

Lack of Association between Carotid Artery Stenosis and Stroke or Myocardial Injury after Noncardiac Surgery in High-risk Patients

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ABSTRACT

Background: Whether carotid artery stenosis predicts stroke after noncardiac surgery remains unknown. We therefore tested the primary hypothesis that degree of carotid artery stenosis is associated with in-hospital stroke or 30-day all-cause mortality after noncardiac surgery. As carotid artery stenosis is also a marker for cardiovascular disease, our secondary hypothesis was that degree of carotid artery stenosis is associated with postoperative myocardial injury.

Methods: We included adults who had noncardiac, noncarotid surgery at Cleveland Clinic from 2007 to 2011 and had carotid duplex ultrasound performed either within 6 months before or 1 month after surgery. Internal carotid artery peak systolic velocity (ICA PSV) was used as a measure of carotid artery stenosis severity. A multivariate (*i.e.*, multiple outcomes per patient) generalized estimating equation model was used to assess the association between highest ICA PSV and the composite of stroke and 30-day mortality after adjusting for predefined potentially confounding variables.

Results: Of 2,110 patients included, 112 (5.3%) died within 30 days and 54 (2.6%) suffered postoperative in-hospital stroke. ICA PSV was not associated with this composite outcome (odds ratio of 1.0 [95% confidence interval: 0.99, 1.02] for a 10-unit increase, $P = 0.55$). ICA PSV was also not associated with postoperative myocardial injury (odds ratio 1.00 [0.99, 1.02], $P = 0.49$).

Conclusions: This cohort represents a high-risk population, as carotid duplex examinations were likely prompted by neurological symptoms. There was nonetheless no association between carotid artery stenosis and perioperative stroke or 30-day mortality after noncardiac surgery. (**ANESTHESIOLOGY 2014; 121:922-9**)

THE incidence of stroke after noncardiac surgery ranges from 0.1 to 0.44% in reports spanning the last decade.¹⁻³ However, an incidence as high as 1.0% has been reported in cohorts of high-risk patients having major noncardiac surgery.⁴ The mortality after stroke in perioperative settings is two- to three-fold greater than stroke in nonsurgical settings.⁵ For example, Bateman *et al.*⁴ reported in-hospital death as high as 32% after perioperative stroke in patients having noncardiac surgery. Furthermore, at least half of perioperative strokes leave patients seriously debilitated.

The perioperative period encompasses substantial hemodynamic stress and provokes an intense inflammatory response; both potentially enhance the risk of cerebrovascular events in patients with carotid artery stenosis. The generally accepted mechanism is thought to be embolization from unstable plaque.⁶ However, high-grade stenosis can also provoke supply-demand mismatch and watershed infarcts. Advanced age, heart failure, atrial fibrillation, recent myocardial infarction, hypertension, diabetes, and a history of stroke are significant predictors of postoperative stroke after noncardiac surgery.^{1,3,4}

What We Already Know about This Topic

- Whether carotid artery stenosis predicts stroke after noncardiac surgery remains unknown

What This Article Tells Us That Is New

- Of 2,110 patients who had an internal carotid duplex ultrasound performed within 6 months before or 1 month after noncarotid, noncardiac surgery, 5.3% died within 30 days of surgery and 2.6% suffered postoperative in-hospital stroke
- The degree of stenosis, as measured by peak systolic velocity, was not associated with risk of stroke or myocardial injury

Most of these risk factors are unmodifiable. In contrast, carotid artery stenosis is a potentially modifiable risk factor—although endovascular or surgical treatment of carotid artery stenosis itself poses substantial risk of morbidity and stroke.

The extent to which carotid artery stenosis is a risk factor for perioperative stroke after noncardiac surgery remains unknown, and no recommendations on carotid revascularization before undergoing noncardiac surgery have been

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published. We therefore tested the primary hypothesis that among noncardiac surgical patients who undergo perioperative carotid duplex ultrasound scanning, there is an association between severity of stenosis and the collapsed composite outcome of in-hospital stroke or 30-day all cause mortality. We simultaneously evaluated the association between carotid artery stenosis and ipsilateral stroke.

Asymptomatic carotid artery stenosis, in addition to being an established risk factor for stroke, is an important marker of cardiovascular atherosclerotic disease. As might thus be expected, patients with carotid artery stenosis are at increased risk of myocardial infarction.⁷ Our secondary hypothesis was thus that there is an association between severity of carotid artery stenosis and postoperative myocardial injury.

Materials and Methods

This analysis was conducted with approval of the Cleveland Clinic Institutional Review Board and waived informed consent. Adults who had noncardiac surgery at Cleveland Clinic from 2007 to 2011 were considered for inclusion when they had at least one carotid duplex ultrasound examination performed at the Clinic within 6 months before or 1 month after surgery. We chose to include carotid duplex examinations performed up to 1 month after the surgery, such that the patients being evaluated for perioperative stroke would be included. Patients who had carotid endarterectomy or stenting performed between the date of carotid duplex and date of surgery were excluded, as were patients having carotid artery surgery. Only the initial Cleveland Clinic Main Campus operation was considered in patients who had multiple operations during the study period.

Patient characteristics and intraoperative data were obtained from prospectively collected institutional databases. Carotid duplex data were obtained from the Noninvasive Vascular Laboratory database and chart review. We retrieved basic demographic data including age and gender, along with history of comorbidities including coronary artery disease, chronic obstructive pulmonary disease, atrial fibrillation, diabetes mellitus, hypertension, and peripheral artery disease. We also recorded cumulative intraoperative hypotension, preoperative antiplatelet drug therapy, duration of surgery, and type of surgery.

The lowest perioperative hemoglobin was defined as each patient's lowest recorded value from among all intraoperative determinations and the first postoperative hemoglobin. For patients who did not have intraoperative or postoperative hemoglobin measurements, we considered the most recent preoperative hemoglobin measurement to be the lowest perioperative hemoglobin.

All invasive and noninvasive blood pressure readings were extracted for each surgery. Artifacts were removed by considering (1) artifact recorded by clinicians;

(2) logical checks (out of range) and trend analysis; and, (3) visual plots. Specifically, we considered blood pressure values to be artifactual when systolic arterial pressure was equal to diastolic arterial pressure; when there were extremely high or low reading values (*i.e.*, systolic arterial pressure ≥ 300 mmHg or ≤ 20 , pulse pressure ≤ 5 mmHg, or diastolic arterial pressure ≤ 5 mmHg); and when trend analysis identified rapid and implausibly large blood pressure changes.

Cumulative intraoperative hypotension was defined as the contiguous or noncontiguous total time with mean arterial pressure < 70 mm Hg. Preoperative antiplatelet therapy was defined by administration of any antiplatelet medication (including aspirin, clopidogrel, ticlopidine, or prasugrel) on the day of surgery or the day before surgery. Operations were classified as mild, intermediate, or high-risk procedures based on American College of Cardiology and American Heart Association guidelines.⁸

Estimating Severity of Carotid Artery Stenosis

The presence and severity of internal carotid artery (ICA) stenosis was estimated from the carotid duplex examination closest to the date of surgery. Results were available from two vascular laboratories at Cleveland Clinic: (1) the Heart and Vascular Institute; and, (2) Neuroradiology. While both laboratories use similar scanning protocols to assess for plaque within the carotid arteries and perform extensive spectral Doppler interrogation of the vessels to document velocities throughout the carotid system, the laboratories use different diagnostic criteria for determining percentage stenosis of the ICA based upon the highest peak systolic and end-diastolic velocity measurements recorded in the ICA. As a result, these two methods cannot be directly compared.

There is currently no national standard for diagnostic criteria for ICA stenosis. Vascular laboratories may use previously published or internally developed diagnostic criteria, though laboratories must validate their laboratory diagnostic criteria compared to carotid angiography.* To allow for comparability of data, we thus *a priori* selected internal carotid artery peak systolic velocity (ICA PSV), which is a routine aspect of any carotid duplex ultrasound examination, as our measure of carotid artery stenosis severity.

Internal carotid artery peak systolic velocity is inversely related to vessel diameter, with stenosis thus increasing peak velocity. The relationship between ICA PSV and angiographically determined percentage of ICA stenosis is linear over most of the physiologic range.^{9,10} However, flow decreases to near zero with total or near-total vessel occlusion and then, the ICA PSV parameters are not applicable. The lack of blood flow on color and spectral Doppler examination establishes total occlusion. For the purpose of analysis, we replaced the ICA PSV velocities of patients with total or near-total occlusion, identified with Doppler, with the highest value ICA PSV recorded in the entire cohort of patients.

* IAC Standards and Guidelines for Vascular Testing Accreditation (2013). Available at: <http://intersocietal.org/vascular/standards/IAC-VascularTestingStandards2013.pdf>. Accessed January 4, 2014.

Measuring Outcomes

Surgical episodes of patients with International Classification of Diseases (ninth revision) diagnostic codes for acute stroke were identified within the eligible cohort. The electronic medical records of these patients were reviewed individually to confirm that the reported strokes occurred postoperatively. Patients who were admitted with stroke or who had an acute stroke before the noncardiac surgery were excluded from the cohort. The laterality of the strokes was also recorded. Thirty-day all-cause mortality was determined from hospital records, supplemented by the Social Security Death Index.

Vascular events in surgery patients cohort evaluation (VISION), a recent large prospective cohort study, showed that patients with a peak serum troponin T > 0.03 ng/ml during the initial three postoperative days have markedly increased 30-day mortality.¹¹ As in that study, we considered perioperative myocardial injury or myocardial injury after noncardiac surgery (MINS) to be defined by new-onset postoperative troponin T concentration ≥ 0.03 ng/ml within 30 days of surgery unexplained by sepsis, renal failure, or any other noncardiac cause.¹² Because our analysis was retrospective, we were limited to troponin measurements that had been ordered for clinical reasons. We also included patients having International Classification of Diseases (ninth revision) diagnostic codes for acute myocardial infarction. The

electronic medical records of all candidate patients in the current cohort were individually reviewed to confirm that each satisfied the criteria for MINS.

Statistical Methods

The primary exposure was the highest ICA PSV measured from either side, and the primary outcome was a composite of in-hospital stroke and 30-day all-cause mortality. The secondary outcomes included MINS and ipsilateral stroke.

Demographic factors, comorbidities, type of surgery, and perioperative factors were summarized using standard descriptive statistics. Associations with the primary exposure were evaluated using the Pearson chi-square test, analysis of variance, and Kruskal–Wallis test, as appropriate.

Primary Analysis

We assessed the association between the highest ICA PSV and the composite outcome using an average relative-effect generalized estimating equation (GEE) model which averaged the log-odds ratios for the two primary outcome components (stroke and 30-day mortality) in a single model while adjusting for the within-subject correlation among the outcomes and all confounding variables in table 1. The average relative effect model is a “distinct effects” GEE model which first estimates the association between the exposure and each primary outcome component and then averages

Table 1. Baseline and Intraoperative Characteristics for Noncardiac Surgical Patients (N = 2,110)

Variable	ICA PSV*			P Value†
	<125 (N = 1,338)	125–230 (N = 495)	>230 (N = 277)	
Baseline				
Age, yr	67 ± 13	70 ± 11	71 ± 11	0.001
Gender (female), %	40	48	40	0.006
Risk of surgical procedure‡, %				0.02
Low	31	31	40	
Intermediate	47	49	42	
High	23	21	17	
Medical history				
Coronary artery disease, %	50	61	70	<0.001
COPD, %	23	31	24	0.002
Atrial fibrillation, %	18	15	11	0.007
Diabetes, %	40	47	44	0.016
Hypertension, %	81	89	90	<0.001
Peripheral vascular disease, %	43	57	60	<0.001
Cerebrovascular disease, %	19	37	49	<0.001
Perioperative characteristics				
Antiplatelet therapy, %	46	53	61	<0.001
Duration of surgery, hr	3.2 (2.0, 4.8)	3.4 (2.0, 5.0)	3.5 (2.0, 5.6)	0.15
Lowest hemoglobin, g/dl	10.5 ± 2.2§	10.0 ± 2.2	10.2 ± 2.2#	<0.001
Cumulative minutes of intraoperative MAP <70 mmHg	19 (3, 54)	24 (6, 67)	23 (4, 68)	0.047

Data are presented as % of patients, mean ± SD, or median (Q1, Q3), respectively.

* PSV (in cm/s) was grouped into three categories according to severity of carotid artery stenosis based on Society of Radiologists in Ultrasound consensus criteria. † Pearson's chi-square test, ANOVA and Kruskal–Wallis test, as appropriate. ‡ Surgical procedures were classified according to ACC/AHA 2007 guidelines—high risk, vascular surgery; intermediate risk, intraperitoneal/intrathoracic surgery, head and neck surgery, orthopedic surgery, prostate surgery; and low risk, endoscopic procedures, superficial procedures, cataract surgery, breast surgery, ambulatory surgery. § Present 39 missing data. || Present 12 missing data. # Present 8 missing data.

ACC/AHA = American College of Cardiology/American Heart Association; COPD = chronic obstructive pulmonary disease; MAP = mean arterial pressure.

them.¹³ Mascha and Imrey¹⁴ showed that it is preferred over the more traditional *any-versus-none* analysis and GEE global odds ratio (or common effect) methods whenever the relative effects (*e.g.*, odds ratios) are at least as important as absolute differences. This is because the latter approaches are easily driven by components with higher overall frequency, independent of the treatment effects, whereas the average relative effect test is not. An analogous distinct effects GEE model was used to test whether the relationship with ICA PSV was consistent across the components, *i.e.*, assessing the interaction between the components and ICA PSV.

Regardless of whether an interaction was detected, we planned to assess the association between ICA PSV and each component of the primary outcome in separate multivariable logistic regression models while controlling the type I error at 0.05 with a Bonferroni correction (*i.e.*, significance criterion = 0.05/2).

Secondary Analyses

We do not know how linear the association might be between ICA PSV and the true degree of carotid artery stenosis, and nonlinearity could influence our conclusions. In a sensitivity analysis, we thus assessed the association between dichotomized ICA PSV (any stenosis [ICA PSV > 125 cm/s] *vs.* no stenosis [≤ 125 cm/s]) and the primary outcomes in an average relative effect GEE model analogous to the primary analysis. An ICA PSV > 125 cm/s is associated with a >50% carotid artery stenosis based on the Society of Radiologists in Ultrasound consensus criteria.¹⁵ We also conducted another sensitivity analysis using the cutoff value of ICA PSV > 230 cm/s, which is associated with a >70% carotid artery stenosis.¹⁵

Finally, we evaluated the association between severity of carotid artery stenosis and MINS using multivariable logistic regression. A subgroup study was conducted to explore the univariable association between laterality of highest ICA PSV and ipsilateral stroke for patients who had a stroke.

The methods for this study, including outcome definitions and statistical analysis, were established before data acquisition, and the study was conducted as planned. SAS statistical software version 9.2, Carey, NC, was used for all analyses.

Results

We identified 2,116 patients who satisfied our inclusion criteria (fig. 1). Among these, six were excluded as they had fewer than three blood pressure measurements recorded during surgery. Because only 2.8% of patients were missing perioperative hemoglobin concentrations, we used the median of perioperative hemoglobin to replace the missing values in the multivariable analysis. One hundred and forty-nine patients were excluded as they had carotid revascularization (endarterectomy or stenting) after carotid duplex examination but before noncardiac surgery, and 317 were excluded because of preoperative stroke. Among patients with more than one surgical episode, only the first surgical episode was included; 4.3% of our patients had either total or near-total

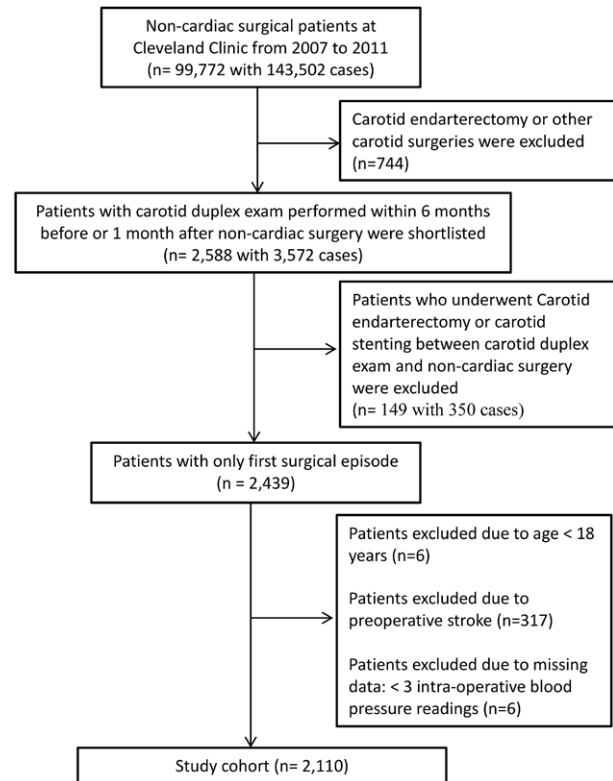


Fig. 1. Flow chart illustrating selection of the study cohort.

occlusion of ICA and, as described above, the ICA PSV in these patients was replaced by the highest ICA PSV velocity in our cohort (695 cm/s).

The median ICA PSV was 102 cm/s (Q1, Q3: 87, 164). Table 1 shows the summary statistics of baseline and intraoperative characteristics of patients with various severities of carotid stenosis, defined by ICA PSV <125, 125–230, and >230 cm/s.¹⁵ The incidence of having either component of the primary outcome, in-hospital stroke or 30-day all-cause mortality, was 7.5% (158 patients). Fifty-four patients (2.6%) had postoperative in-hospital strokes, and 112 patients (5.3%) died within 30 days. Among patients who had in-hospital strokes, eight died within 30 days. One hundred and eighty-six patients (8.8%) met the criteria for MINS.

Internal carotid artery peak systolic velocity was not associated with the primary composite outcome of in-hospital stroke or 30-day all-cause mortality after adjusting for potential confounding variables ($P = 0.55$, table 2), with estimated average relative effect odds ratio of 1.00 (95% confidence interval [CI]: 0.99, 1.02) for a 10-unit increase in ICA PSV. Furthermore, the odds ratio was consistent across the components of the primary outcome (interaction $P = 0.07$), with odds ratio of 1.00 (97.5% CI: 0.98, 1.02) ($P = 0.64$) on 30-day all-cause mortality, and 1.01 (0.99, 1.03) ($P = 0.23$) on postoperative in-hospital strokes.

In our sensitivity analysis on the primary exposure, “any stenosis” (ICA PSV > 125 cm/s) was present in 37% of patients, and was not associated with the composite

Table 2. The Associations between ICA PSV and Primary and Secondary Outcomes among 2,110 Noncardiac Surgical Patients

Primary Outcome	Incidence	OR (95% CI)	P Value
Primary analysis: stroke or death	158 (7.5%)	1.00 (0.99, 1.02)	0.55
Individual components			
30-day mortality	112 (5.3%)	1.00 (0.98, 1.02)*	0.64
Postoperative stroke	54 (2.6%)	1.01 (0.99, 1.03)*	0.23
Secondary outcome			
Postoperative myocardial injury	186 (8.8%)	1.00 (0.99, 1.02)	0.49

For the primary analysis an average relative effect generalized estimating equation odds ratio was estimated across the composite outcome components. The interaction between ICA PSV and the components of the primary outcome was not significant ($P = 0.07$). Odds ratios for the relationship between ICA PSV and individual components or the secondary outcome were assessed using separate logistic regression models. Significance criterion was $P < 0.05$ for the primary analysis and secondary outcome, but 0.025 when primary outcome components were analyzed separately (Bonferroni correction).

* 97.5% CI

ICA PSV = internal carotid artery peak systolic velocity (highest from either side of patient); OR = odds ratio for a 10-unit increase in ICA PSV adjusting for all variables in table 1.

outcome [average relative effect odds ratio (95% CI) of 0.91 (0.61, 1.35), $P = 0.64$]. Also, high-grade stenosis (defined as ICA PSV > 230 cm/s) was present in 13% of the patients, and was not associated with the composite outcome (average relative effect odds ratio [95% CI] of 0.96 [0.57, 1.63], $P = 0.89$).

Among the Doppler examinations we considered, 17% were conducted within a postoperative month. A sensitivity analysis performed after excluding these postoperative scans also showed that ICA PSV was not associated with the primary composite outcome, after adjusting for potential confounding variables (average relative effect odds ratio [95% CI] of 1.01 [0.99, 1.03], $P = 0.32$). Among those patients who had a stroke ($N = 54$), the left, right, and both sides of laterality of stroke were 25 (46%), 18 (33%), and 11 (20%), respectively. The association between side of highest ICA PSV and laterality of stroke was not significant, with Pearson chi-square $P = 0.57$.

The degree of carotid artery stenosis was not associated with the secondary outcome (MINS) after adjusting for confounding variables (odds ratio [95% CI] of 1.00 [0.99, 1.02] for a 10-unit increase, $P = 0.49$).

Discussion

There was no association between either the presence of any carotid artery stenosis or severity of stenosis, and our composite outcome of postoperative stroke and 30-day mortality. By virtue of evaluating 2,110 patients of whom 54 suffered strokes and 112 died, our well-powered study indicates that the results of carotid ultrasound studies do not reliably predict the risk of perioperative stroke. It is unlikely that our finding represents a false-negative conclusion (note the small 95% CIs). We also did not find an association between severity of stenosis and postoperative stroke or mortality when analyzed separately.

Our results are consistent with a previous under-powered analysis. Evans *et al.*¹⁶ retrospectively evaluated 284 patients who had carotid duplex examinations within a year before having noncardiac, nonvascular surgery. Only 10 patients (2.8%) had perioperative ischemic strokes within 30 days of

surgery. Among 224 patients who had any degree of carotid artery stenosis, there was no association between severity of stenosis and perioperative stroke. A previous study evaluated the association between carotid bruit and stroke after noncardiac surgery, and found no significant association.¹⁷ However, carotid bruit is not a reliable indicator of either presence or severity of carotid artery stenosis making the results difficult to interpret.¹⁸

Our study could be criticized for using ICA PSV (measured using carotid ultrasonography) as a measure of carotid artery stenosis. Currently, most vascular laboratories use various internally validated criteria, due to lack of nationally (or internationally) accepted ultrasound-based criteria for grading stenosis. Degrees of ICA stenosis estimated by various criteria are substantially different from one another, and thus cannot be grouped together in an analysis. However, ICA PSV is the primary criterion used for estimating carotid artery stenosis for the majority of diagnostic criteria.

Although ultrasound-based estimations of ICA stenosis have been criticized for not being as accurate as carotid angiography,¹⁹ the invasive nature of angiography and associated morbidity prevents its use for screening. A meta-analysis which evaluated the ability of ICA PSV to determine various degrees of angiographically determined ICA stenosis, found ICA PSV to have more than 90% sensitivity and specificity.²⁰ Also, ICA PSV has been shown to increase in proportion to the degree of angiographic stenosis.^{9,10} But, the correlation of velocity and degree of stenosis is poor at highest grades of stenosis, as the flow decreases to 0. We circumvented this by replacing ICA PSV velocities of patients with total or near-total ICA occlusion, identified by Doppler, with the highest recorded value ICA PSV in our entire cohort. Despite its limitations, ICA PSV remains the single variable that is universally obtained in typical carotid ultrasound examinations and can thus serve as a surrogate to estimated degree of ICA stenosis.

Another important consideration is that 149 patients, who had carotid artery revascularization between the carotid duplex examination and noncardiac surgery, were *a priori* excluded from our cohort. They presumably had high-grade

stenosis or carotid stenosis with associated neurological symptoms who, after carotid duplex examination, were deemed to have been at such high risk for stroke that they were scheduled for carotid revascularization. Also, it is possible that among a limited number of patients scheduled to undergo elective noncardiac surgeries, the surgery itself would have been postponed or even cancelled in light of very severe carotid disease. Our results thus apply only to patients who were not considered to be at such high risk that immediate revascularization was proposed and accepted. That said, 4.3% of our cohort had either complete or nearly complete carotid artery occlusions, and 13% of our cohort did have high-grade carotid stenosis (with ICA PSV > 230 cm/s). Our analysis is thus based on the full range of occlusion values.

The 2011 multidisciplinary U.S. guidelines for management of extracranial cerebrovascular disease recommends considering carotid endarterectomy for asymptomatic patients with ICA stenosis of more than 70% by North American Symptomatic Carotid Endarterectomy Trial-based criteria, after taking into consideration comorbidities, perioperative risk, and patient preference.²¹ While this guideline strongly recommends in favor of endarterectomy or carotid artery stenting for symptomatic patients (ipsilateral stroke or transient ischemic attacks in the last 6 months), with more than 70% carotid artery stenosis if the anticipated perioperative stroke and death rate is less than 6%.²¹ These recommendations are for medical patients presenting with carotid artery disease rather than in the context of preoperative evaluation for noncardiac surgery.

There is no analogous recommendation for patients with carotid artery stenosis who present for noncardiac surgery. A recent review by Ng *et al.*⁵ on perioperative stroke after noncardiac surgery briefly addresses the issue. They suggest offering revascularization to patients who have both symptoms and more than 70% stenosis. But as the authors recognize, this recommendation is not supported by strong evidence. Our results suggest that high-grade stenosis, at least in the absence of symptoms, does not necessarily warrant revascularization because high-grade stenosis alone does not predict increased perioperative stroke risk. Furthermore, the lack of relationship between laterality of carotid artery stenosis and perioperative strokes suggests that strokes after noncardiac surgeries are more likely to be associated with systemic embolic causes than carotid artery stenosis.

Duplex ultrasound results were available to clinicians before surgery in about 85% of the cases. Presumably, the degree of carotid artery stenosis was incorporated into the anesthetic plan, for example by maintaining higher perioperative blood pressures, which in turn ameliorated stroke risk. Thus while we conclude that even substantial carotid artery stenosis need not delay noncardiac surgery because the risk of perioperative stroke is independent of stenosis, it does not follow that Doppler evaluation of carotid arteries is unwarranted because the results may well have had salutary effects on anesthetic management.

Our results differ distinctly from cardiac surgery in which there is a clear relationship between carotid artery stenosis and stroke.^{22,23} The most likely explanation is that cardiac surgery, with extracorporeal circulation and manipulation of the great vessels, presents a higher risk for stroke and that patient carotid arteries are thus more important in that context. In addition, significant carotid artery stenosis is a marker for high atherosclerotic burden in arterial tree, including the aortic arch, and thus increases the risk of atheroembolization and stroke with aortic cross-clamping.

In the nonoperative setting, carotid artery stenosis is a powerful predictor of nonfatal cardiovascular events and cardiovascular death.^{7,24} For example, Second Manifestations of Arterial disease trial was a prospective observational study which evaluated 2,684 patients with risk factors for arterial disease. Patients with carotid artery stenosis exceeding 50% were at substantially enhanced risk for myocardial infarction.⁷ In contrast, there was no independent association between carotid artery stenosis and perioperative MINS in our patients.

Lack of association between carotid artery stenosis and MINS should be considered in context. For example, our analysis was restricted to patients who had carotid duplex examinations. All participants were thus already thought to be at risk of stenosis by their physicians. Our analysis was thus entirely conducted within a population deemed to be at high risk, rather than being a comparison across the entire risk spectrum. Also, postoperative troponins were not measured in all patients, but only in those thought to be at high risk or clinical suspicion of coronary ischemia. In addition, a subset of patients with high-grade carotid artery stenosis, and thus advanced atherosclerotic disease, were excluded from our cohort, as they had carotid revascularization before the proposed noncardiac surgery. Our results should thus not be interpreted to mean that carotid disease is unimportant; only that within the high-risk population we evaluated, carotid disease did not predict perioperative cardiovascular events.

Along those lines, the results we present are adjusted for numerous baseline comorbidities—including many such as diabetes and hypertension that are likely to be colinear with atherosclerotic disease. Thus our conclusion that there was no *independent* association with MINS, should not be taken to mean that there is no relationship. It is also worth considering that carotid duplex evaluations occurred up to 6 months before surgery. Clinicians and patients thus usually had considerable opportunity to institute pharmacologic and lifestyle changes to reduce the risk of cardiovascular events including myocardial infarction.

Duplex scans in our patients were generally performed for medical indications or because of carotid bruits or neurological symptoms as we do not routinely obtain carotid duplex examinations before noncardiac surgery. It is thus unsurprising that the overall incidence of postoperative stroke, 2.6%, was higher than generally reported. The high stroke rate was especially impressive in that it included only patients with clinically apparent strokes. It is likely that transient

neurological deficits were overlooked, especially since postoperative sedation hinders neurological assessment.

In the nonsurgical setting, imaging studies show that most strokes go undetected. It thus remains possible, although unlikely, that carotid artery stenosis is associated with silent strokes, although it was not associated with those that were clinically apparent. However, such silent strokes are considerably less serious than those that are clinically apparent.

In summary, there was no association between carotid artery stenosis and perioperative stroke or 30-day mortality after noncardiac surgery. Decision about carotid revascularization should thus be based on the presence of symptoms and grade of stenosis rather than the need for noncardiac surgery.

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Competing Interests

The authors declare no competing interests.

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