using the macro provided by Desquilbet et al.[24] Because patients without stroke did not have a "stroke time," this analysis was restricted to patients with prior stroke. Knots were placed at p10, p25, p50, p75, and p90; p50 was used as the reference. Because of high proportions of missing values, the smoking (24% missing) and alcohol (16% missing) variables were not included in our main analyses. However, we performed a sensitivity analysis based on imputed values using the SAS "proc mi" procedure (5 imputations), followed by "proc logistic" and "proc mianalyze." Values were considered missing at random. Because some patients had more than 1 surgery performed during the study period, we performed a sensitivity analysis including only the first surgery for each patient to ensure that the assumption of independence of observations was not violated. As an additional sensitivity analysis, we calculated the propensity of having a history of stroke by multivariable logistic regression models including all variables from Table 1 except for surgeries (C=0.893) on the "cleaned" subpopulation (as specified in eFigure 1 in the Supplement). We defined a propensity-, sex-, and surgery group- (16 categories) matched cohort using the Greedy matching macro (http://www.mayo.edu/research/documents/gmatch.sas/DOC-10027248). Odds ratios associated with prior stroke for the propensity score–matched cohort were calculated using conditional logistic regression models. Two-sided $P<.05$ was considered statistically significant. All

Table 1. Baseline Characteristics[a]

Characteristics	Surgeries in Patients With No Prior Stroke (n = 474 046)	Surgeries in Patients With Prior Stroke (n = 7137)
Age, mean (SD), y	53.7 (17.0)	69.7 (12.1)
Men	205 224 (43.3)	4027 (56.4)
Prior smoking	71 769 (19.9)	1564 (29.5)
Current smoking	114 130 (31.6)	1699 (32.0)
Missing smoking data	113 141 (23.9)	830 (25.6)
Nondrinker	205 784 (52.0)	2731 (45.8)
Missing alcohol use data	78 032 (16.5)	1167 (16.4)
Body mass index, mean (SD)[b]	26.2 (4.9)	26.0 (5.0)
Missing body mass index data	3790 (0.8)	129 (1.8)
Comorbidities		
Acute myocardial infarction	6201 (1.3)	426 (6.0)
Chronic heart failure	28 070 (5.9)	1574 (22.1)
Ischemic heart disease	19 751 (4.2)	1306 (18.3)
Atrial fibrillation	12 540 (2.6)	1029 (14.4)
Diabetes	28 701 (6.1)	1235 (17.3)
Peripheral artery disease	6507 (1.4)	611 (8.6)
Anemia	10 436 (2.2)	666 (9.3)
Cancer with metastases	9983 (2.1)	308 (4.3)
Renal disease	6666 (1.4)	428 (6.0)
Rheumatologic disease	4826 (1.0)	172 (2.4)
COPD	9826 (2.1)	626 (8.8)
Liver disease	3352 (0.7)	116 (1.6)
Medications		
Statins	64 704 (13.6)	3715 (52.1)
Antithrombotic therapy[c]	55 633 (11.4)	5295 (65.4)
β-Blockers	45 712 (9.6)	1716 (24.0)
RAS inhibitors	80 049 (16.9)	2848 (39.9)
Aldosterone blockers	5936 (1.3)	310 (4.3)
Glucose-lowering agents	26 904 (5.7)	1032 (14.5)
Thiazides	40 429 (8.5)	1258 (17.6)
Calcium channel blockers	46 770 (9.9)	1700 (23.8)
Loop diuretics	24 356 (5.1)	1331 (18.6)
Digoxin	5944 (1.3)	450 (6.3)
Vitamin K antagonists	11 143 (2.4)	765 (10.7)
Surgical categories[d]		
Ear/nose/throat	12 342 (2.6)	108 (1.5)
Major orthopedic	147 025 (31.0)	2144 (30.0)
Minor orthopedic	39 842 (8.4)	426 (6.0)
Abdominal, bowel	14 265 (3.0)	446 (6.2)
Abdominal, nonbowel	59 479 (12.5)	928 (13.0)
Breast	12 280 (2.6)	101 (1.4)
Plastic	22 723 (4.8)	480 (6.7)
Endocrine	4904 (1.0)	62 (0.9)
Eye	10 195 (2.2)	220 (3.1)
Female reproductive	62 352 (13.2)	345 (4.8)
Male reproductive	8229 (1.7)	130 (1.8)
Neurological	19 071 (4.0)	276 (3.9)
Arterial vessels	6315 (1.3)	362 (5.1)
Nonarterial vessels	22 263 (4.7)	148 (2.1)
Thoracic/pulmonary	5200 (1.1)	114 (1.6)
Urology	27 561 (5.8)	847 (11.9)
Surgical risk		
Low	80 175 (16.9)	1029 (14.4)
Intermediate	388 239 (81.9)	5787 (81.1)
High	5632 (1.2)	321 (4.5)

Abbreviations: COPD, chronic obstructive pulmonary disease; RAS, renin-angiotensin system.

[a] Data are expressed as No. (%) unless otherwise indicated.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Antithrombotic therapy includes acetylsalicylic acid, dipyridamol, and clopidogrel.

[d] For patients without and with stroke, 6.0% and 11.5% of the surgeries were cancer related, respectively.

Table 2. Unadjusted Outcomes in Patients With and Without Stroke

Outcomes	Stroke <3 mo Prior (n=862)	Stroke 3 to <6 mo Prior (n=469)	Stroke 6 to <12 mo Prior (n=898)	Stroke ≥12 mo Prior (n=4908)	All Strokes (n=7137)	No Prior Stroke (n=474 046)
Crude events, No. (%)						
30-d MACE	153 (17.7)	34 (7.2)	37 (4.1)	165 (3.4)	389 (5.5)	1923 (0.4)
Acute myocardial infarction	7 (0.8)	5 (1.1)	2 (0.2)	20 (0.4)	34 (0.5)	449 (0.1)
Ischemic stroke	103 (11.9)	21 (4.5)	16 (1.8)	70 (1.4)	210 (2.9)	368 (0.1)
Cardiovascular death	43 (5.0)	8 (1.7)	19 (2.1)	75 (1.5)	145 (2.0)	1106 (0.2)
30-d all-cause mortality	66 (7.7)	21 (4.5)	29 (3.2)	138 (2.8)	254 (3.6)	2914 (0.6)
Incidence rate per 1000 patients (95% CI)						
30-d MACE	177.5 (149.4-205.6)	72.5 (48.1-96.9)	41.2 (27.9-54.5)	33.6 (28.5-38.7)	54.4 (49.1-59.9)	4.1 (3.9-4.2)
Acute myocardial infarction	8.1 (2.1-14.1)	10.7 (1.3-20.0)	2.2 (0.0-5.3)	4.1 (2.3-5.9)	4.8 (3.2-6.4)	0.9 (0.9-1.0)
Ischemic stroke	119.5 (96.4-142.6)	44.8 (25.6-63.9)	17.8 (9.1-26.5)	14.3 (10.9-17.6)	29.4 (25.4-33.4)	0.8 (0.7-0.9)
Cardiovascular death	49.9 (35.0-64.8)	17.1 (5.2-28.9)	21.2 (11.6-30.7)	15.3 (11.8-18.7)	20.3 (17.0-23.6)	2.3 (2.2-2.5)
30-d all-cause mortality	76.6 (58.1-95.0)	44.8 (25.6-63.9)	32.3 (20.5-44.0)	28.1 (23.4-32.8)	35.6 (31.2-40.0)	6.1 (5.9-6.4)
Unadjusted odds ratio (95% CI)						
30-d MACE	53.0 (44.3-63.5)	19.2 (13.5-27.3)	10.6 (7.6-14.7)	8.5 (7.3-10.0)	14.2 (12.7-15.8)	1 [Reference]
Acute myocardial infarction	8.3 (4.1-18.3)	11.4 (4.7-27.6)	2.4 (0.6-9.5)	4.3 (2.8-6.8)	5.0 (3.6-7.2)	1 [Reference]
Ischemic stroke	174 7 (138.8-219.8)	60.3 (38.5-94.6)	23.4 (14.1-38.7)	18.6 (14.4-24.1)	39.0 (32.9-46.3)	1 [Reference]
Cardiovascular death	22.5 (16.4-30.7)	7.4 (3.7-15.0)	9.2 (5.8-14.6)	6.6 (5.2-8.4)	8.9 (7.4-10.6)	1 [Reference]
30-d all-cause mortality	13.4 (10.4-17.3)	7.6 (4.9-11.8)	5.4 (3.7-7.8)	4.7 (3.9-5.6)	6.0 (5.2-6.8)	1 [Reference]

Abbreviation: MACE, major adverse cardiovascular events (ischemic stroke, acute myocardial infarction, or cardiovascular death).

calculations were performed with SAS, version 9.4 (SAS Institute Inc).

Results

Population

The population included 481 183 noncardiac surgeries, of which 7137 surgeries (1.5%) were performed in patients with a history of stroke. On average, patients with prior stroke were 16 years older, were more often men, were more frequently treated with cardiovascular medications, and had a higher prevalence of comorbidities (Table 1). The median number of surgeries per patient was 1 (interquartile range, 1-1; 95th percentile, 3). A total of 1310 patients with prior stroke (24.3%) and 77 268 patients without prior stroke (21.4%) had more than 1 surgery performed between 2005 and 2011.

Outcomes

Crude events, incidence rates, and unadjusted odds ratios for patients with no prior stroke, patients with stroke any time prior to surgery, and stratified by time between stroke and surgery for 30-day MACE, its components, and 30-day all-cause mortality are presented in **Table 2**. Incidence rates of 30-day ischemic stroke were 149.6-fold higher in patients with stroke less than 3 months prior to surgery compared with patients without stroke, whereas incidence rates of 30-day all-cause mortality were 12.6-fold higher in patients with stroke less than 3 months prior compared with patients without stroke.

Association of Time Elapsed Between Stroke and Surgery With Perioperative Risk

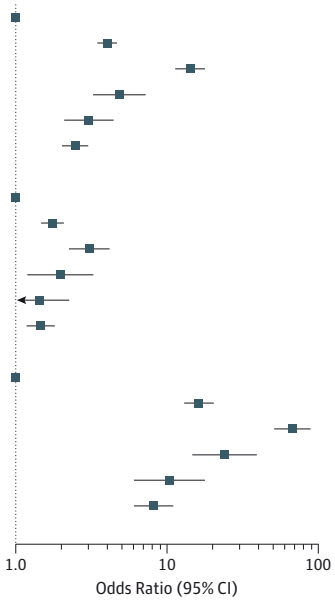
There was a stepwise decline in risk associated with prior stroke for longer time distances between stroke and surgery (**Figure 1**). For the subgroup with stroke less than 3 months prior, the OR of 30-day MACE was 14.23 (95% CI, 11.61-17.45), whereas the OR for stroke 12 months or more prior was 2.47 (95% CI, 2.07-2.95) compared with patients without prior stroke. The odds ratios for MACE were the same or higher for low-risk surgery (OR, 9.96; 95% CI, 5.49-18.07 for stroke <3 months prior) and intermediate-risk surgery (OR, 17.12; 95% CI, 13.68-21.42 for stroke <3 months) compared with high-risk surgery (2.97; 95% CI, 0.98-9.01 for stroke <3 months prior; overall P = .003 for interaction) (eFigure 2 in the Supplement). The elevated risk of MACE associated with prior stroke were to a large extent driven by a high risk of recurrent stroke (Figure 1), with an adjusted OR of 67.6 for recurrent stroke among the subgroup with stroke less than 3 months prior. There was no significant association between prior stroke and risk of acute myocardial infarction (eFigure 3 in the Supplement). The risk of cardiovascular death (as a separate end point) was also increased for patients with prior stroke (OR, 4.35; 95% CI, 3.06-6.19 for stroke <3 months prior); crude events and full ORs are available in eFigure 3.

Splines

Based on the cubic regression splines among patients with prior stroke, we found that the ORs leveled off around 9 months for MACE, all-cause mortality, and ischemic stroke (P<.001 for nonlinearity for all end points) (**Figure 2**).

Figure 1. Adjusted Odds Ratios of 30-Day Major Adverse Cardiac Events Stratified by Stroke Prior to Surgery and Time Elapsed Between Stroke and Surgery

Source	Crude Events, No.	Sample Size, No.	Odds Ratio (95% CI)
30-d MACE			
No prior stroke	1923	474 046	1 [Reference]
Prior stroke anytime	389	7137	4.03 (3.55-4.57)
Stroke <3 mo prior	153	862	14.23 (11.61-17.45)
Stroke 3 to <6 mo prior	34	469	4.85 (3.32-7.08)
Stroke 6 to <12 mo prior	37	898	3.04 (2.13-4.34)
Stroke ≥12 mo prior	165	4908	2.47 (2.07-2.95)
30-d all-cause mortality			
No prior stroke	2914	474 046	1 [Reference]
Prior stroke anytime	254	7137	1.75 (1.51-2.03)
Stroke <3 mo prior	66	862	3.07 (2.30-4.09)
Stroke 3 to <6 mo prior	21	469	1.97 (1.22-3.19)
Stroke 6 to <12 mo prior	29	898	1.45 (0.95-2.20)
Stroke ≥12 mo prior	138	4908	1.46 (1.21-1.77)
30-d ischemic stroke			
No prior stroke	368	474 046	1 [Reference]
Prior stroke anytime	210	7137	16.24 (13.23-19.94)
Stroke <3 mo prior	103	862	67.60 (52.27-87.42)
Stroke 3 to <6 mo prior	21	469	24.02 (15.03-38.39)
Stroke 6 to <12 mo prior	16	898	10.39 (6.18-17.44)
Stroke ≥12 mo prior	70	4908	8.17 (6.19-10.80)



MACE indicates major adverse cardiac events (acute myocardial infarction, ischemic stroke, or cardiovascular death). Adjusted for sex, age, body mass index, all comorbidities, all pharmacotherapy, surgery group, and surgery risk.

Sensitivity Analyses

Analyses including imputed values on alcohol and smoking as covariates in the models did not change the estimates substantially (ORs are shown in eTable 7 in the Supplement). Excluding surgeries of potential acute/emergent etiology yielded similar results to the main analyses, with stepwise declines in risk associated with prior stroke for longer time elapsed between stroke and surgery (eFigure 4 in the Supplement). Compared with no stroke, ORs associated with MACE were 22.10 (95% CI, 16.85-29.00), 9.14 (95% CI, 5.97-13.99), 3.45 (95% CI, 2.17-5.48), and 2.83 (95% CI, 2.24-3.58) for stroke less than 3 months, stroke 3 to less than 6 months, stroke 6 to less than 12 months, and stroke 12 months or more prior to surgery, respectively.

Among the subgroup of patients undergoing primary hip and knee replacement surgery, 12 of 59 (20%) with stroke less than 3 months, 7 of 50 (14%) with stroke 3 to less than 6 months, 7 of 99 (7.1%) with stroke 6 to less than 12 months, and 14 of 538 (2.6%) with stroke 12 months or more prior to surgery had a MACE within 30 days compared with 223 of 39 396 (0.6%) in the nonstroke group. Adjusted ORs associated with MACE for the stroke groups were of similar magnitudes as those seen in the other analyses (OR, 27.71; 95% CI, 13.96-54.97 for stroke <3 months prior; OR, 16.13; 95% CI, 6.85-38.00 for stroke 3 to <6 months prior; OR, 9.22; 95% CI, 4.10-20.77 for stroke 6 to <12 months prior; and OR, 2.68; 95% CI, 1.50-4.79 for stroke ≥12 months prior compared with the nonstroke group). Results for ischemic stroke and all-cause mortality are shown in eTable 8 in the Supplement.

There were no major differences between stroke patients and controls in propensity score–matched subgroups (baseline characteristics are shown in eTable 9 in the Supplement). The analyses yielded similar relationships between stroke groups and risk of adverse outcomes as the main analyses (**Table 3**).

The sensitivity analysis including only the first surgery during the study period also yielded similar results to our main results; ORs for 30-day MACE were 14.48 (95% CI, 11.49-18.25) for stroke less than 3 months prior, 5.37 (95% CI, 3.47-8.32) for stroke 3 to less than 6 months prior, 2.97 (95% CI, 1.97-4.48) for stroke 6 to less than 12 months prior, and 2.39 (95% CI, 1.94-2.93) for stroke 12 months or more prior compared with the nonstroke group (full results are shown in eFigure 5 in the Supplement).

Secondary Analyses

We found a history of stroke to be associated with greater risk of 30-day MACE in patients without atrial fibrillation (OR, 4.74; 95% CI, 4.12-5.46) compared with patients with atrial fibrillation (OR, 2.18; 95% CI, 1.64-2.89; $P<.001$ for interaction). We also found prior stroke to be associated with lower risk of 30-day MACE for use of antithrombotic therapy (OR, 3.10; 95% CI, 2.67-3.61) compared with no use of antithrombotic therapy (OR, 6.28; 95% CI, 5.06-7.80; $P<.001$ for interaction). Similarly, ORs for 30-day MACE among patients treated with statins were 3.59 (95% CI, 2.99-4.31) compared with 4.36 (95% CI, 3.66-5.19) among patients not receiving statin treatment ($P=.046$ for interaction) (see eFigure 6 in the Supplement for additional interaction analyses). Associated risks did not differ between men and women ($P=.50$ for interaction). Also, there was no statistically significant difference in association between stroke group and risk of MACE for calendar year ($P=.46$ for interaction).

Discussion

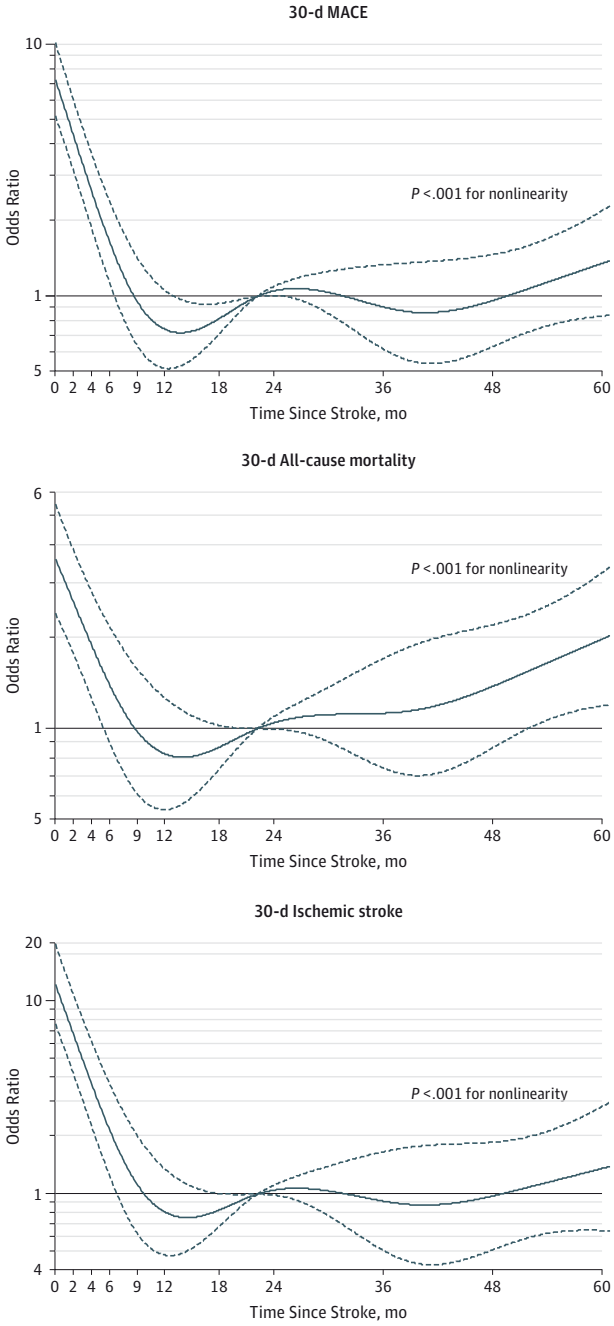
In this nationwide study, we included all elective surgeries in Denmark in 2005-2011 to study the importance of timing of surgery in patients with a history of stroke for the risk of MACE and death following surgery. In summary, we demonstrated that prior ischemic stroke, irrespective of time between ischemic stroke and surgery, was associated with an adjusted 1.8- and 4.8-fold increased relative risk of 30-day mortality and 30-day MACE, respectively, compared with patients without prior stroke. Second, we demonstrated a strong time-dependent relationship between prior stroke and adverse postoperative outcome, with patients experiencing a stroke less than 3 months prior to surgery at particularly high risk. The risk stabilized after approximately 9 months. Third, the increased relative risks associated with prior stroke were found to be of at least similar magnitudes in low- and intermediate-risk surgeries, as in high-risk surgeries.

Studies investigating the importance of timing of surgery in patients who have had a stroke are sparse. In patients who have had a myocardial infarction, a 3-month limit[3] and a 6-month limit[1,5] have been suggested for increased risk of postoperative complications (repeat myocardial infarction, cardiac arrest, and overall mortality). For stroke, a similar time-dependent risk was apparent, but our results suggested that patients with stroke should be considered at particularly increased risk until 9 months following stroke. As only elective surgeries were included in this study, we believe that the data reflected a true risk rather than confounding by indication (ie, emergent surgeries were excluded), although we were not able to evaluate causal relationships because of the observational design of this study.

Previous studies have demonstrated that a history of stroke is associated with increased perioperative risk in high-risk surgeries[25-27] as well as intermediate- and low-risk surgeries.[28,29] A recent study including patients with prior stroke undergoing coronary artery bypass graft surgery concluded that prior stroke was associated with an increased risk of postoperative stroke and death.[26] However, in contrast to our results, they found the relative risk to increase with increasing time between prior stroke and coronary artery bypass graft surgery.[26] The effect of time between prior stroke and surgery as a risk factor for adverse outcomes has been investigated as a dichotomous variable in patients undergoing intermediate- and high-risk surgeries (total hip replacement, total knee replacement, or surgery for abdominal aortic aneurysms), ie, before and after 6 months prior, because of insufficient power for further stratification.[30] The study did not demonstrate any reduced risk in patients with a stroke more than 6 months prior to surgery.[30] Our results were based on a larger number of patients undergoing various types of noncardiac elective surgery. In addition, time between stroke and surgery was analyzed as a continuous variable in cubic spline regression models and was further stratified into 5 groups, which provided a more detailed presentation of the time dependence in stroke associated risk of adverse events following elective surgery than prior studies.

Although some of the subgroup analyses stratified by surgery risk included rather few surgeries, it was noticeable that

Figure 2. Restricted Cubic Splines for Risk of 30-Day MACE, 30-Day All-Cause Mortality, and 30-Day Ischemic Stroke by Time Between Stroke and Surgery



Splines of the association of time elapsed between stroke and risk of major adverse cardiac events (MACE), mortality, and ischemic stroke, respectively, among patients with prior stroke. Dashed lines represent 95% confidence intervals. All splines were adjusted for sex, age, and surgical category. The median time between stroke and surgery (665 days) served as the reference.

Table 3. Results From Propensity Score–Matched Population

Stroke, No. of mo Prior	30-d MACE			30-d All-Cause Mortality			30-d Ischemic Stroke		
	No. of Events/Total (%)		Odds Ratio (95% CI)	No. of Events/Total (%)		Odds Ratio (95% CI)	No. of Events/Total (%)		Odds Ratio (95% CI)
	Cases	Controls		Cases	Controls		Cases	Controls	
<3	79/500 (15.80)	6/500 (1.20)	19.25 (7.05-52.60)	23/500 (4.60)	6/500 (1.20)	4.40 (1.67-11.62)	60/500 (12.00)	2/500 (0.40)	30.00 (7.33-122.73)
3 to <6	27/326 (8.28)	5/326 (1.53)	5.40 (2.08-14.02)	9/326 (2.76)	6/326 (1.84)	1.50 (0.53-4.21)	19/326 (5.83)	1/326 (0.31)	19.00 (2.54-141.93)
6 to <12	20/688 (2.91)	8/688 (1.16)	2.71 (1.14-6.46)	12/688 (1.74)	8/688 (1.16)	1.50 (0.61-3.67)	11/688 (1.60)	2/688 (0.29)	5.50 (1.22-24.81)
≥12	85/3688 (2.30)	35/3688 (0.95)	2.47 (1.66-3.68)	49/3688 (1.33)	44/3688 (1.19)	1.12 (0.74-1.69)	48/3688 (1.30)	5/3688 (0.14)	9.60 (3.82-24.11)

Abbreviation: MACE, major adverse cardiovascular events (ischemic stroke, acute myocardial infarction, or cardiovascular death).

the highest relative risk of MACE for the group with stroke within 3 months was observed among the intermediate-risk surgeries and that low-risk surgeries were not associated with better outcomes than high-risk surgeries. Thus, it seems important to take a history of recent stroke seriously, including in the context of minor surgical procedures.

Interestingly, we found the risk of prior stroke to be less adverse among patients with atrial fibrillation compared with patients without atrial fibrillation. The cause of stroke was unfortunately not known in our study, but it is likely that a greater proportion of patients with atrial fibrillation might have had thromboembolic stroke compared with stroke secondary to severe intracranial atherosclerosis. Although speculative, the risk of recurrent stroke in response to hemodynamic alterations may be greater for patients with pronounced intracranial atherosclerotic manifestations compared with patients who had stroke due to a thrombus originating in the heart. Another possibility could be that patients with atrial fibrillation receive better antithrombotic prophylactic therapy than patients without atrial fibrillation. More research is needed to investigate these theories.

Our study included a large, unselected contemporary cohort of patients presenting with a wide range of indications for surgery. This enabled us to investigate relatively rare perioperative and postoperative outcome events in several subgroups of patients, with an accuracy that is rather unique to Denmark. During our study period, guidelines and opinions regarding the discontinuation of antithrombotic therapy prior to elective surgery varied substantially. Unfortunately, we could not adjust for strategy of preoperative antithrombotic management because in-hospital medication was not registered. It is therefore not known whether these findings are explained by perioperative use of antithrombotic agents, and the same applies to use of other medications. Furthermore, only in-hospital diagnoses, which have been validated, were considered when defining comorbidities, which may have led to an underestimation of the burden of comorbidities in our cohort. We were also not able to discern between thromboembolic and atherothrombotic strokes, which perhaps could have refined risk assessment further (we found that the thromboembolic diagnosis of stroke was very infrequently used in our registries [data not shown]).

The observational nature of this study makes it impossible to appreciate if surgeries were postponed because of a history of stroke or whether the surgeries were performed at any given time regardless of a history of stroke. Additionally, the study design does not exclude the possibility of residual confounding by information not available in the registries. Among other data, we lacked information on severity of stroke sequelae indication for surgery, pulmonary crackles, accelerating chest pain, left ventricular ejection fraction, third heart sounds, and valvular heart disease, which might explain some of the increased risk associated with stroke less than 3 months prior to surgery. Finally, the study was undertaken in Denmark in a predominantly white population, and the generalizability of our findings to other countries and nonwhite populations is unknown.

Conclusions

A history of stroke was associated with increased risk of MACE and mortality in patients undergoing elective noncardiac surgery, particularly if time elapsed between stroke and surgery was less than 9 months. Low- and intermediate-risk surgeries seemed to pose at least the same relative risk of MACE in patients with recent stroke compared with high-risk surgery. Our findings need to be confirmed but may warrant consideration in future perioperative guidelines.

ARTICLE INFORMATION

Author Contributions: Drs Jørgensen and Andersson had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Jørgensen, Torp-Pedersen, Gislason, Jensen, Andersson.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Jørgensen.
Critical revision of the manuscript for important intellectual content: Torp-Pedersen, Gislason, Jensen, Berger, Christiansen, Overgaard, Schmiegelow, Andersson.
Statistical analysis: Jørgensen, Torp-Pedersen, Gislason, Schmiegelow, Andersson.
Administrative, technical, or material support: Gislason, Christiansen.
Study supervision: Torp-Pedersen, Gislason, Jensen, Overgaard, Andersson.

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REFERENCES

1. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation*. 1999;100(10):1043-1049.

2. Noordzij PG, Poldermans D, Schouten O, Bax JJ, Schreiner FA, Boersma E. Postoperative mortality in the Netherlands: a population-based analysis of surgery-specific risk in adults. *Anesthesiology*. 2010;112(5):1105-1115.

3. Vicenzi MN, Meislitzer T, Heitzinger B, Halaj M, Fleisher LA, Metzler H. Coronary artery stenting and non-cardiac surgery—a prospective outcome study. *Br J Anaesth*. 2006;96(6):686-693.

4. Brilakis ES, Banerjee S, Berger PB. Perioperative management of patients with coronary stents. *J Am Coll Cardiol*. 2007;49(22):2145-2150.

5. Livhits M, Ko CY, Leonardi MJ, Zingmond DS, Gibbons MM, de Virgilio C. Risk of surgery following recent myocardial infarction. *Ann Surg*. 2011;253(5):857-864.

6. Hawn MT, Graham LA, Richman JS, Itani KM, Henderson WG, Maddox TM. Risk of major adverse cardiac events following noncardiac surgery in patients with coronary stents. *JAMA*. 2013;310(14):1462-1472.

7. van Kuijk JP, Flu WJ, Schouten O, et al. Timing of noncardiac surgery after coronary artery stenting with bare metal or drug-eluting stents. *Am J Cardiol*. 2009;104(9):1229-1234.

8. Fleisher LA, Beckman JA, Brown KA, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery); American Society of Echocardiography; American Society of Nuclear Cardiology; Heart Rhythm Society; Society of Cardiovascular Anesthesiologists; Society for Cardiovascular Angiography and Interventions; Society for Vascular Medicine and Biology; Society for Vascular Surgery. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2007;116(17):e418-e499.

9. Poldermans D, Bax JJ, Boersma E, et al; Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery; European Society of Cardiology. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery. *Eur Heart J*. 2009;30(22):2769-2812.

10. Aries MJ, Elting JW, De Keyser J, Kremer BP, Vroomen PC. Cerebral autoregulation in stroke: a review of transcranial Doppler studies. *Stroke*. 2010;41(11):2697-2704.

11. Seshadri S, Beiser A, Kelly-Hayes M, et al. The lifetime risk of stroke: estimates from the Framingham Study. *Stroke*. 2006;37(2):345-350.

12. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health*. 2011;39(7)(suppl):30-33.

13. Gaist D, Sørensen HT, Hallas J. The Danish prescription registries. *Dan Med Bull*. 1997;44(4):445-448.

14. Andersson C, Norgaard ML, Hansen PR, et al. Heart failure severity, as determined by loop diuretic dosages, predicts the risk of developing diabetes after myocardial infarction: a nationwide cohort study. *Eur J Heart Fail*. 2010;12(12):1333-1338.

15. Andersson C, Lyngbæk S, Nguyen CD, et al. Association of clopidogrel treatment with risk of mortality and cardiovascular events following myocardial infarction in patients with and without diabetes. *JAMA*. 2012;308(9):882-889.

16. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT. The predictive value of *ICD-10* diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol*. 2011;11:83.

17. Nordic Medico-statistical Committee. *NOMESCO Classification of Surgical Procedures*. 2009. http://nowbase.org/Publikationer/-/media/Projekt%20sites/Nowbase/Publikationer/NCSP/NCSP%201_14.ashx. Accessed June 20, 2014.

18. Andersson C, Mérie C, Jørgensen M, et al. Association of β-blocker therapy with risks of adverse cardiovascular events and deaths in patients with ischemic heart disease undergoing noncardiac surgery: a Danish nationwide cohort study. *JAMA Intern Med*. 2014;174(3):336-344.

19. Boersma E, Kertai MD, Schouten O, et al. Perioperative cardiovascular mortality in noncardiac surgery: validation of the Lee cardiac risk index. *Am J Med*. 2005;118(10):1134-1141.

20. Ng JL, Chan MT, Gelb AW. Perioperative stroke in noncardiac, nonneurosurgical surgery. *Anesthesiology*. 2011;115(4):879-890.

21. Mashour GA, Sharifpour M, Freundlich RE, et al. Perioperative metoprolol and risk of stroke after noncardiac surgery. *Anesthesiology*. 2013;119(6):1340-1346.

22. Krarup LH, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a National Register of Patients. *Neuroepidemiology*. 2007;28(3):150-154.

23. Madsen M, Davidsen M, Rasmussen S, Abildstrom SZ, Osler M. The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of mortality and hospital discharge data with the Danish MONICA registry. *J Clin Epidemiol*. 2003;56(2):124-130.

24. Desquilbet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. *Stat Med*. 2010;29(9):1037-1057.

25. Hogue CW Jr, Murphy SF, Schechtman KB, Dávila-Román VG. Risk factors for early or delayed stroke after cardiac surgery. *Circulation*. 1999;100(6):642-647.

26. Bottle A, Mozid A, Grocott HP, et al. Preoperative stroke and outcomes after coronary artery bypass graft surgery. *Anesthesiology*. 2013;118(4):885-893.

27. Sharifpour M, Moore LE, Shanks AM, Didier TJ, Kheterpal S, Mashour GA. Incidence, predictors, and outcomes of perioperative stroke in noncarotid major vascular surgery. *Anesth Analg*. 2013;116(2):424-434.

28. Mashour GA, Shanks AM, Kheterpal S. Perioperative stroke and associated mortality after noncardiac, nonneurologic surgery. *Anesthesiology*. 2011;114(6):1289-1296.

29. Bateman BT, Schumacher HC, Wang S, Shaefi S, Berman MF. Perioperative acute ischemic stroke in noncardiac and nonvascular surgery: incidence, risk factors, and outcomes. *Anesthesiology*. 2009;110(2):231-238.

30. Sanders RD, Bottle A, Jameson SS, et al. Independent preoperative predictors of outcomes in orthopedic and vascular surgery: the influence of time interval between an acute coronary syndrome or stroke and the operation. *Ann Surg*. 2012;255(5):901-907.