Carotid endarterectomy remains safe in high-risk patients

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ABSTRACT

Objective: Carotid endarterectomy (CEA) is a proven intervention for stroke risk reduction in symptomatic and asymptomatic patients. High-risk patients are often offered carotid stenting to minimize the risk and optimize the outcomes. As a referral center for high-risk patients, we evaluated and analyzed our experience with high-risk CEA patients.

Methods: We retrospectively reviewed consecutive patients who had undergone CEA at a tertiary referral center. The demographics, indications for surgery, physiologic and anatomic risk factors, intraoperative surgical management, perioperative complications, morbidity, and mortality were analyzed. The high-risk physiologic factors identified included an ejection fraction <30%, positive preoperative stress test results, and compromised pulmonary function test results. The high-risk patients included those requiring home oxygen, those with a partial pressure of oxygen of <60 mm Hg, and patients with a forced expiratory volume in 1 second of <30%. The high-risk anatomic factors identified included previous head and/or neck radiation, a history of ipsilateral neck surgery, contralateral nerve palsy, redo CEA, previous ipsilateral stenting, contralateral occlusion, contralateral CEA, nasotracheal intubation, and digastric muscle division. After propensity score matching, patients with and without high-risk physiologic and anatomic factors were compared. The primary outcomes were a composite of stroke, myocardial infarction, and 30-day mortality. The secondary outcomes were cranial injury and surgical site infection.

Results: During a 10-year period, 1347 patients had undergone CEA at the Cleveland Clinic main campus. Of the 1347 patients, 1152 met the criteria for analysis. Propensity score matching found adequate matches for 424 high-risk patients, with 173 patients having at least one physiologic high-risk factor and 293 at least one anatomic high-risk factor. No significant differences were found in the primary composite outcome or any of its components. Overall, the stroke rate for the standard-risk and high-risk patients was 1.9% and 1.4%, respectively. The high-risk patients were significantly more likely to have experienced a cranial nerve injury, although most were temporary. When patients with one or multiple risk factors were analyzed, no significant difference was found in the primary composite outcome or any of its components. Patients with two or more risk factors were significantly more likely to have experienced a cranial nerve injury, with most being temporary.

Conclusions: In our large series, CEA remained a viable and safe surgical solution for patients with high-risk anatomic and physiologic risk factors, with acceptable stroke, myocardial infarction, and 30-day mortality rates. (J Vasc Surg 2021;73:1675-82.)

Keywords: Carotid endarterectomy; High-risk CEA; Stroke risk

Carotid endarterectomy (CEA) has proven itself as the standard procedure for stroke risk reduction in symptomatic and asymptomatic patients with significant carotid bifurcation disease.[1,2] As endovascular technology evolved in the late 1990s and early 2000s, carotid artery stenting (CAS) emerged as a therapeutic alternative for those deemed at high risk for CEA. Trials such as SAPPHIRE (stenting and angioplasty with protection in patients at high risk for endarterectomy) documented the noninferiority of CAS compared with CEA for selected high-risk patients.[3-5] However, CAS is not without its complications. The presence of difficult anatomy, occurrence of stent fractures, an increased stroke risk, and early thrombosis in select subgroups decreases our threshold to perform CEA.[4-7] In addition, transfemoral CAS will not be reimbursed when performed for asymptomatic high-risk patients as outlined in the National Coverage Determination by the Centers for Medicare and Medicaid Services (CMS).[8] The development of transcarotid artery revascularization (TCAR) has allowed for the treatment of asymptomatic high-risk patients according to data from the Society for Vascular Surgery (SVS) Vascular Quality Initiative (VQI).

Patient selection for CAS is often dictated by high-risk physiologic and anatomic criteria as set forth by multiple clinical trials. The CAS outcomes in these situations has been well described. However, few modern studies

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have documented the CEA experience for patients with high-risk physiologic and anatomic criteria. Thus, we sought to review our experience with patients considered for CAS but who had undergone CEA.

ARTICLE HIGHLIGHTS

- **Type of Research:** A single-institution retrospective study
- **Key Findings:** During a 10-year period, 450 patients with one or multiple physiologic and anatomic high-risk factors had undergone carotid endarterectomy. Patients with a single risk factor had a stroke rate of 1.3% and those with multiple high-risk factors had a stroke rate of 1.4%.
- **Take Home Message:** Carotid endarterectomy remains a viable and safe surgical solution for patients with high-risk anatomic and physiologic risk factors with an acceptable stroke risk.

METHODS

We performed a retrospective review of consecutive patients who had undergone CEA at the Cleveland Clinic from 2008 to 2018. After approval from our institutional review board, patients were identified using Current Procedural Terminology code 35301, and the data were stored using a secured REDCap database, version 9.1.3 (REDCap, Nashville, Tenn). Patient consent was not required for our project. Both symptomatic and asymptomatic patients were included in our review. The practice at our institution is to consider asymptomatic patients for surgery when the stenosis is >80%. Patients are risk stratified with appropriate testing by the staff physician, and, when indicated, patients are referred to the appropriate service for consultation and further tests. Depending on the risk profile, the patient is offered CEA or medical management. In the present study, the patient demographics, indications for surgery, physiologic and anatomic risk factors, intraoperative surgical management, perioperative complications, morbidity, and mortality were analyzed. Patients who had undergone a concurrent procedure were excluded. After propensity score matching, patients with and without high-risk physiologic and anatomic risk factors were compared. The physiologic high-risk factors were an ejection fraction of <30%, a positive preoperative stress test, severe pulmonary disease, home oxygen use, a partial pressure of oxygen of <60 mm Hg, and/or forced expiratory volume in 1 second of <30%. Positive stress tests included the finding of active and nonactive ischemia. Anatomic high-risk patients were defined by previous head and/or neck radiation, a history of ipsilateral neck surgery, contralateral nerve palsy, redo CEA, previous ipsilateral stenting, contralateral occlusion, contralateral CEA, nasotracheal intubation, and/or an operation requiring digastric muscle division. We used digastric muscle division as a surrogate for a high bifurcation or extended internal carotid artery disease. The primary outcome was a composite of stroke, myocardial infarction (MI; positive enzyme results with corresponding electrocardiographic changes), and 30-day mortality. The secondary outcomes were cranial injury and surgical site infection as defined by the SVS reporting standards.[9] In addition to our initial data analysis of the individual risk factors and outcomes, the outcomes of patients with one or multiple high-risk factors were analyzed. Furthermore, the outcomes were analyzed for those with one or multiple high-risk factors after the omission of the presence of contralateral CEA as a high-risk factor. Patients with previous contralateral CEA were included in the standard-risk patient group. Patients with previous contralateral CEA were only included in the high-risk group if other risk factors had qualified them as such. The outcomes analyzed were the same as previously described.

Statistical analysis. Categorical factors are presented as frequencies and percentages. For the dichotomous variables (yes vs no), only the yes response findings were summarized in the tabular data. Continuous measures were summarized using the mean ± standard deviation and/or the median and range. Comparisons between patients with complete data on the high-risk and outcomes measures, and those excluded because of missing data were performed using two-sample *t*-tests for continuous factors and the Pearson χ^2 test or Fisher exact test for categorical factors.

Propensity score matching was used to match patients by the demographics and surgical factors. The characteristics that constituted the definition of high-risk surgery, outcomes, and predictors with a very low frequency were not included in the matching procedure. The variables included in the propensity score model were age, body mass index, hypertension, chronic kidney disease, diabetes, shunt usage, stump pressure measured, aspirin usage, clopidogrel (Plavix; Bristol-Myers Squibb, New York, NY) usage, sex, smoking status, neurological symptoms, and surgical technique. For variables with missing data, multiple imputation for these measures was performed using the fully conditional specification method for arbitrary missing data patterns. A maximum matching caliper of 0.12 (25% of the estimated logit) was used. The propensity scores from each imputation dataset were averaged, and 1:1 matching was performed using a greedy matching algorithm.

High-risk and non high-risk patients were compared on the matching factors before and after matching, using analysis of variance, two-sample *t*-tests, Pearson χ^2 tests, and Fisher exact tests. To compare these groups by the composite and individual outcomes, mixed effect logistic regression models were fit with a random intercept for the matched pairs, and odds ratios and 95%

confidence intervals were computed for the increased risk of these events for high-risk patients. When the overall test results were significant, pairwise comparisons were performed using a Bonferroni correction to control the overall error rate. SAS software, version 9.4 (SAS Institute, Cary, NC), was used for all analyses, and a significance level of $P = .05$ was assumed.

RESULTS

From 2008 to 2018, 1347 patients underwent CEA at the Cleveland Clinic. Of these 1347 patients, 54 had undergone a concurrent cardiac procedure (coronary artery bypass grafting, left ventricular assist device procedure, valve surgery) and were excluded from the present analysis. In addition, another 138 patients with incomplete data variables and 3 with incomplete data outcomes were excluded from the present study, leaving a final cohort of 1152 patients for analysis. The excluded patients tended to be younger, were more likely to be smokers, and were less likely to have hypertension or to be taking aspirin (Supplementary Table I, online only). In addition, the excluded patients were more likely to have undergone eversion endarterectomy; however, no significant differences were found in the surgical outcomes.

The demographic data before and after propensity matching for the final 1152 patients are presented in Supplementary Tables II and III (online only). Of the 1152 patients, 450 (39%) had had high-risk factors. Propensity score matching found adequate matches for 424 of the 450 high-risk patients (94%). Before matching, those meeting the high-risk criteria were significantly more likely to be smokers, have chronic kidney disease, have had a shunt used, and be taking clopidogrel (Plavix). However, after matching, no significant differences for any factor were observed. The patients in the matched groups tended be men and had an average age of 69 years. Most patients were former smokers and had hypertension. The indication for intervention was asymptomatic disease in 73% of the patients, transient ischemic attack or amaurosis in ~21%, and stroke in almost 5% of patients. Almost all patients (~95%) were treated with patch angioplasty, and roughly one half of the patients had undergone shunting, with 40% having the stump pressure checked during the procedure. Aside from the stump pressures, information on other neuroprotective strategies was not included in our review because the data are not reliably accessible in our electronic medical system. A few patients in the non high-risk and high-risk groups (7 and 11, respectively) had had an additional proximal common carotid stent placed during CEA.

The anatomic and physiologic factors before matching are listed in Tables I and II. After matching, 173 patients had had at least one physiologic high-risk factor and 293 had had at least one anatomic high-risk factor (Tables III and IV). Of the 173 matched patients, 104 (67.5%) had had a positive preoperative stress test, 21 an ejection fraction of <30% (12.6%), 72 (41.6%) New York Heart Association class III/IV congestive heart failure, and 20 (11.6%) severe pulmonary disease, qualifying them as patients with high-risk physiologic factors. Contralateral occlusion was a common anatomic high-risk factor, present in 79 patients (27%). High lesions requiring digastric muscle division and redo CEA were other common high-risk features, present in 52 (17.7%) and 36 (12.3%) patients, respectively. Less common anatomic high-risk features included head/neck radiation (n = 25; 8.5%), a history of ipsilateral neck surgery (n = 11; 3.8%), preoperative contralateral nerve palsy (n = 11; 3.8%), nasotracheal intubation (n = 7; 2.4%), and previous ipsilateral carotid stenting (n = 5; 1.7%). The matching process did not greatly alter the distribution of these criteria compared with before matching.

The comparisons of the outcomes among the matched patients are presented in Table V. No significant differences in the primary composite outcome or any of its components were observed. The overall stroke rate in non high-risk patients and high-risk patients was 1.9% and 1.4%, respectively. Three patients in both groups had died within 30 days. MI within 30 days was rare, occurring in one patient in the low-risk group and four patients in the high-risk group. The high-risk patients were significantly more likely to have experienced a secondary composite end point, cranial nerve injury. Temporary cranial nerve injury occurred in 24 high-risk patients (5.7%) and only seven non high-risk patients (1.7%). The odds of a high-risk patient experiencing a temporary cranial nerve injury was 3.59 times greater than that for patients without high-risk surgery ($P = .004$). In the two groups, five patch infections had developed that required excision and vein patching.

The outcomes of the patients with one or multiple high-risk factors are presented in Table VI. Of the 1152 patients, 450 had had high-risk features. After matching the high-risk patients to the non high-risk patients, 303 patients had had one high-risk factor and 121 had had two or more high-risk factors. No significant differences in the primary composite outcome or any of its components were observed between the patients with one or two or more high-risk factors. Patients with two or more high-risk factors had had a composite stroke, death, and MI rate of 2.5% (2.4% vs 2.5%; $P = .87$), with stroke occurring in 1.7% (1.9% vs 1.7%; $P = .84$). No 30-day mortalities had occurred in the two or more high-risk factor group. High-risk patients with two or more risk factors were also significantly more likely to experience a secondary composite end point complication (n = 15; 12.4%). Of these 15 patients, 14 had had a nerve injury, 11 of which were temporary. The last patient had developed a surgical site infection.

Contralateral endarterectomy is not a classic high-risk factor; thus, we decided to analyze our outcomes

Table I. Physiologic variables before matching

Factor	Overall (N = 1152)		Not high risk (n = 969)		High risk (n = 183)	
	Patients, No.	Value	Patients, No.	Value	Patients, No.	Value
NYHA class III/IV CHF, No. (%)	1151	75 (6.5)	969	0 (0.00)	182	75 (41.2)
Severe pulmonary disease,[a] No. (%)	1152	21 (1.8)	969	0 (0.00)	183	21 (11.5)
EF before CEA, %						
Mean ± SD	1079	57.7 ± 10.4	903	59.0 ± 8.8	176	51.1 ± 14.5
Median	1079	59.0	903	60.0	176	55.0
Range	1079	15.0-93.0	903	30.0-93.0	176	15.0-90.0
EF <30, N (%)	1079	22 (2.0)	903	0 (0.00)	176	22 (12.5)
Abnormal stress test result, N (%)	964	110 (11.4)	801	0 (0.00)	163	110 (67.5)

CEA, Carotid endarterectomy; *CHF*, congestive heart failure; *EF*, ejection fraction; *NYHA*, New York Heart Association; *SD*, standard deviation.
[a]Home oxygen use, partial pressure of oxygen of <60 mm Hg, or forced expiratory volume in 1 second of <30%.

Table II. Anatomic variables before matching

Factor	Overall (N = 1152)		Not high risk (n = 839)		High risk (n = 313)	
	Patients, No.	No. (%)	Patients, No.	No. (%)	Patients, No.	No. (%)
Head/neck radiation therapy	1152	27 (2.3)	839	0 (0.00)	313	27 (8.6)
History of ipsilateral neck surgery	1152	11 (0.95)	839	0 (0.00)	313	11 (3.5)
Contralateral nerve palsy	1152	11 (0.95)	839	0 (0.00)	313	11 (3.5)
Redo CEA	1152	41 (3.6)	839	0 (0.00)	313	41 (13.1)
Previous ipsilateral stent	1152	5 (0.43)	839	0 (0.00)	313	5 (1.6)
Contralateral occlusion	1152	82 (7.1)	839	0 (0.00)	313	82 (26.2)
Contralateral CEA	1151	148 (12.9)	839	0 (0.00)	312	148 (47.4)
High bifurcation maneuver						
Nasotracheal intubation	1152	8 (0.69)	839	0 (0.00)	313	8 (2.6)
Takedown digastric muscle division	1152	55 (4.8)	839	0 (0.00)	313	55 (17.6)

CEA, Carotid endarterectomy.

Table III. Physiologic variables after matching

Factor	Overall (N = 848)		Not high risk (n = 675)		High risk (n = 173)	
	Patients, No.	Value	Patients, No.	Value	Patients, No.	Value
NYHA class III/IV CHF, No. (%)	848	72 (8.5)	675	0 (0.00)	173	72 (41.6)
Severe pulmonary disease,[a] No. (%)	848	20 (2.4)	675	0 (0.00)	173	20 (11.6)
EF before CEA, %						
Mean ± SD	797	57.1 ± 10.7	630	58.7 ± 8.8	167	51.2 ± 14.6
Median	797	59.0	630	60.0	167	55.0
Range	797	15.0-90.0	630	30.0-90.0	167	15.0-90.0
EF <30%, no. (%)	797	21 (2.6)	630	0 (0.00)	167	21 (12.6)
Abnormal stress test result, No. (%)	716	104 (14.5)	562	0 (0.00)	154	104 (67.5)

CEA, Carotid endarterectomy; *CHF*, congestive heart failure; *EF*, ejection fraction; *NYHA*, New York Heart Association; *SD*, standard deviation.
[a]Home oxygen use, partial pressure of oxygen of <60 mm Hg, or forced expiratory volume in 1 second of <30%.

without that variable affecting our data. The patients were matched using a similar method as discussed previously. Supplementary Table IV (online only) and the Fig show the comparisons of outcomes among the propensity score-matched patients without contralateral endarterectomy as a risk factor. Again, no significant differences in the primary composite outcome or any of its components were observed. The stroke rate was higher for the patients with two or more high-risk factors (1.8% vs 2.1%; $P < .05$) but no strokes had occurred in the patients with one high-risk factor. High-risk patients with one risk factor were significantly more likely to have

Table IV. Anatomic variables after matching

Factor	Overall (N = 848)		Not high risk (n = 555)		High risk (n = 293)	
	Patients, No.	No. (%)	Patients, No.	No. (%)	Patients, No.	No. (%)
Head/neck radiation therapy	848	25 (2.9)	555	0 (0.00)	293	25 (8.5)
History of ipsilateral neck surgery	848	11 (1.3)	555	0 (0.00)	293	11 (3.8)
Contralateral nerve palsy	848	11 (1.3)	555	0 (0.00)	293	11 (3.8)
Redo CEA	848	36 (4.2)	555	0 (0.00)	293	36 (12.3)
Previous ipsilateral stent	848	5 (0.59)	555	0 (0.00)	293	5 (1.7)
Contralateral occlusion	848	79 (9.3)	555	0 (0.00)	293	79 (27.0)
Contralateral CEA	847	139 (16.4)	555	0 (0.00)	292	139 (47.6)
High bifurcation maneuver						
Nasotracheal intubation	848	7 (0.83)	555	0 (0.00)	293	7 (2.4)
Takedown digastric muscle division	848	52 (6.1)	555	0 (0.00)	293	52 (17.7)

CEA, Carotid endarterectomy.

Table V. Outcomes stratified by high-risk status after matching

Outcome	Not high risk (n = 424)	High risk (n = 424)	OR (95% CI)	*P* value[a]
Primary composite end point[b]	10 (2.4)	12 (2.8)	1.21 (0.51-2.83)	.67
Stroke	8 (1.9)	6 (1.4)	0.75 (0.26-2.18)	.59
Perioperative MI within 30 days	1 (0.24)	4 (0.94)	4.03 (0.45-36.42)	.21
30-Day mortality	3 (0.71)	3 (0.71)	1.00 (0.20-5.01)	.99
Secondary composite end point[c]	17 (4.0)	39 (9.2)	2.43 (1.35-4.37)	**.003**
Nerve injury/palsy	9 (2.1)	31 (7.3)	3.65 (1.71-7.78)	**<.001**
Temporary cranial nerve injury	7 (1.7)	24 (5.7)	3.59 (1.52-8.46)	**.004**
Permanent cranial nerve injury	2 (0.47)	7 (1.7)	3.54 (0.73-17.23)	.12
Surgical site infection	8 (1.9)	8 (1.9)	1.00 (0.37-2.70)	.99

CI, Confidence interval; *MI,* myocardial infarction; *OR,* odds ratio.
Data presented as number (%), unless indicated otherwise. Boldface *P* values represent statistical significance.
[a] *P* values correspond to univariate generalized mixed effect models accounting for matching.
[b] Stroke, death, and MI.
[c] Surgical site infection and cranial nerve injury.

experienced a secondary composite end point, nerve injury and temporary cranial nerve injury, compared with the group with no high-risk factors (4.1% vs 11.3%; $P < .05$). The group with two or more risk factors were significantly more likely to have experienced a nerve injury and temporary cranial nerve injury compared with the group with no high-risk factors.

DISCUSSION

In our single-institution experience, patients with anatomic and physiologic high-risk factors who had undergone CEA experienced an incidence of stroke, death, or MI within 30 days of 2.8%. This percentage was not significantly different from that for the matched non high-risk patients. Furthermore, the incidence of stroke between the high-risk and non high-risk patients was not significantly different (1.4% vs 1.9%). Despite the favorable composite outcome of stroke, death, and MI, our high-risk patients did experience a greater incidence of surgical site infection and temporary nerve injury. In addition, our analysis of patients with two or more high-risk factors showed no differences in stroke, death, or MI but did show a significantly greater incidence of temporary nerve injury. Furthermore, when omitting contralateral CEA as risk factor, we continued to find no differences in the composite end point between the standard-risk and high-risk patients.

The SAPPHIRE trial was the first randomized trial to assess CAS and CEA for high-risk patients.[5] The SAPPHIRE trial defined high-risk patients as those with clinically significant cardiac disease (ie, congestive heart failure, abnormal stress test result, the need for open heart surgery), severe pulmonary disease, contralateral occlusion, contralateral laryngeal nerve palsy, previous radical neck surgery or radiation, recurrent carotid disease after previous CEA, or age >80 years. These conditions have been adopted as conditions for which the CMS will reimburse providers for CAS.[8] In the CEA arm

Table VI. Outcomes stratified by high-risk status, including one and two or more factors, after matching

Outcome	Not high risk (n = 424)	High risk: One factor (n = 303)	High risk: Two or more factors (n = 121)	*P* value[a]
Primary composite end point[b]	10 (2.4)	9 (3.0)	3 (2.5)	.87
Stroke	8 (1.9)	4 (1.3)	2 (1.7)	.84
Perioperative MI within 30 days[c]	1 (0.24)	3 (0.99)	1 (0.83)	.45
30-Day mortality	3 (0.71)	3 (0.99)	0 (0.00)	.74
Secondary composite end point[d]	17 (4.0)	24 (7.9)	15 (12.4)	**.004**
Nerve injury/palsy	9 (2.1)	17 (5.6)	14 (11.6)	**<.001**
Temporary cranial nerve injury	7 (1.7)	13 (4.3)	11 (9.1)	**.002**
Permanent cranial nerve injury	2 (0.47)	4 (1.3)	3 (2.5)	.19
Surgical site infection	8 (1.9)	7 (2.3)	1 (0.83)	.62

MI, Myocardial infarction.
Data presented as number (%). Boldface *P* values represent statistical significance.
[a] *P* values from generalized mixed effect model.
[b] Stroke, death, and MI.
[c] Diagnosed by positive enzyme results with corresponding electrocardiographic changes.
[d] Surgical site infection and cranial nerve injury.

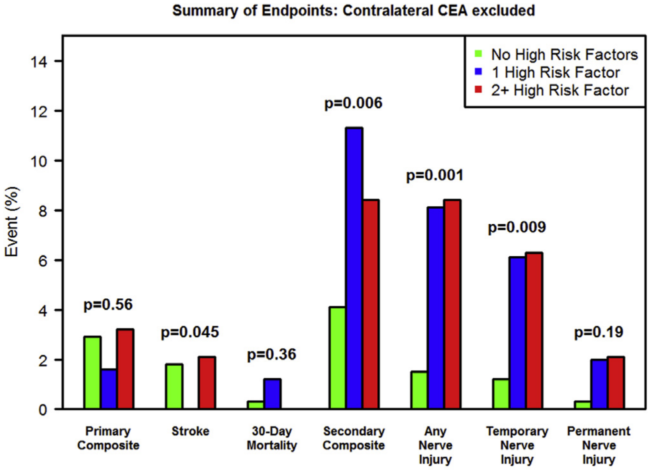

Fig. Outcomes stratified by high risk status and omitting contralateral carotid endarterectomy (*CEA*) after matching.

of the SAPPHIRE trial, 64% of the patients had had one high-risk factor, and the cumulative incidence of 30-day stroke, MI, and death was as high as 9.8% and 4.8% in the stenting arm. Ultimately, the SAPPHIRE trial concluded that CAS was not inferior to CEA for patients with severe carotid stenosis and preexisting high-risk conditions. In addition to the SAPPHIRE trial, multiple other CAS trials in the 2000s established efficacy and safety, leading to the adoption of CAS for high-risk patients.[10-12]

Since the establishment of the high-risk criteria, studies have both supported and questioned the efficacy of CEA for high-risk patients. We documented almost 20 years ago, a composite stroke, MI, and death rate of 7.4% in a high-risk CEA population.13 On solitary analysis, the stroke rate was 3.5%.[13] During the time the SAPPHIRE data were reported, a few studies documenting successful experience with high-risk endarterectomy were reported. The Mayo Clinic documented a stroke rate of 1.9% in high-risk anatomic and physiologic patients.[14] In addition, Reed et al[15] showed a combined 30-day stroke and death rate of 2.7% and 5.1% for patients with one or two high-risk factors, respectively. The stroke rate was 2.3% with two high-risk factors.[15] More recent studies of high-risk patients undergoing CEA and transfemoral CAS (TFCAS) have been performed. In a recent VQI review of 51,942 patients who had undergone CEA or CAS with high-risk CMS criteria, the overall 30-day stroke and death rate of the high-risk patients was 2.3%, which was lower than the 3.6% for those who had undergone CAS.[16] The stroke rate was 1.4%. Our results are similar to these data, with a high-risk stroke rate of 1.4%, and congruent with the investigators conclusions that high-risk CEA patients will have significantly better outcomes compared with high-risk CAS patients. Furthermore, the VQI review data showed, after logistic regression analysis, favorable outcomes for CEA compared with CAS for high-risk patients.

Most recently, Rao et al[17] analyzed 25,788 patients with high-risk physiologic and anatomic criteria who had undergone CEA from 2011 to 2017 using the National Surgical Quality Improvement Program (NSQIP) database. They documented a stroke and death rate of 4.6% in the physiologic high-risk patients and 3.1% in the high-risk anatomic patients. Furthermore, when stratifying the results by asymptomatic and symptomatic disease, they reported similar findings, with significantly greater rates of stroke and death compared with normal risk patients, with the largest difference found in asymptomatic physiologic high-risk patients.[17] Our results of a combined stroke, death, and MI rate of 2.8% at 30 days compared favorably with those of the NSQIP study. The NSQIP study included 51% and 46% of symptomatic patients in the physiologic and anatomic groups, respectively, compared with only 27% of symptomatic patients in our study. Furthermore, which specific high-risk criteria were found for each patient was not available in the NSQIP study because the module does not collect such data.[17] The investigators concluded that other methods of revascularization should be considered for asymptomatic disease because the stroke rate was greater than the SVS recommendation of 3%.[9]

In 2015, Bennett et al[18] used the NSQIP database to report the incidence of nerve injury in 3762 CEA cases. The overall incidence of injury was 2.2%. The study did not indicate whether the injuries had been permanent or temporary. The independent risk factors for nerve injury were operative time, the need for reoperation, the presence of a bleeding disorder, and older age.[18] Despite our favorable primary composite end point of stroke, death, and MI, we did find a composite secondary end point of surgical site infection and temporary nerve injury rate of 11.3% and 8.4% in the single and multiple high-risk patients, respectively, when contralateral CEA was included in the standard-risk group. When surgical site infection and cranial nerve injury were separated from each other, the temporary nerve injury or palsy rate was 6.3%. Although our nerve injury rate was greater than that reported by the NSQIP study,[17] we evaluated the outcomes for high-risk patients in contrast to evaluating all CEA cases as in the NSQIP study. We did not record the operating room times; however, redo CEA does tend to require a longer operating room time and can involve aggressive retraction, leading to temporary nerve injury. Our discussion would not be complete without mentioning TCAR. The initial ROADSTER (safety and efficacy study for reverse flow used during carotid artery stenting procedure) trial of 141 patients documented a stroke rate of 1.4%, which was the lowest of any CAS trial.[19] Standard high-risk criteria were used in the trial. Major adverse events occurred in only 3.5% of the patients.[19] A recent review of the VQI database for TCAR showed a combined stroke, death, and MI rate of 2.2% for 638 patients. The total neurological events rate was 1.9%.[15] These data were even more favorable than our results of 1.6% and 3.2% for those with one and two or more high-risk factors, respectively. Although the power of TCAR is evolving, it has its own limitations, and the role for high-risk CEA will persist. The ENROUTE transcarotid neuroprotection system (Silk Road Medical Inc, Sunnyvale, Calif) instructions for use dictate a minimum of 5 cm of common carotid distance from the clavicle to the carotid bifurcation and a common carotid diameter of 6 mm.[20] Other characteristics that could exclude patients from TCAR are lesions with intraluminal thrombus, the requirement for more than two stents, a string sign or occlusion of the target vessel, and lesions resistant to angioplasty. Wu et al[21] studied the anatomic limitations of TCAR in 236 carotid arteries. They found that 68% of their reviewed patients were anatomically eligible for TCAR, with 75% having an adequate clavicle to bifurcation length. In addition, about one quarter of the patients were not eligible for TFCAS.[21]

The present study had limitations. First, we performed a retrospective review of a single-institution experience. In addition, as a tertiary referral center, the results from our study might not be generalizable to other institutions and communities. Specific aspects of our high-risk patients also deserve discussion. Our physiologic high-risk patients were those with a positive stress test result, which included active and nonactive ischemia. In addition, as a surrogate for high carotid bifurcation, aspects of the surgical procedure were included instead. These included nasotracheal intubation, digastric muscle division, and mobilization of the hypoglossal nerve. Finally, the performance of a contralateral CEA was included as a high-risk feature; however, in our previous analysis, we excluded had excluded this as a risk factor.

CONCLUSIONS

In the present study, we have reported our 10-year experience of high-risk patients with carotid disease who were considered for both CEA and TFCAS but underwent CEA. Our results have documented that patients with high-risk factors can safely undergo CEA with a composite end point of stroke, death, and MI rate of 2.8% and stroke rate of 1.4%. In addition, patients with multiple high-risk factors had a stroke rate of 1.7%. Although the emergence of TCAR will decrease the need for TFCAS, patients who do not meet the instructions for use for TCAR will continue and will require high-risk CEA.

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AUTHOR CONTRIBUTIONS

Conception and design: ND, SL, CS, JR, LK, FC
Analysis and interpretation: ND, SL, FC
Data collection: ND
Writing the article: ND, SL, FC
Critical revision of the article: ND, SL, CS, JR, LK, FC
Final approval of the article: ND, SL, CS, JR, LK, FC
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Supplementary Table I (online only). Demographics stratified by inclusion

Factor	Excluded (n = 141)		Included (n = 1152)		*P* value
	Patients, No.	Mean ± SD or No. (%)	Patients, No.	Mean ± SD or No. (%)	
BMI, kg/m^2	141	28.1 ± 5.8	1151	28.8 ± 6.7	.19[a]
Age, years	141	67.1 ± 11.1	1152	69.8 ± 9.7	**.006**[a]
Sex	141		1152		.91[b]
Male		93 (66.0)		754 (65.5)	
Female		48 (34.0)		398 (34.5)	
Tobacco use	141		1150		**.005**[b]
Never		37 (26.2)		217 (18.9)	
Former		68 (48.2)		717 (62.3)	
Current		36 (25.5)		216 (18.8)	
HTN	132	122 (92.4)	1152	1132 (98.3)	**<.001**[c]
NYHA class III/IV CHF	128	7 (5.5)	1151	75 (6.5)	.65[b]
CKD	131	16 (12.2)	1151	154 (13.4)	.71[b]
ESRD	16	0 (0.00)	154	22 (14.3)	.23[c]
Severe pulmonary disease[d]	128	2 (1.6)	1152	21 (1.8)	.99[c]
NIDDM	131	30 (22.9)	1151	353 (30.7)	.066[b]
IDDM	30	13 (43.3)	352	130 (36.9)	.49[b]

BMI, Body mass index; *CHF*, congestive heart failure; *CKD*, chronic kidney disease; *ESRD*, end-stage renal disease; *HTN*, hypertension; *IDDM*, insulin-dependent diabetes mellitus; *NIDDM*, non insulin-dependent diabetes mellitus; *NYHA*, New York Heart Association; *SD*, standard deviation.
Boldface *P* values represent statistical significance.
[a]Satterthwaite *t*-test.
[b]Pearson's χ^2 test.
[c]Fisher's exact test.
[d]Home oxygen use, partial pressure of oxygen of <60 mm Hg, or forced expiratory volume in 1 second of <30%.

Supplementary Table II (online only). Demographics stratified by high-risk status before matching

Factor	Overall (n = 1152)		Not high risk (n = 702)		High risk (n = 450)		*P* value
	Patients, No.	Mean ± SD or No. (%)	Patients, No.	Mean ± SD or No. (%)	Patients, No.	Mean ± SD or No. (%)	
BMI, kg/m^2	1151	28.8 ± 6.7	701	28.5 ± 6.7	450	29.1 ± 6.7	.17[a]
Age, years	1152	69.8 ± 9.7	702	70.2 ± 9.6	450	69.3 ± 9.8	.12[a]
Sex	1152		702		450		.57[b]
Male		754 (65.5)		455 (64.8)		299 (66.4)	
Female		398 (34.5)		247 (35.2)		151 (33.6)	
Tobacco use	1150		701		449		**<.001**[b]
Never		217 (18.9)		157 (22.4)		60 (13.4)	
Former		717 (62.3)		423 (60.3)		294 (65.5)	
Current		216 (18.8)		121 (17.3)		95 (21.2)	
HTN	1152	1132 (98.3)	702	686 (97.7)	450	446 (99.1)	.078[b]
CKD	1151	154 (13.4)	701	78 (11.1)	450	76 (16.9)	**.005**[b]
Diabetes	1151	353 (30.7)	702	207 (29.5)	449	146 (32.5)	.28[b]
Stent in place	1144	17 (1.5)	699	8 (1.1)	445	9 (2.0)	.23[b]
Neurologic symptoms	1146		698		448		.091[b]
TIA or amaurosis		267 (23.3)		177 (25.4)		90 (20.1)	
Stroke		55 (4.8)		30 (4.3)		25 (5.6)	
Asymptomatic		824 (71.9)		491 (70.3)		333 (74.3)	
Surgical technique	1144		695		449		.36[b]
Patch		1079 (94.3)		652 (93.8)		427 (95.1)	
Eversion		65 (5.7)		43 (6.2)		22 (4.9)	
Shunt used	1149	585 (50.9)	701	334 (47.6)	448	251 (56.0)	**.006**[b]
Stump pressure measured	1151	493 (42.8)	701	318 (45.4)	450	175 (38.9)	**.030**[b]
Additional proximal intervention	1148	22 (1.9)	698	9 (1.3)	450	13 (2.9)	.054[b]
Antiplatelet drug							
Aspirin	1152	1084 (94.1)	702	659 (93.9)	450	425 (94.4)	.69[b]
Clopidogrel (Plavix)	1152	282 (24.5)	702	148 (21.1)	450	134 (29.8)	**<.001**[b]

BMI, Body mass index; *CKD,* chronic kidney disease; *HTN,* hypertension; *SD,* standard deviation; *TIA,* transient ischemic attack.
Boldface *P* values represent statistical significance.
[a] *t*-test.
[b] Pearson's χ^2 test.

Supplementary Table III (online only). Demographics stratified by high-risk status after matching

Factor	Overall (N = 848)		Not high risk (n = 424)		High risk (n = 424)		*P* value
	Patients, No.	Mean ± SD or No. (%)	Patients, No.	Mean ± SD or No. (%)	Patients, No.	Mean ± SD or No. (%)	
BMI, kg/m^2	847	29.0 ± 6.8	423	29.0 ± 7.4	424	29.0 ± 6.2	.90[a]
Age, years	848	69.5 ± 9.8	424	69.4 ± 10.0	424	69.5 ± 9.7	.95[b]
Sex	848		424		424		.61[c]
Male		569 (67.1)		288 (67.9)		281 (66.3)	
Female		279 (32.9)		136 (32.1)		143 (33.7)	
Tobacco use	846		423		423		.88[c]
Never		121 (14.3)		62 (14.7)		59 (13.9)	
Former		547 (64.7)		270 (63.8)		277 (65.5)	
Current		178 (21.0)		91 (21.5)		87 (20.6)	
HTN	848	843 (99.4)	424	423 (99.8)	424	420 (99.1)	.37[d]
CKD	848	122 (14.4)	424	61 (14.4)	424	61 (14.4)	.99[c]
Diabetes	847	264 (31.2)	424	131 (30.9)	423	133 (31.4)	.86[c]
Stent in place	844	15 (1.8)	423	6 (1.4)	421	9 (2.1)	.43[c]
Neurologic symptoms	843		421		422		.88[c]
TIA or amaurosis		179 (21.2)		91 (21.6)		88 (20.9)	
Stroke		43 (5.1)		20 (4.8)		23 (5.5)	
Asymptomatic		621 (73.7)		310 (73.6)		311 (73.7)	
Surgical technique	844		420		424		.85[c]
Patch		799 (94.7)		397 (94.5)		402 (94.8)	
Eversion		45 (5.3)		23 (5.5)		22 (5.2)	
Shunt used	846	454 (53.7)	424	221 (52.1)	422	233 (55.2)	.37[c]
Stump pressure measured	847	337 (39.8)	423	169 (40.0)	424	168 (39.6)	.92[c]
Additional proximal intervention	845	20 (2.4)	421	7 (1.7)	424	13 (3.1)	.18[c]
Antiplatelet drug							
Aspirin	848	796 (93.9)	424	397 (93.6)	424	399 (94.1)	.77[c]
Clopidogrel (Plavix)	848	235 (27.7)	424	122 (28.8)	424	113 (26.7)	.49[c]

BMI, Body mass index; *CKD,* chronic kidney disease; *HTN,* hypertension; *SD,* standard deviation; *TIA,* transient ischemic attack.
[a] Satterthwaite *t*-test.
[b] *t*-test.
[c] Pearson's χ^2 test.
[d] Fisher's exact test.

Supplementary Table IV (online only). Outcomes stratified by high-risk status, including one and two or more factors, omitting contralateral carotid endarterectomy (CEA), after matching

		High risk		
Factor	**Not high risk (n = 342)**	**One factor (n = 247)**	**Two or more factors (n = 95)**	***P* value**
Primary composite end point[a]	10 (2.9)	4 (1.6)	3 (3.2)	.56[b]
Stroke	6 (1.8)	0 (0.00)	2 (2.1)	**.045**[c]
Perioperative MI within 30 days	3 (0.88)	2 (0.81)	1 (1.05)	.98[b]
30-Day mortality	1 (0.29)	3 (1.2)	0 (0.00)	.36[b]
Secondary composite end point[d]	14 (4.1)	28 (11.3)	8 (8.4)	**.006**[b]
Nerve injury/palsy	5 (1.5)	20 (8.1)	8 (8.4)	**.001**[b]
Temporary cranial nerve injury	4 (1.2)	15 (6.1)	6 (6.3)	**.009**[b]
Permanent cranial nerve injury	1 (0.29)	5 (2.0)	2 (2.1)	.19[c]
Surgical site infection	9 (2.6)	8 (3.2)	0 (0.00)	.22[c]

MI, Myocardial infarction.
Data presented as number (%). Boldface *P* values represent statistical significance.
[a]Stroke, death, and MI.
[b]Generalized mixed effect model.
[c]Fisher's exact test.
[d]Surgical site infection and cranial nerve injury.