

ORIGINAL RESEARCH

# Procedural Safety Comparison Between Transcarotid Artery Revascularization, Carotid Endarterectomy, and Carotid Stenting: Perioperative and 1-Year Rates of Stroke or Death

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**BACKGROUND:** Transcarotid artery revascularization (TCAR) was approved by the Food and Drug Administration in 2015 for patients with carotid artery stenosis. However, no randomized trial to evaluate TCAR has been performed to date, and previous reports have important limitations. Accordingly, we measured stroke or death after TCAR compared with carotid endarterectomy (CEA) and transfemoral carotid artery stenting (TF-CAS).

**METHODS AND RESULTS:** We used the Vascular Quality Initiative registry to study patients who underwent TCAR, CEA, or TF-CAS from September 2016 to June 2021. Our primary outcomes were perioperative and 1-year stroke or death. We used logistic regression for risk adjustment for perioperative outcomes and Cox regression for risk adjustment for 1-year outcomes. We used a 2-stage residual inclusion instrumental variable (IV) method to adjust for selection bias and other unmeasured confounding. Our instrument was a center's preference to perform TCAR versus CEA or TF-CAS. We performed a subgroup analysis stratified by presenting neurologic symptoms. We studied 21 234 patients who underwent TCAR, 82 737 who underwent CEA, and 14 595 who underwent TF-CAS across 662 centers. The perioperative rate of stroke or death was 2.0% for TCAR, 1.7% for CEA, and 3.7% for TF-CAS ( $P<0.001$ ). Compared with TCAR, the IV-adjusted odds ratio of perioperative stroke or death for CEA was 0.74 (95% CI, 0.55–0.99) and for TF-CAS was 1.66 (95% CI, 0.99–2.79). Results were similar among both symptomatic and asymptomatic patients. The 1-year rate of stroke or death was 6.4% for TCAR, 5.2% for CEA, and 9.7% for TF-CAS ( $P<0.001$ ). Compared with TCAR, the IV-adjusted hazard ratio of 1 year stroke or death for CEA was 0.97 (95% CI, 0.80–1.17), and for TF-CAS was 1.45 (95% CI, 1.04–2.02). IV analysis further demonstrated that symptomatic patients with carotid stenosis had the lowest 1-year likelihood of stroke or death with TCAR (compared with TCAR, symptomatic IV-adjusted hazard ratio for CEA: 1.30 [95% CI, 1.04–1.64], and TF-CAS: 1.86 [95% CI, 1.27–2.71]).

**CONCLUSIONS:** Perioperative stroke or death was greater following TCAR when compared with CEA. However, at 1 year there was no statistically significant difference in stroke or death between the 2 procedures. TCAR performed favorably compared with TF-CAS at both time points. Although CEA remains the gold standard procedure for patients with carotid stenosis, TCAR appears to be a safe alternative to CEA and TF-CAS when used selectively and may be useful when treating symptomatic patients.

**Key Words:** carotid endarterectomy ■ carotid revascularization ■ carotid stenting ■ CEA ■ instrumental variable ■ TCAR ■ TF-CAS

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## CLINICAL PERSPECTIVE

### What Is New?

- This is the first large-scale study comparing transcatheter carotid artery revascularization (TCAR), carotid endarterectomy, and transfemoral carotid artery stenting using instrumental variable methodology.
- Perioperative stroke or death was greater following TCAR when compared with carotid endarterectomy. At 1 year, there was no statistically significant difference in stroke or death between the 2 procedures. TCAR performed favorably when compared with transfemoral carotid artery stenting at both time points.
- Symptomatic patients with carotid stenosis demonstrated the most favorable results at 1 year with TCAR.

### What Are the Clinical Implications?

- Although carotid endarterectomy remains the gold standard procedure for treating carotid stenosis, TCAR appears to be a safe alternative to carotid endarterectomy and transfemoral carotid artery stenting.
- TCAR may be useful in treating symptomatic patients with carotid stenosis.

## Nonstandard Abbreviations and Acronyms

<b>BMT</b>	best medical therapy
<b>CEA</b>	carotid endarterectomy
<b>TCAR</b>	transcatheter carotid artery revascularization
<b>TF-CAS</b>	transfemoral carotid artery stenting
<b>VQI</b>	Vascular Quality Initiative

Carotid artery stenosis is a major risk factor for stroke, the fifth leading cause of death in the United States.<sup>1</sup> The mainstay for stroke-risk reduction for patients with carotid stenosis is noninvasive best medical therapy (BMT), including risk factor identification and amelioration using lifestyle interventions and appropriate medications.<sup>2-4</sup> In addition to BMT, carotid endarterectomy (CEA) has been demonstrated repeatedly to incrementally reduce the risk of stroke among appropriately selected patients (Table 1).<sup>5-9</sup>

Two additional procedures have since been widely adopted in the treatment of carotid occlusive disease, under the assumption that they too will provide a stroke-reduction benefit over BMT. In the 2000s the Food and Drug Administration approved transfemoral carotid artery stenting (TF-CAS) to treat patients with carotid stenosis, despite mixed evidence surrounding

its periprocedural risks compared with CEA.<sup>10-14</sup> More recently, in 2015 the Food and Drug Administration approved a third procedure to treat high-risk patients, called transcatheter carotid artery revascularization (TCAR).<sup>15,16</sup> This approval was granted in the absence of a dedicated randomized trial comparing it to BMT or other procedures. TCAR has since been rapidly adopted into practice and now accounts for ≈1 in 5 carotid procedures across the 247 US centers that offer it as of June 2020.<sup>17</sup> Moreover, in May 2022 the approved indications were broadened to include standard-risk patients.<sup>18</sup>

However, despite its rapid uptake, TCAR's rightful place in the treatment armamentarium of carotid stenosis remains unknown.<sup>3,4</sup> With no completed or enrolling randomized trial underway, the evaluation of TCAR currently rests exclusively on observational studies comparing TCAR with CEA and TF-CAS. It should be noted that prior reports comparing TCAR to CEA and TF-CAS have important methodologic limitations, and have not accounted for selection bias and other forms of unmeasured confounding.<sup>17,19-21</sup> As such, optimal procedure selection remains a focus of controversy, and the quality of evidence to guide the use of TCAR in clinical practice remains low.<sup>3,4</sup>

Therefore, it was our objective to compare results after TCAR, CEA, and TF-CAS accounting for selection bias and other forms of unmeasured confounding. To do this, we used an instrumental variable (IV) method for risk-adjustment. IV techniques are the optimal methods available to account for unmeasured factors in situations where randomization is not available, such as with TCAR.<sup>22</sup> Our hypothesis was that TCAR is a viable procedural alternative to CEA or TF-CAS in the treatment of carotid stenosis. Our results add important information to guide clinical decision making for patients being considered for TCAR, CEA, or TF-CAS.

## METHODS

### Human Subjects Protection

This study was approved by the Institutional Review Board at Dartmouth-Hitchcock Medical Center. All data were deidentified before analysis, and therefore the need for consent was waived. Data are available upon application and peer-review approval from the VQI (Vascular Quality Initiative; [www.vqi.org](http://www.vqi.org)).

### Data Source

We used the VQI registry to study patients treated with TCAR, CEA, or TF-CAS. The VQI is an international quality improvement registry for the Society for Vascular Surgery and includes more than 900 centers in the United States, Europe, and Canada ([www.vqi.org](http://www.vqi.org)). As part of TCAR's Food and Drug Administration

**Table 1. Patient Subgroups That Have a Stroke-Risk Reduction Benefit With CEA Over BMT Alone Based on Historical Randomized Clinical Trials.**<sup>5-9</sup>

1	Symptomatic women with 70%–99% carotid stenosis undergoing surgery within 2–3 weeks of their same-sided neurologic event with a 3–5-year life expectancy
2	Symptomatic men with 70%–99% carotid stenosis undergoing surgery within 3 months of an ipsilateral neurologic event with a 3–5-year life expectancy
3	Symptomatic men with 50%–69% carotid stenosis undergoing surgery within 2–3 wks of their same-sided neurologic event with a 3–5-year life expectancy
4	Asymptomatic men with 60%–99% stenosis aged 75–80 years with a 5-year life expectancy who were free of any major life-threatening condition

BMT indicates best medical therapy; and CEA, carotid endarterectomy.

approval process, the TCAR Surveillance Project was started, which requires that all patients who undergo the procedure be captured by the VQI registry on a prospective basis. Audits of device sales records indicate that more than 95% of TCAR procedures are included in the Surveillance Project, which began in September 2016.<sup>23</sup> Therefore, we analyzed data surrounding the 3 procedures from September 2016 (start of the TCAR Surveillance Project) until June 2021 (end of data availability).

### Inclusion and Exclusion Criteria

All patients in the VQI registry who underwent TCAR, CEA, or TF-CAS during the study interval were considered for inclusion. We excluded patients who underwent TCAR, CEA, or TF-CAS for reasons other than atherosclerotic disease or neointimal hyperplasia (eg, for traumatic injury or arterial dissection). We excluded patients who underwent TCAR, CEA, or TF-CAS combined with another procedure (eg, as an adjunct to an intracranial procedure or combined with coronary artery bypass grafting).

### Primary Exposure and Assumptions

Our primary exposure was procedure type: TCAR, CEA, or TF-CAS. We assumed that the associated risks and benefits of TCAR, CEA, or TF-CAS, respectively, in addition to BMT, were discussed by the treating clinician with each patient, and the decision was then made to undertake a procedure. It was not our objective to imply anything about the indications for a specific procedure or the respective efficacy compared with BMT in reducing the risk of stroke. These questions will optimally be addressed by currently enrolling trials.<sup>24</sup> However, because TCAR is not included in these studies, observational research remains an important component of assessing TCARs safety profile.

### Primary Outcomes and Definitions

Our primary outcome was a composite of any stroke or death. We determined outcomes in the perioperative (in-hospital) period, and at 1 year. Secondary

outcomes included any stroke alone (defined by the VQI registry as new clinical neurologic symptoms lasting more than 24 hours after the index procedure), any ipsilateral stroke (ipsilateral to the index carotid procedure), death alone (as assessed from the Social Security Death Index), cranial nerve injury (any clinically detected neurologic changes that were deemed related to the technical conduct of the procedure rather than an ischemic or hemorrhagic cerebral event), transient ischemic attack (any transient neurologic event resolving within 24 hours without evidence of stroke on imaging), myocardial infarction (any rise in cardiac biomarkers, clinical ischemic symptoms, new electrocardiographic changes, or new wall motion abnormalities), reperfusion syndrome (symptoms clinically attributed to increased cerebral flow at the discretion of the treating clinician), dysrhythmia (any postoperative change in cardiac rhythm requiring treatment with medications or cardioversion), acute heart failure (pulmonary edema requiring treatment or monitoring in an intensive care unit or step-down unit), operative time (time from skin incision to procedure completion), reoperation or additional procedures to control bleeding (percutaneous or surgical procedures to control bleeding or hematoma evacuation that were caused by the index procedure), hospital length of stay more than 1 day, and technical failure of the intended procedure (the intended procedure was aborted and a different procedure may or may not have been performed).

### Statistical Analysis

Patient characteristics and outcomes were calculated out of the known (nonmissing) values for each variable. We summarized continuous measures with means and SDs or medians with interquartile ranges as appropriate and compared them with Student's *t* test or the Wilcoxon rank-sum test as appropriate. We report proportions as percentages and compared them with chi-square analysis. We used Kaplan–Meier estimation for 1-year outcomes.

We created a logistic regression model to estimate the adjusted odds ratio (OR) of stroke or death for TCAR versus CEA and TF-CAS in the perioperative

period. We then created a Cox-proportional hazards model to estimate the adjusted hazard ratio (HR) of stroke or death for TCAR versus CEA and TF-CAS over time. In both models, we included all variables in [Table 2](#) in the regression, and we additionally adjusted for the association of the hospital center and of calendar time. TCAR served as the referent value for all point estimates. We performed a subanalysis of the primary outcomes stratified by the presence or absence of focal neurologic symptoms at the time of the procedure (ie, asymptomatic or symptomatic patients with carotid stenosis). Symptomatic status was defined as the presence of temporary or permanent focal neurologic symptoms upon evaluation by the attending proceduralist. We conducted sensitivity analyses including percent carotid stenosis as a covariate and adjusting for the association of the proceduralist as a random effect.

### Instrumental Variable Analysis

To account for selection bias and other unmeasured confounding when modeling whether or not stroke or death occurs, we employed an IV procedure designed for nonlinear models known as 2-stage residual inclusion.<sup>25</sup> The proposed IV analysis identifies patients who would have undergone TCAR at one institution, but CEA or TF-CAS at another, in relation to the value of the instrument.<sup>22</sup> Under the assumptions of the model, the IV analysis accounts for unmeasured and unmeasurable confounding between the type of procedure and the outcome of stroke or death in patients who are eligible for both procedures.<sup>22,26,27</sup>

We conducted 1 set of models for the perioperative results, and 1 for the 1-year results. For the perioperative results, in the first stage of the method a linear regression model regresses procedure type on the instrument and all measured potential confounding variables. In the second stage of the method, a logistic regression model regresses the binary dependent variable indicator for stroke or death on procedure type and all potential measured confounders and the residuals from the first stage model. Under the IV assumptions, controlling for the residuals serves the purpose of approximately controlling for the net effect of any unmeasured confounders.

We used a similar technique for the 1-year results. To account for the greater proportion of censored observations at 1 year of follow-up, we used a recently developed 2-stage residual inclusion method adapted for time-to-event outcomes analyzed using the Cox model.<sup>28–31</sup> The first stage is the same as for the perioperative outcome. In the second stage the independent variables are the procedure type, the observed covariates, and the residuals from the first stage, and the dependent variable is time to stroke or death, which could be observed or censored. In addition, the

predictor side of the second stage equation includes a frailty term which accounts for the part of the residual from the first stage that is independent of the unmeasured confounders and whose inclusion helps the residual to control for unmeasured confounders. Therefore, the second stage of the procedure involves a Cox proportional hazards frailty model, not the standard Cox model.<sup>28,29</sup>

Our proposed instrument was a center's preference to perform TCAR versus other procedures for carotid revascularization.<sup>32</sup> We calculated this preference as the proportion of TCAR out of the total procedures performed at a given center in the 6 months before the index procedure for each patient, similar to prior work by us and others.<sup>28–32</sup> The F-statistic was strong for both of these instruments individually and overall ([Figure S1](#)). More details on the IV procedures are available in [Data S1](#).

## RESULTS

### Patients

We studied 21 234 patients who underwent TCAR, 82 737 who underwent CEA, and 14 595 who underwent TF-CAS across 662 centers ([Table 2](#); [Figure S2](#)). Patients were  $\approx 70$  years of age (TCAR: mean  $73.2 \pm 9.0$  years, CEA: mean  $70.7 \pm 9.5$  years, TF-CAS: mean  $70.2 \pm 9.6$  years,  $P < 0.001$ ); and one third were female (TCAR: 36.4%, CEA: 39.2%, TF-CAS: 35.5%,  $P < 0.001$ ). Approximately half of patients presented with neurologic symptoms, but this was most common for TF-CAS (TF-CAS 65.7%, versus TCAR: 49.6%, CEA 50.1%,  $P < 0.001$ ). Patients who underwent TCAR or TF-CAS were more likely to have had a prior ipsilateral carotid procedure (TCAR: 14.4%, TF-CAS 20.0%, versus CEA 1.8%,  $P < 0.001$ ) and to be on dual antiplatelet therapy (TCAR: 80.5%, TF-CAS 70.8%, versus CEA 31.6%,  $P < 0.001$ ).

The indication for TCAR and TF-CAS was an anatomic high-risk lesion in 44.6% and 41.6% of cases respectively ([Table 2](#), see legend for high-risk definitions).<sup>33</sup> Most carotid procedures were performed for severe ( $\geq 70\%$ ) carotid stenosis (TCAR: 83.2%, CEA: 77.7%, TF-CAS: 83.2%,  $P < 0.001$ ). Most TCAR and CEA procedures were performed under general anesthesia (TCAR: 82.4%, CEA 93.2%, versus TF-CAS 20.0%,  $P < 0.001$ ).

### Stroke or Death: Perioperative

The perioperative rate of stroke or death was 2.0% for TCAR, 1.7% for CEA, and 3.7% for TF-CAS ( $P < 0.001$ ; [Table 3](#)). Compared with TCAR, the adjusted OR of perioperative stroke or death was 0.82 (95% CI, 0.72–0.95) for CEA, and 1.41 (95% CI, 1.18–1.69) for TF-CAS ([Figure 1](#)). After IV adjustment for unmeasured

**Table 2. Patient Characteristics**

	TCAR	CEA	TF-CAS	TCAR versus CEA	TCAR versus TF-CAS
Variable	n=21 234	n=82 737	n=14 595	P value	P value
Characteristic, % (unless otherwise noted)					
Age, y (SD)	73.2 (9.0)	70.7 (9.5)	70.2 (9.6)	<0.001	<0.001
Female sex	36.4	39.2	35.5	<0.001	0.089
Obesity (BMI, kg/m <sup>2</sup> >30)	33.4	34.6	35.7	0.001	<0.001
Race					
White	90.4	89.4	<0.001	<0.001	<0.001
Black	0.4	4.7	<0.001	<0.001	0.296
Other Race*	9.1	5.8	<0.001	<0.001	<0.001
Neurologic symptoms	49.6	50.1	65.7	0.204	<0.001
CAD	51.4	26.4	46.0	<0.001	<0.001
CHF	17.0	11.5	17.3	<0.001	0.554
Coronary revascularization	39.9	34.1	37.1	<0.001	<0.001
Hypertension	90.9	89.6	89.1	<0.001	<0.001
COPD	25.6	23.1	26.9	<0.001	0.011
Home oxygen	3.4	2.2	2.9		0.016
Diabetes	38.4	36.7	39.5	<0.001	0.050
Chronic kidney disease (creatinine >1.7 mg/dL)	6.2	5.4	6.2	<0.001	0.997
Smoking					
Never	26.9	26.2	26.0	0.030	0.054
Active	22.1	25.0	27.4	<0.001	<0.001
Prior	50.9	48.8	46.4	<0.001	<0.001
Prior ipsilateral carotid procedure	14.4	1.8	20.0	20.0	<0.001
Prior contralateral carotid procedure	14.2	13.5	13.2	0.005	0.010
Preoperative medications					
Aspirin	89.8	84.3	86.1	<0.001	<0.001
P2y12 inhibitor	87.6	37.4	77.4	<0.001	<0.001
Dual antiplatelet	80.5	31.6	70.8	<0.001	<0.001
Statin	89.7	85.4	83.5	<0.001	<0.001
Beta blocker	56.5	54.1	53.1	<0.001	<0.001
Anticoagulation	14.4	6.6	13.2	<0.001	0.001
Angiotensin-converting enzyme inhibitor	53.1	53.3	49.8	0.621	<0.001
Functional status					<0.001
Ambulatory	94.7	98.6	94.9	<0.001	0.579
Wheelchair	3.7	1.2	4.0	<0.001	0.059
Confined to bed	0.1	0.1	0.2	<0.028	0.098
Insurance					
Medicare	69.21	53.02	59.79	<0.001	<0.001
Medicaid	3.11	3.88	4.92	<0.001	<0.001
Private	26.54	35.86	33.45	<0.001	<0.001
Non US, or none	26.54	35.86	33.45	<0.001	<0.001

Variable definitions: age, age in years at the time of the index procedure; female, sex at birth; obesity, BMI >30 at the time of the index procedure; race, self-reported where available, otherwise identified from the medical record; neurologic symptoms, see article text; CAD, history of coronary disease on medical record review; CHF, history of heart failure on medical record review; COPD, history of COPD on medical record review; coronary revascularization, any prior coronary bypass or percutaneous revascularization procedure; hypertension, based on medical record review or any blood pressure documented >130/80mmHg; smoking, patient reported where available, otherwise based on medical record review; prior carotid procedure, any history of a carotid procedure on medical record review; preoperative medications, medications being taken within 36 hours of the procedure; functional status, based on medical record review; insurance, based on medical record review.

BMI indicates body mass index; CAD, coronary artery disease; CEA, carotid endarterectomy; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; TCAR, transcarotid artery revascularization; and TF-CAS, transfemoral carotid artery stenting.

\*This category includes: Asian, American Indian, Alaskan Native, Native Hawaiian or Pacific Islander, and More than One Race.

**Table 3. Procedural Characteristics and Perioperative Outcomes**

	TCAR	CEA	TF-CAS	TCAR versus CEA	TCAR versus TF-CAS
Variable	n=21234	n=82737	n=14595	P value	P value
Procedural characteristics, %					
High risk					
Anatomic	44.6	3.9	41.6	<0.001	<0.001
Medical	54.1	NA	38.0		<0.001
Refused for surgery	21.0	NA	22.2		0.009
Degree of stenosis					
<50%	3.2	3.9	4.0	<0.001	<0.001
50–69%	12.0	14.5	11.0	<0.001	0.004
70–79%	32.3	34.3	28.7	<0.001	<0.001
80–99%	49.5	42.1	49.9	<0.001	0.535
Occluded	1.5	1.3	4.6	0.011	<0.001
Urgency					
Elective	88.8	86.7	74.5	<0.001	<0.001
Urgent	11.0	12.7	20.7	<0.001	<0.001
Emergent	0.2	0.6	4.8	<0.001	<0.001
American Society of Anesthesiologists class					
1	0.6	0.5	1.5	0.042	<0.001
2	3.2	3.5	15.0	0.015	<0.001
3	68.0	74.2	58.4	<0.001	<0.001
4	27.5	21.6	17.1	<0.001	<0.001
5	0.0	0.0	0.3	0.638	<0.001
Anesthetic type					
General	82.4	93.2	20.0	<0.001	<0.001
Local/Regional	17.5	6.8	79.8	<0.001	<0.001
Procedural anticoagulation					
Protamine	98.9	99.1	96.1	<0.001	<0.001
Balloon angioplasty after stenting	41.0	0.0	63.7	<0.001	<0.001
Perioperative outcomes, % (unless otherwise noted)					
Stroke/death	2.0	1.7	3.7	0.007	<0.001
Stroke	1.4	1.2	2.2	0.058	<0.001
Ipsilateral stroke	1.2	0.9	1.8	0.001	<0.001
TIA	0.6	0.5	0.8	0.100	0.003
In hospital death	0.4	0.3	1.1	0.005	<0.001
30-d death	0.8	0.7	1.9	0.098	<0.001
MI	0.5	0.7	0.5	0.086	0.543
Reperfusion syndrome	0.2	0.1	0.8	0.040	<0.001
Dysrhythmia	1.4	1.3	1.6	0.083	0.178
Acute heart failure	0.3	0.3	0.4	0.791	0.177
Cranial nerve injury	0.2	2.5	0.0	<0.001	<0.001
Operative time, median [interquartile range]	66 [51–85]	110 [86–139]	61 [45–85]	<0.001	<0.001
Reoperation for bleeding	0.9	1.6	0.4	<0.001	<0.001
Length of stay >1 d	29.2	31.1	35.5	<0.001	<0.001
Technical failure	0.5	0.0	0.6	<0.001	0.017

High-risk criteria include anatomic: a contralateral carotid artery occlusion, tandem stenoses >70%, "high" carotid lesion, restenosis after CEA, bilateral carotid stenosis requiring treatment, or a hostile neck; clinical: patient age>75 years, >2-vessel coronary artery disease or unstable angina, New York Heart Association class III or IV heart failure, severe left ventricular dysfunction, recent MI, severe pulmonary disease, or creatinine >2.5 mg/dL<sup>6</sup>.

Urgency is defined as elective (planned or scheduled procedure), urgent (surgery within 24 hours of admission or the patient cannot be discharged until after surgery), and emergent (surgery within 6 hours of admission).

Stroke: Permanent focal neurologic symptoms detected clinically or evidence of stroke on imaging attributable to the procedure; TIA: transient focal neurologic symptoms detected clinically without imaging evidence of a stroke; MI: evidence of infarction on electrocardiogram or by enzyme assay; reperfusion syndrome: clinical changes attributable to increased cerebral blood flow; dysrhythmia: new rhythm disturbance requiring treatment with medications or cardioversion; acute heart failure: new pulmonary edema requiring treatment in intensive care unit or stepdown. CEA indicates carotid endarterectomy; MI, myocardial infarction; TCAR, transcarotid artery revascularization; and TF-CAS, transfemoral carotid artery stenting.

confounding and selection bias, the OR of stroke or death was 0.74 (95% CI, 0.55–0.99) for CEA, and 1.66 (95% CI, 0.99–2.79) for TF-CAS (ANOVA simultaneous test of the 3 procedures  $P=0.022$ ).

### Stroke or Death: 1-Year

The 1-year rate of stroke or death was 6.4% for TCAR, 5.2% for CEA, and 9.7% for TF-CAS (log-rank  $P<0.001$ ; Figure 2). Compared with TCAR, the adjusted HR of 1-year stroke or death was 0.86 (95% CI, 0.79–0.94) for CEA, and 1.38 (95% CI, 1.23–1.55) for TF-CAS (Figure 1). After IV adjustment, the HR of stroke or death was 0.97 (95% CI, 0.80–1.17) for CEA, and 1.45 (95% CI, 1.04–2.02) for TF-CAS.

### Stroke or Death Stratified by Presenting Symptoms: Perioperative and 1-Year

Stroke or death was highest among patients presenting with focal neurologic symptoms. The perioperative rate of stroke or death for asymptomatic patients was 1.2% for TCAR, 1.1% for CEA, and 1.8% for TF-CAS ( $P<0.001$ ). For symptomatic patients, the perioperative rate of stroke or death was 2.7% for TCAR, 2.4% for CEA, and 4.6% for TF-CAS ( $P<0.001$ ).

Findings were similar at 1 year (Figure 3). Among asymptomatic patients, the 1-year rate of stroke or death was 4.9% for TCAR, 3.8% for CEA, and 6.6% for TF-CAS (log-rank  $P<0.001$ ). For symptomatic patients, the

rate was 8.0% for TCAR, 6.5% for CEA, and 11.3% for TF-CAS (log-rank  $P<0.001$ ).

The adjusted and IV-adjusted ORs and HRs of stroke or death were similar for most comparisons when stratified by presenting symptoms (Figure 4). However, in contrast to the Cox regression models, the IV-adjusted models demonstrated that patients presenting with focal neurologic symptoms appeared to have the lowest 1-year HR of stroke or death with TCAR. The traditional Cox regression models showed that compared with TCAR, the 1-year HR of stroke or death among symptomatic patients who underwent CEA was 0.95 (95% CI, 0.85–1.06), and for those who underwent TF-CAS was 1.43 (95% CI, 1.25–1.65). Conversely, when compared with TCAR, the IV-adjusted HR among symptomatic patients who underwent CEA was 1.30, (95% CI, 1.04–1.64) and for those who underwent TF-CAS was 1.86 (95% CI, 1.27–2.71).

### Secondary Outcomes

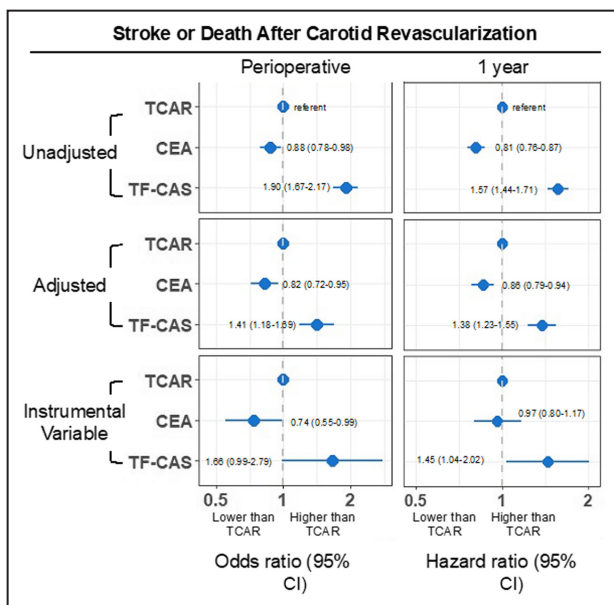
The rate of perioperative myocardial infarction was low for all 3 procedures (TCAR: 0.5%, CEA: 0.7%, TF-CAS: 0.5%,  $P=0.027$ ; Table 3). Cranial nerve injury was highest for CEA (CEA: 2.5%, versus TCAR: 0.2%, TF-CAS: 0%,  $P<0.001$ ). Operative times were longest for CEA (CEA: median: 110 minutes, versus TCAR median: 66 minutes, TF-CAS median: 61 minutes,  $P<0.001$ ). The rate of technical failure was low (TCAR: 0.5%, CEA: 0%, TF-CAS: 0.6%,  $<0.001$ ).

### Sensitivity Analyses

There were 3744 patients who were missing data about their percent stenosis category before surgery. Including this as a covariate in the model did not meaningfully change the point estimates of the primary analyses, with similar findings for including the proceduralist as a random effect and including both percent stenosis and the proceduralist. Results can be found in Table S1 and Table S2.

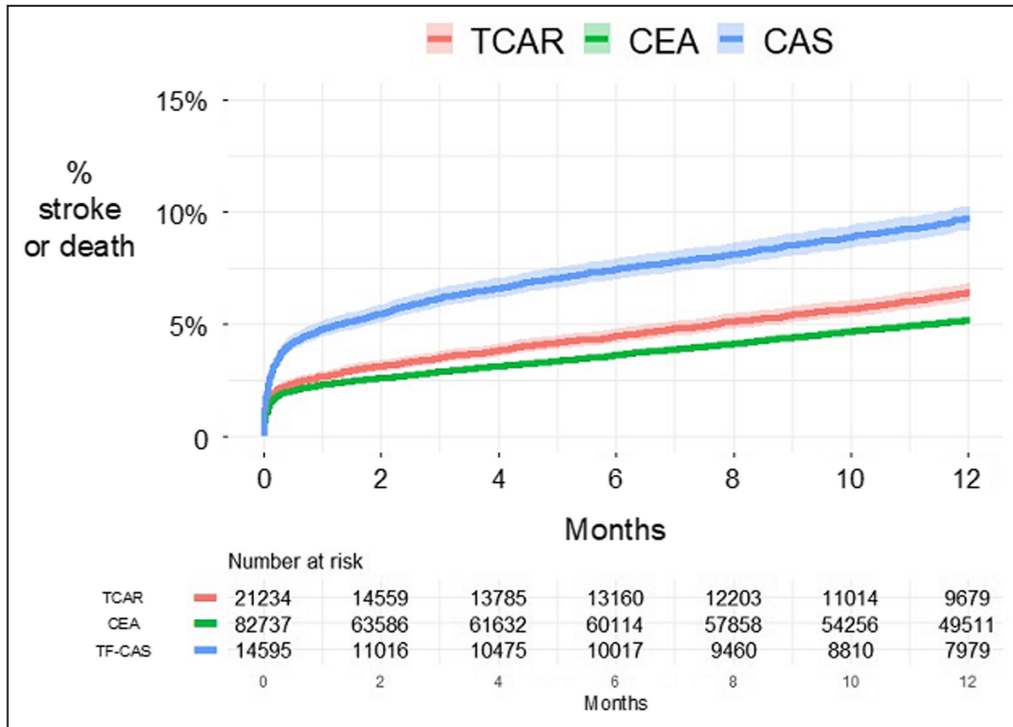
### DISCUSSION

To our knowledge, this is the first large scale real-world comparison of TCAR to CEA and TF-CAS using IV methodology to account for selection bias and unmeasured confounding, which has been an important limitation of prior studies. We determined that the rate of perioperative stroke or death was greater following TCAR compared with CEA. However, after 1 year there was no statistically significant difference in stroke or death between the 2 procedures in the IV-adjusted models. Moreover, TCAR and CEA demonstrated a decreased rate of stroke or death than TF-CAS at both time points, consistent with existing evidence.<sup>10–14,34,35</sup>



**Figure 1. Relative likelihood of stroke or death after TCAR, CEA, and TF-CAS, perioperative, and at 1 year.**

CEA indicates carotid endarterectomy; TCAR, transcatheter arterial revascularization; and TF-CAS, transfemoral carotid artery stenting.

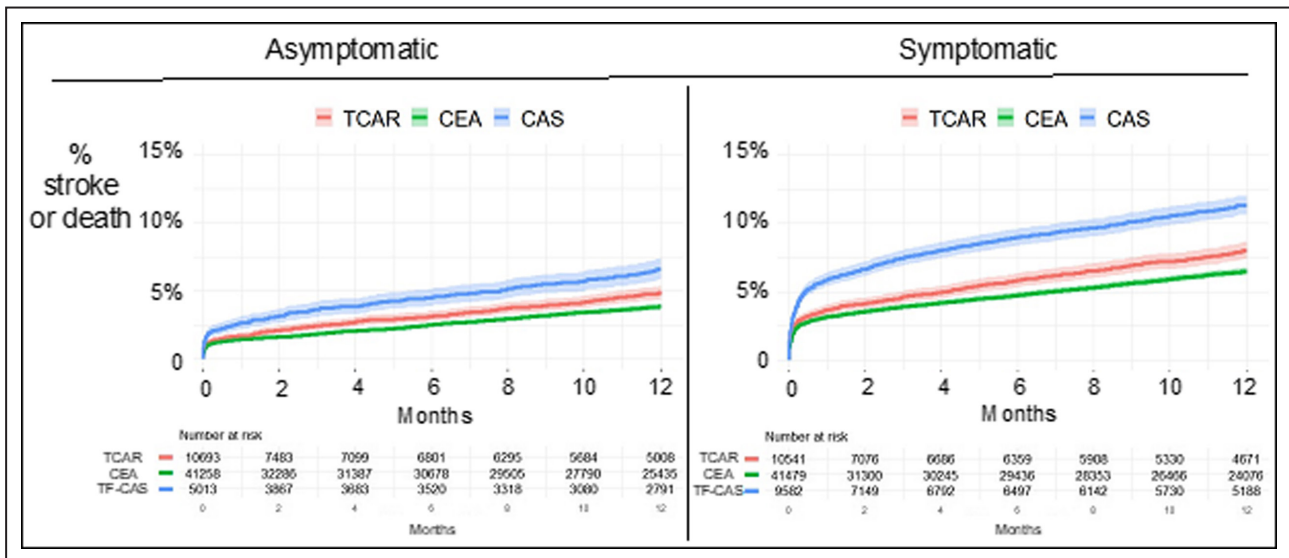


**Figure 2.** Kaplan–Meier estimated rate of stroke or death for TCAR, CEA, and TF-CAS. CAS indicates carotid artery stenting; CEA, carotid endarterectomy; TCAR, transcarotid artery revascularization; and TF-CAS, transfemoral carotid artery stenting.

Approximately half of procedures were performed in symptomatic patients. Stratifying the cohort into asymptomatic and symptomatic subgroups revealed that symptomatic patients appeared to have the most favorable 1-year result with TCAR. These findings indicate that although CEA remains the gold standard

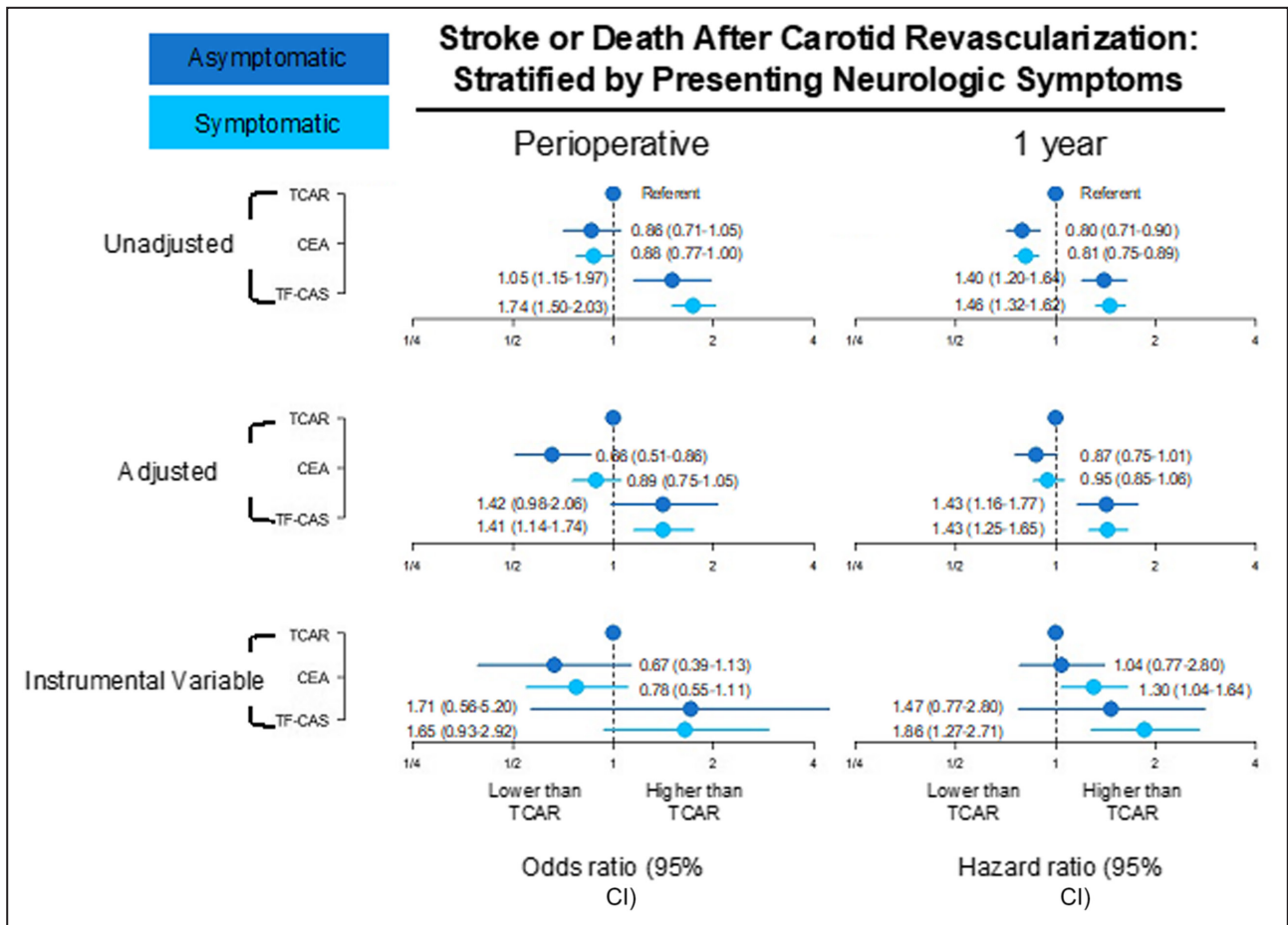
procedure for patients with carotid stenosis, TCAR appears to be a safe alternative to CEA and TF-CAS and may be useful for symptomatic patients.

To date, there has been persistent controversy in the management of carotid artery stenosis. Historical trials of CEA versus BMT have demonstrated a



**Figure 3.** Kaplan–Meier estimated rate of stroke after TCAR, CEA, and TF-CAS, stratified by presenting neurologic symptom status.

CAS indicates carotid artery stenting; CEA, carotid endarterectomy; TCAR, transcarotid artery revascularization; and TF-CAS, transfemoral carotid artery stenting.



**Figure 4.** Relative likelihood of stroke or death after TCAR, CEA, and TF-CAS, perioperative, and at 1 year, stratified by presenting neurologic symptom status. CEA indicates carotid endarterectomy; TCAR, transcarotid artery revascularization; and TF-CAS, transfemoral carotid artery stenting.

stroke-risk reduction benefit in select patient subgroups (Table 1).<sup>5-9</sup> However, advances in BMT have almost certainly led to a reduction in baseline stroke risk from carotid artery stenosis.<sup>36-38</sup> As such, which patients benefit from CEA over BMT alone remains a focus of ongoing debate.<sup>24,36,38-40</sup>

Interestingly, in the backdrop of this ongoing controversy, the Food and Drug Administration approved TCAR in 2015 as an additional procedural option to treat patients with carotid artery stenosis. Somewhat surprisingly, approval was authorized without supporting evidence from a randomized clinical trial, under the stipulation that all procedures be entered into the VQI registry, which captures >95% of TCARs performed. Despite this lack of level 1 evidence, TCAR has been rapidly adopted in the United States, with ≈21 000 implants across nearly 500 centers. Therefore, it is imperative to compare the safety profile of TCAR to the more established CEA and TF-CAS, recognizing that such comparisons provide no insights into TCARs effectiveness over BMT alone.

Prior investigators comparing TCAR to CEA and TF-CAS have reported results, but with methodologic limitations.<sup>19,20</sup> Schermerhorn et al. compared TCAR to TF-CAS in 3286 pairs of propensity-matched patients, reporting a statistically significant lower risk of perioperative in-hospital stroke or death with TCAR (reported relative risk, 0.51 [95% CI, 0.37-0.72]).<sup>19</sup> Malas et al. then compared TCAR to CEA in 6384 pairs of propensity-matched patients, reporting no statistically significant difference in perioperative in-hospital stroke or death (reported relative risk, 1.01 [95% CI, 0.77-1.33]).<sup>20</sup> Although they demonstrate favorable results for TCAR, these studies have important methodologic limitations. Propensity matching can be performed only on known factors contained in the data set. However, clinicians are privy to a myriad of individual patient characteristics that cannot be, or are not, accurately recorded with a registry variable. These include, for example, clinician selection effects on the intended procedure, proceduralist quality, characteristics of the center and post-operative care, varying severities of comorbidities that

may wax and wane over the disease course, anatomic nuances pertinent to the revascularization procedure, and characteristics of the carotid lesion (eg, echolucency, thrombus) that may affect stroke risk. To date, these unmeasured factors have not been sufficiently accounted for in the published literature, and the grade of evidence surrounding TCAR remains low.<sup>3,4</sup>

It was our objective to address the limitations of prior reports and improve our understanding of TCAR's safety profile compared with CEA and TF-CAS. To do this we compared the 3 procedures using an IV method for risk adjustment.<sup>41</sup> IV techniques are the optimal way to account for unmeasured confounding when randomization is not available.<sup>22,28,29,32</sup> Using this methodology, we found that stroke or death after TCAR was higher than CEA in the perioperative period. However, after 1 year of follow-up, there was no statistically significant difference between the 2 procedures. In addition, TCAR was superior to TF-CAS at both time points. Interestingly, Although the unadjusted 1-year rate of stroke or death was higher for TCAR than CEA among symptomatic patients, we found that TCAR had a lower 1-year HR of stroke or death than CEA after IV adjustment. We believe the reason for this is that symptomatic patients may be particularly prone to confounding factors that are difficult to measure, including the presence of crescendo transient ischemic attacks, the severity and/or duration of the transient ischemic attack, and time from the neurologic event to the procedure, among a variety of others, although these findings require further validation.<sup>30,42–44</sup> These factors highlight the utility of using IV methods for situations such as TCAR, where a new procedure is rapidly adopted without randomized trial evidence. Not accounting for unmeasured confounding when studying TCAR may yield incorrect results. Therefore, investigators evaluating results after TCAR should consider both measured and unmeasured factors during risk adjustment.

Our findings highlight areas for future work. Although our results add to the growing body of literature defining the performance of TCAR versus CEA and TF-CAS, there remains no comparison to BMT alone. Although we applied an IV method to adjust for unmeasured confounding and bias, there still remains no level 1 evidence to support the use of TCAR in contemporary practice. Until a randomized trial of TCAR determines its efficacy versus BMT and/or other procedures to treat carotid stenosis, clinical practice guidelines will be limited in its endorsement.<sup>3,4</sup> The fact that TCAR has risen to such rapid popularity despite a lack of level 1 evidence is a bit surprising, and factors related to this should be elucidated in future work with careful attention to patient safety. Furthermore, its rapid uptake highlights the importance of using procedural registries to monitor patient outcomes and inform

clinical practice. To that end, we recommend that all patients with carotid stenosis who are treated with BMT alone, or who undergo TCAR, CEA, or TF-CAS, be entered into a clinical registry for outcome assessment and quality assurance.

Our study has limitations. First, we are unable to comment on the details of neurologic symptoms that patients who were classified as symptomatic were experiencing, including the severity, number of events, and time frame before the procedure. To address this limitation, we incorporated an IV approach, which seeks to account for unmeasured or unmeasurable confounding, including these factors. However, this lack of detail limits the comparison of our findings to other published studies or historical randomized trials. Second, we are unable to comment on some details of the medical therapy among patients who underwent TCAR, CEA, or TF-CAS, such as statin dose and blood pressure. However, we do know details on several important medications including antiplatelet therapy and beta blockers, among others, which we were able to characterize across the patient groups. Third, the IV analysis relies upon several assumptions, which we believe are met (Data S1). The IV analysis requires a larger sample size than traditional regression. This is the primary reason this study is being conducted now rather than early in TCARs development. Now that there are ≈20 000 patients who underwent TCAR, we believe that there is adequate power to provide meaningful information on the relative hazards of TCAR, CEA, and TF-CAS using robust IV modeling techniques, improving upon the limitations of prior published reports using other methods. Finally, we cannot conclude that the unmeasured confounding accounted for in this analysis, which may have been related to treatment decisions, was appropriate with respect to selecting patients likely to benefit from a carotid artery procedure compared with current BMT. Reasons for treatment decisions regarding particular patients require ongoing evaluation at the point of care. Multispecialty teams, including academics, free of financial misincentives are a key requirement for optimizing clinical practice.

## CONCLUSIONS

In this analysis using IV methodology, we found that TCAR had a greater rate of perioperative stroke or death than CEA. However, after 1 year there was no statistically significant difference in stroke or death between the 2 procedures. Moreover, TCAR and CEA demonstrated a lower stroke or death rate than TF-CAS at both time points. Symptomatic patients had the most favorable 1-year result with TCAR, which appears to provide a safe procedural alternative to CEA and TF-CAS for this higher risk cohort. However, given

the lack of randomized trial data comparing TCAR with CEA, TF-CAS, or BMT, further work is needed to elucidate TCARs most appropriate role in the contemporary management of carotid occlusive disease.

## ARTICLE INFORMATION

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### Disclosures

None.

### Supplemental Material

Data S1

Tables S1–S2

Figures S1–S2

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# SUPPLEMENTAL MATERIAL

## Data S1. Supplemental Methods

### Instrumental variable analysis methods

#### *Rationale*

Transcarotid artery revascularization (TCAR) was approved by the FDA in 2015 without a randomized clinical trial.<sup>23</sup> It was specifically approved for clinical and anatomic high-risk patients, criteria which many patients with carotid artery stenosis meet, and are described in the initial single-arm reports documenting results after TCAR.<sup>33</sup> With no comparative trial underway, observational studies are the only way that TCARs effectiveness and safety can be determined in the near future. Our results demonstrate that TCAR is now in use at nearly 500 centers in the United States, making the study of TCAR pertinent to many patients, proceduralists, and institutions.

As a condition of TCARs FDA approval, patients undergoing the procedure must be entered into the Vascular Quality Initiative (VQI) registry. Audits have demonstrated that nearly 95% of all patients undergoing TCAR are entered into this registry.<sup>23</sup> Prior studies using the VQI to compare TCAR to carotid endarterectomy (CEA) or transfemoral carotid artery stenting (TF-CAS) have used propensity-matched cohorts to control for risk differences.<sup>19,33</sup> These studies have important limitations. Proceduralists have access to a variety of factors about their patients that are either not recorded by the registry or are difficult to accurately capture with a continuous or categorical variable. Propensity matching cannot account for these factors, including proceduralist selection bias and other unmeasurable confounding.<sup>42,43</sup> In addition, these studies did not account for calendar time, or the effect of the treating center.<sup>19,33</sup>

### *Instrumental variable technique: perioperative results*

To address these limitations, we employed an instrumental variable (IV) procedure designed for nonlinear models known as two-stage residual inclusion.<sup>25</sup> The proposed IV analysis identifies patients who would have undergone TCAR at one institution, but CEA or TF-CAS at another, in relation to the value of the instrument.<sup>22</sup> This analysis operates under the assumption that patients are randomized to institutions, at least beyond any associations due to proximity or other observed predictors, and, overall, are not related to any unmeasured elements of the severity of a patient's risk profile (i.e., unobserved factors that are independently associated with the outcome). Under this assumption, the IV analysis accounts for unmeasured and unmeasurable confounding between the type of carotid revascularization procedure and the outcome of stroke or death in patients who are eligible for both procedures. The hospital the patient happens to attend is then a determinant in the procedure they undergo lending this subpopulation the name "the population on the margin".<sup>22,25-27</sup>

We conducted two separate IV procedures for perioperative results, one for the comparison of TCAR versus CEA, and one for TCAR versus TF-CAS. In the first stage of the procedure, a linear regression model regresses procedure type (i.e., TCAR versus CEA or TCAR versus TF-CAS, respectively) on the instrument and all potential measured confounding variables. In the second stage of the procedure, a logistic regression model regresses the binary dependent variable indicator for stroke or death on procedure type and all potential measured confounders and the residuals from the first stage model. Under

the IV assumptions, controlling for the residuals serves the purpose of approximately controlling for the net effect of any unmeasured confounders.

#### *Instrumental variable technique: one-year results*

We used a similar technique for the one-year results by again performing two IV procedures, one for TCAR versus CEA, and one for TCAR versus TF-CAS. We used a recently developed two-stage residual inclusion procedure adapted for time-to-event outcomes analyzed using the Cox model.<sup>27,29-31</sup> The first stage is the same as for the perioperative outcome. In the second stage the independent variables are the procedure type, the observed covariates, and the residuals from the first stage, and the dependent variable is time to stroke or death, which could be observed or censored. In addition, the predictor side of the equation includes a frailty term which accounts for the additional variance derived from the first stage and helps the first-stage residual to control for unmeasured confounders. Therefore, the second stage of the procedure involves a Cox proportional hazards frailty model, not the standard Cox model.<sup>27,29</sup>

#### *Proposed instrument*

These two-stage procedures utilize the IV to account for unmeasured and unmeasurable confounding such as selection bias, while also adjusting for known confounding variables.<sup>26,27</sup> The choice of instrument is clearly a crucial part of the procedure. Our proposed instrument was a center's preference to perform TCAR versus other procedures for carotid revascularization.<sup>32</sup> We calculated this preference as the proportion of TCAR out of the total procedures performed at a given center in the six months prior to the index

procedure for each patient, similar to prior work by us and others.<sup>27-32</sup> We calculated the instruments separately for the comparison of TCAR versus CEA, and TCAR versus TF-CAS. For the IV procedure comparing TCAR versus CEA, we calculated the preference to perform TCAR versus CEA as:  $TCAR / [TCAR + CEA]$ . For the IV procedure comparing TCAR versus TF-CAS, we calculated the preference to perform TCAR versus TF-CAS as:  $TCAR / [TCAR + TF-CAS]$ . Using this method, the F-statistic was strong for both instruments individually and overall (Figure S2).

### *Instrument rationale*

A valid instrument must satisfy three conditions: it must be associated with the exposure, it must be independent of any unmeasured confounding for a given exposure, and it cannot be associated with the outcome except through the exposure.<sup>27</sup> We provide justification for these assumptions with reference to the choice of TCAR versus CEA and TF-CAS, noting that an analogous argument may be applied to the choice of CEA versus TCAR or TF-CAS. First, it is expected that a patient treated at an institution that has historically performed many TCARs is more likely to receive TCAR than if that patient was treated at an institution with a much lower utilization of TCAR, or none at all. Therefore, this instrument should logically be associated with the exposure, and is supported by our robust F statistics.

Second, the historical center-level proportion of TCAR use must be independent of any unmeasured confounding. Specifically, there must be no systematic differences in the unmeasured characteristics of patients who are treated at a center with an instrument value of X, versus patients treated at a center with an instrument value of Y. The historical

proportion of TCAR is not related to the characteristics of any index patient who presents to that center for treatment. Therefore, we believe that any unmeasured patient characteristics are independent of the center-level historical proportion of TCAR use, fulfilling the second assumption underlying the IV procedure. There remains the possibility that the historical proportion of TCAR is related to other unmeasured center level characteristics (e.g., hospital advertisement, or specific referral patterns). We have included center as a fixed-effect covariate in all models to control for these associations but remain unable to comment on any such factors within the limitations of the data available.

Third, the instrument must not be associated with the outcome, except through its association with the exposure. If the proportion of TCAR performed was associated with the outcome, then centers who perform fewer TCARs, centers early in their experience, or more skilled operators, would have different rates of perioperative stroke or death than centers who perform TCAR more frequently, or centers with more skilled operators. This would indicate a learning curve for TCAR. This has been previously studied, both other investigators, and in the initial single arm clinical studies used for TCARs FDA approval.<sup>33,45,46</sup> These studies revealed that there is no difference in the outcome of stroke or death between experienced operators, and those early in their adoption of TCAR. In addition, we have included total center procedure volume as a covariate in our models, which should account for any impact of volume. Based on these things, we believe that there is no association with the historical center-level proportion of TCAR use and the outcome of stroke or death, except through its association with the exposure type. Despite this, there may remain residual unmeasured confounding that we are unable to account for

within the limitations of our data. However, with no completed or enrolling randomized comparative trial of TCAR, instrumental variable methods to account for unmeasured confounding are an important method of evaluation of TCARs effectiveness.

### *Limitations*

The IV model is subject to limitations. First, inclusion of additional residuals from the first stage in the second stage of the model increases the variance and therefore the error of measurement. This means that more statistical power is needed for IV models than for non-IV analyses. This was one of the primary reasons why this study is being conducted now, rather than early in TCARs development. Now that there are more than 20,000 patients who underwent TCAR, we believe that there is adequate power to conduct robust IV modeling techniques and improve upon the limitations of prior published reports using other risk-adjustment methods. Second, the IV model relies upon several assumptions which are difficult to prove. As discussed above, we believe that these assumptions are met, and have used this type of model in several prior studies.<sup>28-31</sup> Third, the IV method provides point estimates for patients who would receive TCAR at one hospital, but CEA or TF-CAS at another. In other words, the results apply to patients who are eligible for more than one procedure type. This is similar to the results that would be expected in a randomized trial, where patients who are randomized are restricted to those who are eligible for both procedures being investigated. However, the results of the IV model, as in a randomized trial, do not apply to patients who are not candidates for more than one procedure type. Therefore, the results of the IV analysis are generalizable to patients who would be eligible for more than one procedure type. Finally, we conducted the IV procedure using two

separate instruments, one for the comparison of TCAR versus CEA, and one for TCAR versus TF-CAS, instead of creating one single instrument (e.g., TCAR / [TCAR + CEA + TF-CAS]). We chose this method because it is similar to prior validated work using the recently developed IV procedure with a Cox proportional hazards frailty model, where the exposures tested were binary.<sup>28-31</sup> This means that the population of patients to whom results are generalizable (i.e., “the population on the margin”) may be different for each IV procedure. However, because TF-CAS had a higher likelihood of stroke or death in all calculations, this difference in generalizability is unlikely to be clinically relevant for patients and proceduralists choosing between different carotid revascularization options.

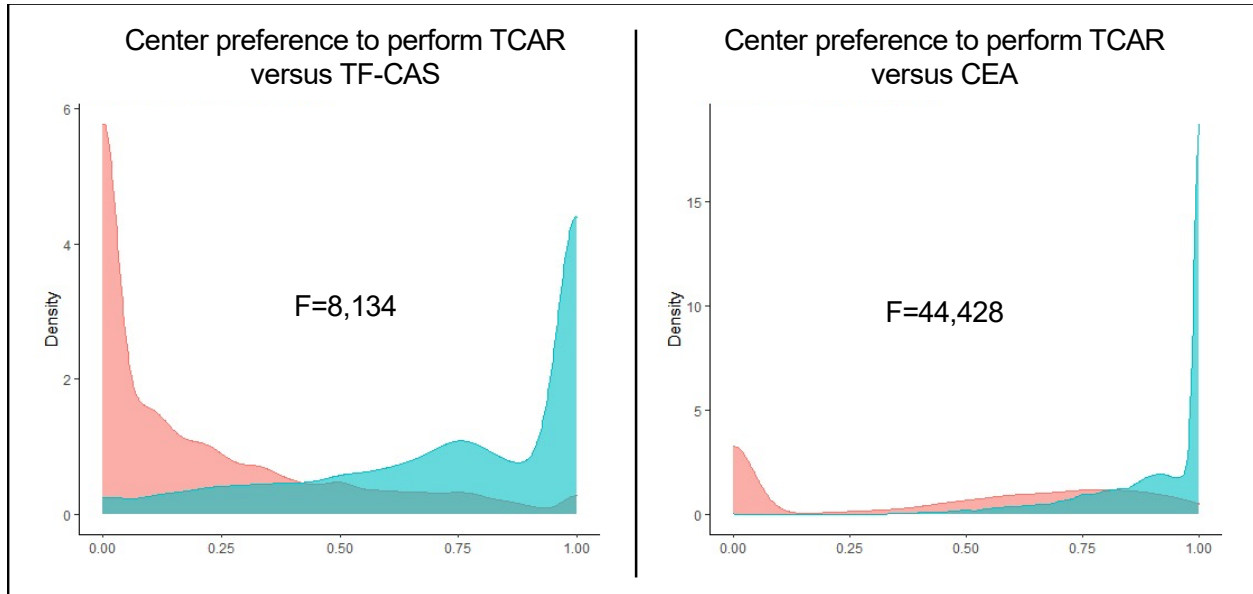
**Table S1. Sensitivity analyses for perioperative stroke or death.**

		<b>Logistic Regression</b>		
	<b>Primary analyses</b>	<b>% stenosis as covariate Missing=3,744</b>	<b>+surgeon as random effect Missing=0</b>	<b>Surgeon and % stenosis Missing=3,744</b>
<b>CEA</b>	0.82 (0.72-0.95)	0.83 (0.72-0.96)	0.83 (0.72-0.96)	0.84 (0.72-0.97)
<b>TF-CAS</b>	1.41 (1.18-1.69)	1.42 (1.18-1.70)	1.44 (1.19-1.73)	1.44 (1.19-1.74)
		<b>2SRI Instrumental Variable</b>		
<b>CEA</b>	0.74 (0.54-0.99)	0.76 (0.56-1.03)	0.77 (0.57-1.06)	0.80 (0.58-1.10)
<b>TF-CAS</b>	1.66 (0.99-2.79)	1.68 (1.00-2.82)	1.85 (1.07-3.19)	1.98 (1.13-3.47)

**Table S2. Sensitivity analyses for one-year stroke or death.**

	Current	Cox Regression		
		% stenosis as covariate Missing=3,744	+surgeon as random effect Missing=0	Surgeon and % stenosis Missing=3,744
<b>CEA</b>	0.86 (0.79-0.94)	0.87 (0.80-0.96)	0.86 (0.78-0.95)	0.87 (0.79-0.96)
<b>TF-CAS</b>	1.38 (1.23-1.55)	1.39 (1.24-1.56)	1.42 (1.25-1.60)	1.41 (1.25-1.60)
2SRI-Fraily Instrumental Variable				
<b>CEA</b>	0.97 (0.80-1.17)	1.01 (0.83-1.22)	1.00 (0.81-1.23)	1.03 (0.83-1.27)
<b>TF-CAS</b>	1.45 (1.04-2.02)	1.51 (1.08-2.10)	1.55 (1.09-2.22)	1.61 (1.12-2.30)

**Figure S1. Distribution of the instrument for the instrumental variable models.**



Legend: TCAR, transcarotid artery revascularization; CEA, carotid endarterectomy; TF-CAS, transfemoral carotid artery stenting.

**Figure S2. Flow diagram of missing data.**

Initial cohort	TCAR n=21,234	CEA n=82,737	TF-CAS n=14,595	Centers n=662
Missing data	TCAR n=939	CEA n=882	TF-CAS =3,222	NA
Included in Adjusted models	TCAR n=20,295	CEA n=81,855	TF-CAS n=11,373	Centers n=656
Cannot compute IV	TCAR n=366	CEA n= 617	TF-CAS n=139	Centers n=33
Included in IV-models	TCAR 19,929	CEA n= 81,238	TF-CAS n=11,234	Centers n=623

Legend: TCAR, transcarotid artery revascularization; CEA, carotid endarterectomy; TF-CAS, transfemoral carotid artery stenting.