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Propensity-Score Matched Analysis of Three Years Survival of Trans Carotid Artery Revascularization Versus Carotid Endarterectomy in the Vascular Quality Initiative Medicare-Linked Database

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Objective: Carotid endarterectomy (CEA) remains the gold standard procedure for carotid revascularization. Transfemoral carotid artery stenting (TFCAS) was introduced as a minimally invasive alternative procedure in patients who are at high risk for surgery. However, TFCAS was associated with an increased risk of stroke and death compared to CEA.

Background: Transcarotid artery revascularization (TCAR) has outperformed TFCAS in several prior studies and has shown similar perioperative and 1-year outcomes compared with CEA. We aimed to compare the 1-year and 3-year outcomes of TCAR versus CEA in the Vascular Quality Initiative (VQI)-Medicare-Linked [Vascular Implant Surveillance and Interventional Outcomes Network (VISION)] database.

Methods: The VISION database was queried for all patients undergoing CEA and TCAR between September 2016 to December 2019. The primary outcome was 1-year and 3-year survival. One-to-one propensity-score matching (PSM) without replacement was used to produce 2 well-matched cohorts. Kaplan-Meier estimates, and Cox regression was used for analyses. Exploratory analyses compared stroke rates using claims-based algorithms for comparison.

Results: A total of 43,714 patients underwent CEA and 8089 patients underwent TCAR during the study period. Patients in the TCAR cohort were older and were more likely to have severe comorbidities. PSM produced two well-matched cohorts of 7351 pairs of TCAR and CEA. In the matched cohorts, there were no differences in 1-year death [hazard ratio (HR) = 1.13; 95% CI, 0.99–1.30; $P = 0.065$]. At 3-years, TCAR was associated with slight increased risk of death (HR = 1.16; 95% CI, 1.04–1.30; $P = 0.008$). When stratifying by initial symptomatic presentation, the increased 3-year death associated with TCAR persisted only in symptomatic patients (HR = 1.33; 95% CI, 1.08–1.63; $P = 0.008$). Exploratory analyses of postoperative stroke rates using administrative sources suggested that validated measures of claims-based stroke ascertainment are necessary.

Conclusions: In this large multi-institutional PSM analysis with robust Medicare-linked follow-up for survival analysis, the rate of death at 1 year was similar in TCAR and CEA regardless of symptomatic status. The slight increase in the risk of 3-year death in symptomatic patients undergoing TCAR is likely confounded by more severe comorbidities despite matching. A randomized controlled trial comparing TCAR to CEA is necessary to further determine the role of TCAR in standard-risk patients requiring carotid revascularization.

Keywords: carotid endarterectomy, carotid stenosis, carotid artery stenting, mortality

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Carotid endarterectomy (CEA) remains the gold standard procedure for carotid revascularization and is favored over transfemoral carotid artery stenting (TFCAS) in most patients with symptomatic and asymptomatic carotid stenosis.[1–4] TFCAS was introduced as a minimally invasive alternative procedure in patients who are at high risk for surgery; however, several multi-institutional randomized controlled trials in North America and Europe have shown that TFCAS (compared with CEA) is associated with higher risks of procedural stroke.[5,6]

Transcarotid artery revascularization (TCAR) has outperformed TFCAS in several observational studies in terms of periprocedural stroke and death.[7–10] This superiority is felt to be mainly because of the avoidance of manipulation of the aortic arch and also the establishment of secure cerebral protection by flow reversal before any manipulation of the carotid plaque in TCAR.[11–13] In addition to short-term outcomes, TCAR has also outperformed TFCAS in 1-year follow-up. A propensity-score matched (PSM) analysis of outcomes of TCAR versus TFCAS revealed that TCAR was associated with a lower risk of ipsilateral stroke or death compared with TFCAS at 1 year (5.1% vs. 9.6%; $P < 0.001$).[7]

Outcomes following TCAR have also been compared to the gold standard "CEA".[14–16] In an analysis of the vascular quality initiative (VQI) TCAR Surveillance Project (TSP), we found no significant difference between TCAR and CEA in terms of in-hospital stroke/death, and TCAR was associated with decreased risks of myocardial infarction (MI) and cranial nerve injury (CNI) compared to CEA.[17] In another PSM analysis of the VQI-TSP project in 4180 pairs of TCAR and CEA, we found no significant difference in 30-day stroke, death, and

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stroke/death rates. However, TCAR was associated with a lower risk of MI (0.55% vs. 1.12%; $P = 0.004$). At 1 year, no significant difference was observed in the risk of the composite outcome of ipsilateral stroke and death between TCAR and CEA (6.49% vs. 5.68%; $P = 0.157$).[18] In another recent VQI registry study by Zhang et al., the outcomes of CEA, TFCAS, and TCAR were compared in patients considered to be standard risk by the Centers for Medicare and Medicaid Services (CMS). They found that TFCAS was associated with an increased risk of perioperative stroke compared to CEA [adjusted odds ratio (aOR) = 1.60; 95% CI, 1.37–1.86; $P < 0.001$] but TCAR was not (aOR = 1.05; 95% CI, 0.84–1.31; $P = 0.659$).[19]

Although TCAR has shown similar perioperative and 1-year outcomes when compared to CEA in terms of death and stroke, no study in the literature has compared outcomes of TCAR to CEA beyond 1-year follow-up. In the present study, we aimed to compare the mid-term (1-year and 3-year) outcomes of TCAR vs. CEA in the VQI-Medicare-Linked (Vascular Implant Surveillance and Interventional Outcomes Network [VISION]) database.

METHODS

Database

We did a retrospective analysis of prospectively collected data using the VQI-Medicare-Linked database. VQI (www.vqi.org) is the most comprehensive registry for vascular surgery procedures in North America. It captures data from 1000 centers throughout the United States and Canada and includes more than 1 million procedures.[20] Vascular Implant Surveillance and Interventional Outcomes Network (VISION) links VQI to CMS claims by using ICD and CPT codes and provides more granular follow-up. In addition to CMS, VISION (www.mdepinet.net/vision) links VQI data to additional follow-up databases including the New York SPARCS and the New York City Clinical Data Research Network (NYC-CDRN) datasets.[21,22]

Patients

We used the CEA and carotid artery stenting (CAS) pathways of the VQI-VISION database. We included patients who underwent CEA or TCAR from September 2016 to December 2019. Two cohorts of TCAR versus CEA were compared. In the CEA cohort, patients undergoing concomitant proximal or distal endovascular interventions, patients undergoing other concomitant arterial interventions, and patients undergoing concomitant coronary artery bypass graft (CABG) were excluded. In the TCAR cohort, nonatherosclerotic lesions (trauma, dissection, fibromuscular dysplasia), patients with two or more treated lesions, as part of intracranial treatment, or for an unknown indication were excluded. Additionally, patients with missing information on the use of cerebral protection and those who underwent transcarotid CAS with an embolic protection device were excluded (Fig. 1).

Background Variables

The background variables studied in two cohorts included age, sex, race, smoking status, comorbidities, prior CABG or percutaneous coronary intervention (PCI), preoperative medications, urgency, anesthesia type, ipsilateral stenosis ≥80%, symptomatic status, and physician volume. Comorbidities

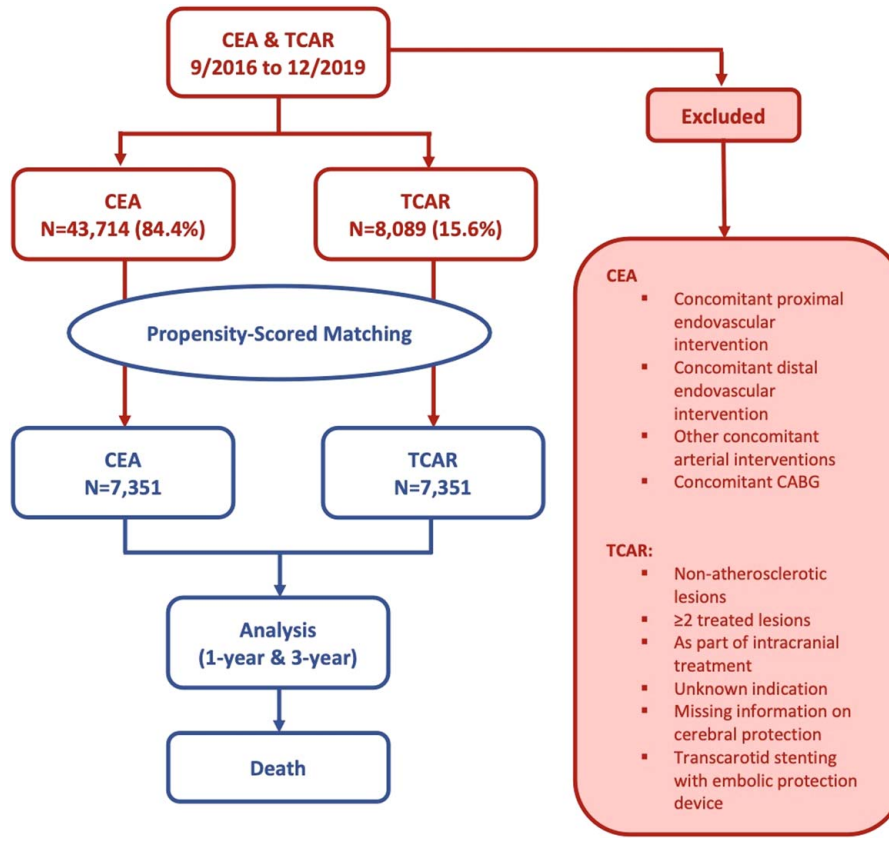

FIGURE 1. Flowchart of the patients in TCAR and CEA cohorts. CABG indicates coronary artery bypass graft; CEA, carotid endarterectomy; TCAR, transcarotid artery revascularization.

included hypertension, diabetes mellitus, coronary artery disease (CAD), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), and dialysis. Preoperative medications included aspirin, clopidogrel, or other P2Y12 inhibitors, statins, and beta-blockers.

Hypertension was defined as a documented history or recorded blood pressure ≥130/80 mm Hg (elevation of either systolic or diastolic) on 3 or more occasions. Diabetes was defined as patients diagnosed with diabetes mellitus who are on a diet, oral medications, or insulin. CAD was defined as any history of angina or MI. CHF included both symptomatic and asymptomatic CHFs. CKD was defined as an estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2 Symptomatic status was defined as the presence of ipsilateral ocular or cortical transient ischemic attacks (TIA), or stroke within 6 months before the index procedure in accordance with Society for Vascular Surgery (SVS) reporting standards.[23] Individual physician procedure volume was divided into 3 quantiles of low, medium, and high physician volumes based on the mean number of cases performed yearly by physicians. The means of low, medium, and high physician volumes for the CEA cohort were 7, 15, and 30 annual patients, respectively. They were 3, 7, and 22 annual patients for the TCAR cohort, respectively.

Outcomes

The primary outcome was 1-year and 3-year death. Death was defined as all-cause mortality and was captured in the VISION database using the denominator file from Medicare claims.[22] We examined stroke rates using previous studies but examined these rates only in exploratory work given recent changes in ICD9 coding algorithms to ICD10 coding algorithms used to ascertain stroke risk.[24]

Statistical Analysis

We used t-test, rank-sum test, Pearson's chi-square test, or Fisher exact test to compare background variables between two cohorts, as needed. Given the significant differences in the distribution of key variables between study groups, we employed PSM to ensure the balance of these covariates. We conducted one-to-one PSM without replacement to produce two well-matched cohorts. We did PSM on 17 dimensions with a caliber of 0.2. We evaluated the balance of covariates between study groups before and after PSM using standardized differences (Std Diff). An absolute Std Diff of ≥0.10 was considered an imbalance of variables between groups.[25]

All the background variables had absolute Std Diff values of <0.10 after PSM and there was no need for double adjustment. One-year and 3-year death in unmatched and matched cohorts were estimated using Kaplan-Meier survival estimates and univariate Cox proportional hazard regression analyses. Cox regression was used to calculate hazard ratios (HR). The HRs were reported with their corresponding 95% CIs. We further evaluated effect modification by the symptomatic status of the procedure type on the 1-year and 3-year death. All tests were 2-sided and alpha was considered 0.05. All analyses were performed by Stata 17.0 software (StataCorp LP, College Station, Texas).

Research Protocol Approval

We performed the analysis following approval from the SVS Research Advisory Committee (Protocol Number # 4648). Following VQI approval, the VISION committee also approved the study protocol. Institutional board review (IRB) approval and informed consent were waived for this study because only deidentified information was used.

RESULTS

Background Variables Before and After PSM

A total of 43,714 patients (84.4%) underwent CEA and a total of 8089 patients underwent TCAR (15.6%) during the study period. Before PSM, patients in the TCAR cohort were older (75.4 ± 7.5 vs. 73.7 ± 7.2; Std Diff = −0.230) and were more likely to have CAD (53.1% vs. 42.5%; Std Diff = 0.213), CHF (18.0% vs. 12.4%; Std Diff = 0.156), and history of prior CABG/PCI (41.4% vs. 36.5%; Std Diff = 0.100) compared to the patients in the CEA cohort. They were also more likely to use preoperative aspirin (89.5% vs. 84.0%; Std Diff = 0.161), P2Y12 inhibitors (87.1% vs. 35.4%; Std Diff = 1.252), and statins (89.7% vs. 84.5%; Std Diff = 0.157) compared to the patients in the CEA cohort. On the other hand, patients in the CEA cohort were more likely to undergo carotid revascularization under general anesthesia (92.8% vs. 81.2%; Std Diff = 0.352) and have preoperative ipsilateral stenosis ≥80% (59.7% vs. 51.4%; Std Diff = 0.167) compared to the patients in the TCAR cohort. TCAR procedures were more likely to be performed by high-volume physicians compared to CEA (42.1% vs. 29.6%; Std Diff = 0.263). One-to-one PSM produced two well-matched cohorts of 7351 pairs of TCAR and CEA. After PSM, all background variables were balanced in two study groups (All Std Diff values < 0.10). Table 1 tabulates the background variables in CEA and TCAR cohorts before and after the PSM.

One-Year and 3-Years Death Before and After PSM

Before PSM, TCAR was associated with increased hazards of death at 1 year compared with CEA (8.1% vs. 5.7%; HR = 1.45; 95% CI, 1.31–1.60; $P < 0.001$). However, there was not any significant difference in hazards of 1-year death after PSM (7.8% vs. 7.0%; HR = 1.13; 95% CI, 0.99–1.30; $P = 0.065$) (Table 2 and Fig. 2). Before PSM, TCAR was associated with increased hazards of death at 3-year compared to CEA (22.0% vs. 16.8%; HR = 1.43; 95% CI, 1.32–1.56; $P < 0.001$). After PSM, a slight increase in the hazards of 3-year death persisted in the TCAR cohort (21.3% vs. 18.8%, HR = 1.16; 95% CI, 1.04–1.30; $P = 0.008$) (Table 2 and Fig. 3).

Subanalysis Stratified by Symptomatic Status

On subanalysis of the data stratified by the initial symptomatic presentation, the increased 3-year death associated with TCAR persisted only in symptomatic patients (24.2% vs. 18.5%; HR = 1.33; 95% CI, 1.08–1.63; $P = 0.008$). There was not any significant difference in hazards of 3-year death in asymptomatic patients undergoing TCAR and CEA (20.3% vs. 18.9%; HR = 1.10; 95% CI, 0.96–1.25; $P = 0.166$) (Table 3).

Exploratory Analyses of Stroke Assessment

We performed the claims-based assessment of stroke using existing claims algorithms as outlined in previous studies.[24] The overall stroke rate seen with administrative assessment derived from ICD-10 data was not commensurate with studies based solely on ICD9 data, suggesting the need for validation and coding refinement. While preliminary, these analyses did not demonstrate significant differences between TCAR and CEA in terms of stroke risk.

TABLE 1. Background Variables in TCAR vs. CEA Cohorts Before and After PSM

	Before Match			After Match		
Variable	CEA N = 43,714 (84.4%)	TCAR N = 8089 (15.6%)	Std diff	CEA N = 7351 (50.0%)	TCAR N = 7351 (50.0%)	Std diff
Age (years)	73.7 ± 7.2	75.4 ± 7.5	−0.230	75.2 ± 7.1	75.1 ± 7.4	0.018
Sex (female)	17,356 (39.7)	3026 (37.4)	0.047	2713 (36.9)	2778 (37.8)	0.018
Race						
White	39,674 (90.8)	7413 (91.7)	0.032	6697 (91.1)	6738 (91.7)	0.020
Black	1917 (4.4)	320 (4.0)	0.021	295 (4.0)	293 (4.0)	0.001
Others	2104 (4.8)	352 (4.4)	0.022	356 (4.8)	316 (4.3)	0.026
Insurance						
Medicare	31,360 (71.8)	6393 (79.3)	0.176	5883 (80.0)	5765 (78.4)	0.040
Medicaid	273 (0.6)	56 (0.7)	0.009	38 (0.5)	54 (0.7)	0.028
Others	12,061 (27.6)	1612 (20.0)	0.179	1430 (19.5)	1532 (20.8)	0.035
Smoking						
Never	11,995 (27.5)	2226 (27.5)	0.002	1954 (26.6)	2002 (27.2)	0.015
Former	22,982 (52.6)	4324 (53.5)	0.018	4031 (54.8)	3934 (53.5)	0.026
Current	8708 (19.9)	1534 (19.0)	0.024	1366 (18.6)	1415 (19.2)	0.017
Hypertension	39,558 (90.6)	7371 (91.2)	0.021	6728 (91.5)	6698 (91.1)	0.015
Diabetes mellitus	16,276 (37.3)	3042 (37.6)	0.007	2748 (37.4)	2779 (37.8)	0.009
CAD	18,553 (42.5)	4292 (53.1)	0.213	3655 (49.7)	3873 (52.7)	0.060
CHF	5411 (12.4)	1452 (18.0)	0.156	1265 (17.2)	1244 (16.9)	0.008
COPD	10,508 (24.1)	2233 (27.6)	0.081	1985 (27.0)	2017 (27.4)	0.010
CKD	16,594 (38.0)	3463 (42.8)	0.099	3021 (41.1)	3126 (42.5)	0.029
Dialysis	492 (1.1)	136 (1.7)	0.047	104 (1.4)	115 (1.6)	0.012
CABG/PCI	15,924 (36.5)	3341 (41.4)	0.100	3137 (42.7)	3062 (41.7)	0.021
Preoperative aspirin	36,705 (84.0)	7236 (89.5)	0.161	6538 (88.9)	6542 (89.0)	0.002
Preoperative P2Y12 inhibitor	15,455 (35.4)	7043 (87.1)	1.252	6315 (85.9)	6342 (86.3)	0.011
Preoperative statin	36,920 (84.5)	7258 (89.7)	0.157	6424 (87.4)	6600 (89.8)	0.075
Preoperative beta-blocker	24,431 (55.9)	4717 (58.3)	0.049	4326 (58.9)	4290 (58.4)	0.010
Urgent/Emergent	5071 (11.6)	749 (9.3)	0.077	714 (9.7)	675 (9.2)	0.018
General anesthesia	40,566 (92.8)	6562 (81.2)	0.352	6239 (84.9)	6331 (86.1)	0.036
Ipsilateral stenosis ≥80%	25,597 (59.7)	4043 (51.4)	0.167	3890 (52.9)	3849 (52.4)	0.011
Symptomatic	12,577 (28.8)	1982 (24.6)	0.096	1774 (24.1)	1859 (25.3)	0.027
Physician volume						
Low	15,711 (35.9)	1936 (23.9)	0.264	1860 (25.3)	1877 (25.5)	0.005
Medium	15,046 (34.4)	2744 (33.9)	0.010	2564 (34.9)	2569 (34.9)	0.001
High	12,957 (29.6)	3409 (42.1)	0.263	2927 (39.8)	2905 (39.5)	0.006

Data presented as mean ± standard deviation for continuous variables and frequency (%) for categorical variables.

CABG indicates coronary artery bypass graft; CAD, coronary artery disease; CEA, carotid endarterectomy; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; TCAR, transcarotid artery revascularization.

DISCUSSION

In this PSM analysis, we found that TCAR is associated with 33% increase in hazards of death at 3 years compared to CEA in symptomatic patients (HR = 1.33; 95% CI, 1.08–1.63; $P = 0.008$). There was no difference in 3-year mortality in asymptomatic patients (HR = 1.10; 95% CI, 0.96–1.25, $P = 0.166$). The 1-year death was similar between matched cohorts of CEA and TCAR. This similarity persisted in both symptomatic and asymptomatic patients. This is the first study that compares the midterm survival of TCAR to CEA up to 3 years in the literature.

CEA is the gold standard for carotid revascularization in most patient populations with carotid stenosis.[2,3] However, certain patients at high medical or anatomic risk may benefit from minimally invasive techniques of carotid revascularization. TFCAS was developed to meet this need; however, multiple randomized controlled trials, as well as observational studies, have confirmed a higher risk of perioperative stroke with this procedure compared to CEA, particularly in symptomatic patients.[5,26,27] Thus, TCAR was introduced as an alternative to TFCAS to reduce postoperative complications by providing dynamic flow reversal to provide cerebral protection prior to

TABLE 2. One-Year and Three-Years Death Following TCAR Versus CEA Before and After PSM

	Outcomes	TCAR (%)	CEA (%)	HR (95% CI) Reference = CEA	P
Before PSM	1-year death	8.1	5.7	1.45 (1.31–1.60)	< 0.001
	3-year death	22.0	16.8	1.43 (1.32–1.56)	< 0.001
After PSM	1-year death	7.8	7.0	1.13 (0.99–1.30)	0.065
	3-year death	21.3	18.8	1.16 (1.04–1.30)	0.008

CEA indicates carotid endarterectomy; CI, confidence interval; HR, hazard ratio; TCAR, transcarotid artery revascularization.

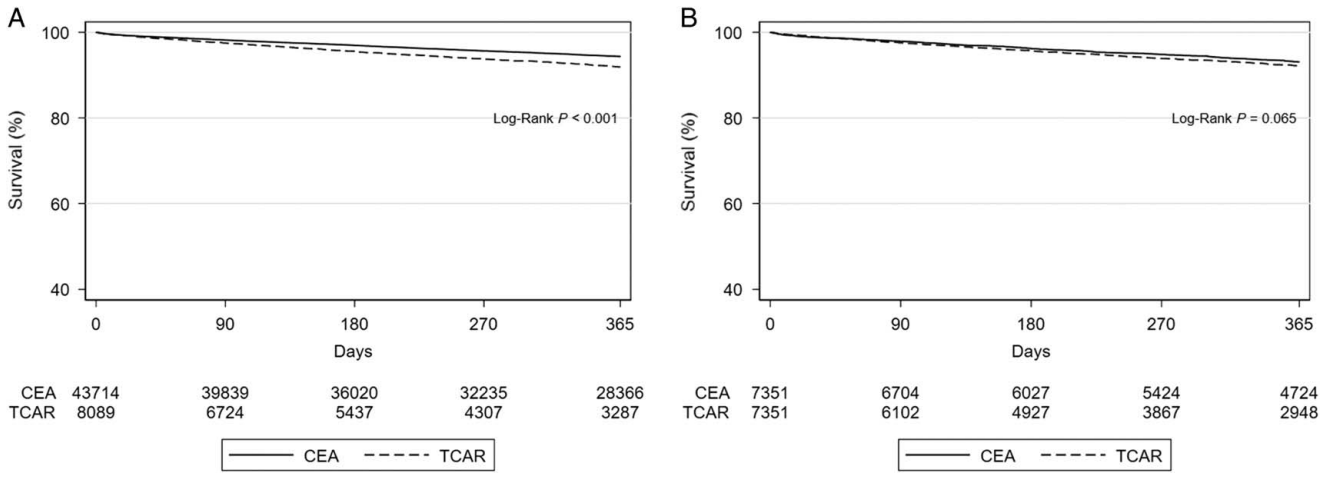

FIGURE 2. One-year survival before (A) and after (B) propensity score matching in TCAR vs. CEA cohorts. CEA indicates carotid endarterectomy; TCAR, transcarotid artery revascularization.

crossing the carotid lesion, in addition to avoiding the manipulation of the atherosclerotic aortic arch.[11–13]

Two single-arm clinical trials have evaluated the safety and efficacy of ENROUTE (Silk Road Medical Inc., Sunnyvale, CA) transcarotid neuroprotection system (NPS) during TCAR. In the Safety and Efficacy Study for Reverse Flow Used During Carotid Artery Stenting Procedure (ROADSTER 1) trial, the overall 30-day stroke rate was 1.4%.[28] In 1 year, there was 96% stroke-free survival.[29] Moreover, short-term outcomes of ROADSTER 2 revealed high technical success combined with low rates of postprocedural stroke and death after TCAR. The composite 30-day stroke/death rate was 2.3%, and the stroke/death/MI rate was 3.2% in intention to treat analysis.[30] Both trials did not have a CEA control group. Moreover, the maximum follow-up was 1 year. In the present study, we compared TCAR and CEA cohorts in the real-world experience using data from a Medicare-Linked database. We found no difference in hazards of death up to 3 years following TCAR versus CEA in asymptomatic patients. A slight increase in the hazards of death was observed in symptomatic patients undergoing TCAR compared to CEA.

In a previous propensity-matched analysis of TSP-VQI data, we compared two matched pairs of TCAR and CEA (n = 6384) and found no significant difference in the risk of in-hospital stroke/death between TCAR and CEA.[17] In another PSM analysis of 4180 matched pairs of TCAR and CEA in the TSP-VQI data, there were no significant differences in 30-day stroke, death, and stroke/death rates. However, TCAR was associated with a lower risk of 30-day stroke/death/MI (2.30% vs. 3.25%; $P = 0.008$). At 1 year, no significant difference was observed in the risk of ipsilateral stroke or death (6.49% vs. 5.68%; $P = 0.157$).[18] Both of these PSM studies used VQI data without Medicare linkage. In addition, the maximum follow-up was up to 1 year. In the present study, we confirmed the similarity of TCAR with CEA in terms of survival analyses under matched conditions up to 1 year. Moreover, we analyzed the data up to 3 years and used Medicare-Linked data (VISION) for mid-term follow-ups.

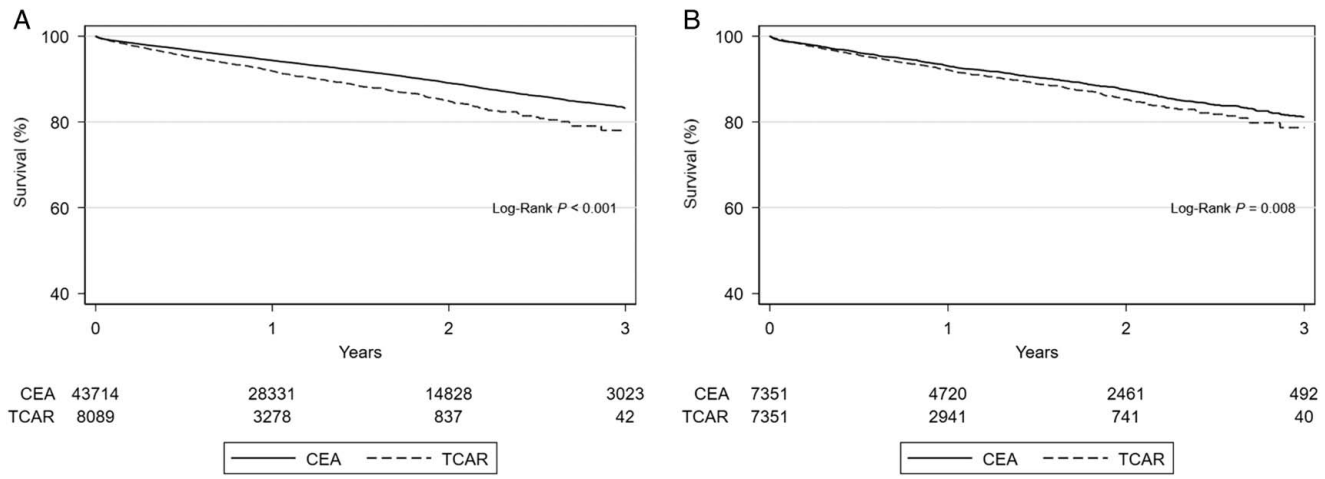

FIGURE 3. Three-year survival before (A) and after (B) propensity score matching in TCAR vs. CEA cohorts. CEA indicates carotid endarterectomy; TCAR, transcarotid artery revascularization.

TABLE 3. One-year and 3-years Death Following TCAR vs. CEA in Matched Cohorts Stratified by Symptomatic Status

Outcomes	TCAR (%)	CEA (%)	HR (95% CI) Reference = CEA	*P*
Asymptomatic				
1-year death	7.1	6.6	1.08 (0.92–1.27)	0.343
3-year death	20.3	18.9	1.10 (0.96–1.25)	0.166
Symptomatic				
1-year death	10.1	8.1	1.25 (0.98–1.60)	0.069
3-year death	24.2	18.5	1.33 (1.08–1.63)	0.008

CEA indicates carotid endarterectomy; CI, confidence interval; HR, hazard ratio; TCAR, transcarotid artery revascularization.

A systematic review and meta-analysis investigating the available literature on TCAR evaluated 4012 patients from 9 nonrandomized studies. We found that the overall 30-day risks following TCAR are stroke/death, 1.89% (95% CI, 1.50–2.37), stroke, 1.34% (95% CI, 1.02–1.75), death, 0.76% (95% CI, 0.56–1.08), MI, 0.60% (95% CI, 0.23–1.59), stroke/death/MI, 2.20% (95% CI, 1.31–3.69), and CNI, 0.31% (95% CI, 0.12–0.83). Four nonrandomized studies reported no statistically significant difference in the 30-day risk of stroke, stroke/death, or stroke/death/MI between TCAR and CEA.[31] Another systematic review and meta-analysis was conducted by Gao and colleagues. They studied 14,200 subjects from 6 comparative studies. They found no statistical difference between TCAR and CEA in terms of stroke/death/MI (OR = 0.85; 95% CI, 0.67–1.07), stroke (OR = 1.03; 95% CI, 0.77–1.37), or death (OR = 1.14; 95% CI, 0.67–1.94). Moreover, they found that TCAR is associated with a lower risk of MI ($P = 0.004$) and CNI ($P < 0.00001$) than CEA.[32] Wu and associates conducted another systematic review and meta-analysis. They included 12 studies and they also find no significant difference in the risks of stroke (OR = 1.07; 95% CI, 0.83–1.37), death (OR = 1.72; 95% CI, 0.82–3.62), stroke/death (OR = 1.05; 95% CI, 0.83–1.33) and stroke/death/MI (OR = 0.95; 95% CI, 0.78–1.16) between TCAR and CEA. Moreover, they did not find a significant difference in MI between TCAR and CEA.[33] All the mentioned meta-analyses used observational studies, investigated the short-term outcomes, and confirmed similar periprocedural profiles of TCAR and CEA in terms of stroke and mortality. However, the present study includes a comparison of mid-term outcomes up to 3 years and reflects the results of real-world practice. We observed a slight increase in 3-year death in TCAR cohort compared to CEA. However, based on the overall high-risk profile of the TCAR cohort, there may be several other confounders that are associated with higher rate of death (persisted only in symptomatic patients in subanalysis) despite propensity matching. Moreover, based on the variables available in VQI-VISION, we were not able to determine if the IFU was followed for the TCAR patients. Based on our outcomes, TCAR continues to be a safe and durable minimally invasive revascularization option for surgically high-risk patients with carotid artery stenosis; however, a randomized controlled trial is necessary to provide level I evidence particularly in standard risk patient.

LIMITATIONS

The present study has several limitations to consider. First, we performed a retrospective analysis of prospectively collected data and the possibility of confounding by indication was not avoidable because of the nonrandom allocation of the intervention groups. Although we performed PSM based on all the variables available in the VQI-VISION database, some degree of confounding from unmeasured variables is inevitable. In addition, the assessment of stroke at follow-ups is not captured in this Medicare-linked claim because of the limitations of CPT and ICD coding. Thus, some patients may have experienced a contralateral or posterior circulation stroke during the follow-up period unrelated to the carotid revascularization of interest. Additionally, using the Medicare-linked database in the present study limits the generalizability to the overall population undergoing carotid revascularization, particularly to the younger populations. Moreover, as with any large database with voluntary participation, coding errors, and selection bias are possible. However, the VQI seeks to limit this through a large sample size as well as routine data auditing procedures.

Finally, ongoing validation analyses of the current claims-based algorithms used to define postoperative stroke in the VISION database have demonstrated a small but persistent contamination of preoperative stroke events in the postoperative stroke outcome, especially among symptomatic individuals, where stroke codes have been found to "carry-over" from preoperative to postoperative codes. As such, we focused our primary outcome on survival in this analysis.

CONCLUSIONS

In this large multi-institutional PSM analysis with robust Medicare-linked follow-up for survival analysis, asymptomatic patients demonstrate little difference in survival between the two procedures, while symptomatic patients live longer after CEA, likely because of residual confounding by more severe comorbidities in the TCAR cohort despite matching. There were no differences in the rates of stroke or stroke/death at 3 years in either symptomatic or asymptomatic patients in the TCAR versus CEA cohorts; however, the development of stronger claims-based algorithms for postoperative stroke assessment after carotid revascularization will help to clarify long-term stroke outcomes between these two procedures. Ultimately, a randomized controlled trial comparing TCAR to CEA is necessary to further determine the role of TCAR in standard-risk patients requiring carotid revascularization.

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DISCUSSANT

Dr. Matthew Mell (Sacramento, CA)

I would like to thank Drs. Farmer, Hawn, Hunt, and the program committee for the opportunity to comment on this paper presented by Dr. Malas on comparative midterm outcomes of TCAR and carotid endarterectomy for carotid stenosis. This work is a continuation of published papers on TCAR by Dr. Malas and colleagues that began in 2019. Dr. Malas has become a leader in TCAR research and this work highlights the importance of studying the dissemination of new technology including its role in disease treatment.

Of particular value in this study is the utilization of a linkage between clinical data from the VQI, the Society of Vascular Surgery Patient Safety Organization, with Medicare data. This allows for the assessment of long-term outcomes after treatment of vascular disease and this linked data is a relatively new tool in our specialty. Such a linkage to relevant and meaningful data can unlock insights that would be otherwise unavailable based on the limitations of data collection for VQI alone.

Overall, the comparative observations are mostly not surprising and consistent with previous studies:

- Patients undergoing TCAR were older and had more medical comorbidities, more likely to be on anti-platelet agents and statins, and less likely to receive general anesthesia compared with those undergoing CEA.
- Before propensity matching, TCAR was associated with increased 1- and 3-year stroke, death, and composite stroke-death outcomes.
- After propensity matching all 1-year outcomes and 3-year stroke rates were similar

A somewhat unexpected observation was that even after propensity matching 3-year mortality remained increased after TCAR compared with CEA. This was largely driven by increased 3-year mortality for patients with symptomatic carotid stenosis.

I have the following questions for the authors:

1. Other vascular studies have shown that utilizing new technologies may be associated with better outcomes when adhering to the Instructions-For-Use. Does the operative VQI data set allow you to determine if TCAR was performed within the IFU (for example diameters of CCA and ICA, distance to bifurcation, quantification of calcification of lesion), and how might have this data impacted the results?
2. Can you expand on the increased 3-year mortality for symptomatic patients undergoing TCAR? As presumably that would not be explained by technical aspects of the

procedure or stroke rates per se which were similar to that of endarterectomy? Was this a statistical consequence of the small number at risk at 3 years? Might it be from more severe stroke and its sequelae with TCAR, which may be concerning? Or perhaps unrelated to carotid disease and a consequence of more severe comorbidity? Or by some other explanation.

3. Your group has TCAR outcomes have been shown to be superior to transfemoral approach. The CREST-2 comparing CEA to transfemoral carotid stent and comparing both to best medical management is nearing completion of enrollment, but TCAR is excluded from the study. Should TCAR largely replace transfemoral stent, and will the CREST-2 study results run the risk of being obsolete? If so, how could or should you address other specialties who perform transfemoral but do not have the skill set for open carotid exposure.

Only just over half of the cohort has ipsilateral stenosis > 80%, and 3 quarters of your cohort had treatment for asymptomatic carotid stenosis with a 1-year stroke rate of approximately 11% for both CEA and TCAR. These real-world outcomes are significantly higher than published rates from randomized studies, including for those managed medically, leading some experts to reconsider the role of any intervention for asymptomatic disease. Could you comment on this observation and the quality of the data, providing your perspective on your recommended role for TCAR for the treatment of carotid stenosis moving forward?

Again, thank you for the opportunity to review your work.

Response From Mahmoud Malas

Thank you so much, Dr. Mell, for your thorough review of our paper and for these important 4 questions.

Regarding your first question: to be anatomically eligible for TCAR, a patient common carotid artery needs to be at least 6 mm in diameter, free of significant atherosclerotic disease with at least 5 cm distance from the clavicle to the carotid bifurcation. This provides an adequate landing zone for the wire to support sheath advancement. Unfortunately, VQI does not have these measurements. However, according to 1 prior study of about 220 carotid CT scans with significant carotid stenosis, 75% of patients had adequate landing zone and more than 95% had no significant disease of the common carotid artery with adequate diameter. There were about 25% of the cohort who did not have enough length from the clavicle to the carotid bifurcation. If some of the patients in our study did not meet these inclusion criteria but still underwent TCAR, you would expect them to have worse outcomes. In this case, the reported postoperative outcomes should improve if we follow IFU for all our patients. The degree of calcification at the proximal common carotid artery is not captured in VQI, but we have data on the calcium burden of the lesion itself at the carotid bifurcation. We've done one prior study that showed a significant reduction of stroke and death in patients with significant calcification undergoing TCAR or CEA compared to transfemoral stenting.

For the second question on the persistent increase in the risk of 3-year mortality, you're correct that it is not related to stroke simply because the stroke and stroke/death rate was similar for both procedures. I also agree that this is related to a smaller number at risk at 3 years for TCAR patients. After matching, the 3-year increased mortality was observed only in symptomatic patients. It is well known that a symptomatic lesion is a marker of diffuse and progressive atherosclerotic disease in sicker patients. Propensity score matching is one of the best statistical methods short of randomization, but it has its own limitations. For example, 2 patients with CAD: one had an MI a year ago and completely changed his lifestyle, quit smoking, lost weight, and stayed on statin and antiplatelet, while the second patient might have active, unstable angina. Most surgeons would offer CEA to the first patient and TCAR for the second. While these 2 patients are matched based on CAD, they are not going to have the same long-term survival. This is why PSM should not replace a well-designed randomized trial.

Regarding the third question on transfemoral stenting, I would agree that every study thus far has shown better outcomes with TCAR. I still think TFCAS has a role in a small portion of patients who are truly high risk for CEA and don't have adequate anatomy for TCAR. Vascular surgeons should continue to participate in and lead clinical trials investigating the best procedural options for vascular patients and collaborate with other specialties such as neurosurgery, neuro-interventional radiology, and interventional cardiology. Treatment guidelines should be formulated across all specialties who treat carotid artery disease and should utilize well performed studies and actual real-world data in addition to RCTs.

And for the final question regarding the higher stroke rate in this study compared to randomized trials. It is well known that RCT selects healthier patients than real-world data. The second important point that I listed clearly in the limitation of this study and any other study that uses Medicare data, is the over-reporting of stroke rate. There is ongoing work to validate stroke rates and correct potential contamination of preoperative stroke that is counted as a postoperative stroke. However, this over-reporting of stroke rate is not exclusive to one procedure versus the other and our overall conclusion of similar stroke or death rates between the 2 procedures at one and 3 years should remain valid.

Dr. Michael Stoner (Rochester, NY)

Mahmoud, first of all, I'd like to just congratulate your group once again on a stellar presentation regarding minimal access carotid technology, and you've done much to bring that success to where it is in this country right now. The question I just wanted to expand upon, which I think is a bit alarming to mention to the membership in this room, is that these data actually threaten the prophylactic nature of asymptomatic carotid revascularization. I wonder if you could expand on that because again, they diverge from ACAS and preliminary CREST data as well. Do you feel that these data support asymptomatic carotid revascularization because I would postulate they do not?

Response From Mahmoud Malas

Thank you Dr. Stoner for your question. Most asymptomatic patients, especially with moderate stenosis should be managed medically, and hopefully CREST-2 will answer that question. However, as Dr. Mell alluded, CREST-2 excluded TCAR. Thus, the idea of VISION of matching VQI with Medicare data to add real work evidence and maybe in the future facilitate conducting randomized trial more efficiently. I believe asymptomatic patients with true high-grade stenosis deserve revascularization, whether it's carotid endarterectomy or TCAR as the outcomes of both procedures so far is equivalent. However, I strongly believe that a randomized trial comparing the 2 procedures is overdue. It is critical when considering carotid revascularization for our patients to ensure they are going to survive at least 4 years to harvest the benefit of our procedures.

This was clearly emphasized in our latest Society of vascular surgery carotid guidelines.

Dr. Omaida Velazquez (Miami, FL)

Omaida Velazquez from Miami. I want to congratulate you, Dr. Malas, and your group, for pioneering and leading this effort to look at this novel way to deal with cervical carotid artery atherosclerotic disease.

My question specifically has to do with the technology in terms of first-generation devices versus the future. Who gets excluded from this technology as it currently exists? In other words, as you mentioned, you need 5 cm of healthy "manly" common carotid artery, otherwise, it's not a good anatomic situation and falls outside Instructions for Use (IFU), and in my experience, the majority of the patients that I evaluate for TCAR do not meet IFU – you said 25% in your experience – but, in our community, we see extensive disease extending into the common carotid artery and many women. The plaque is not localized to the carotid bulb and the common carotid arteries are smaller in caliber and carry significant plaque burden. And in fact, those who have common carotid artery disease tend to have more aortic arch disease, so in a sense, we are thinking we don't want to cross the arch, with the transferal carotid stent, but we then need a normal common carotid artery that often is not present when the arch has an extensive disease.

Those who have normal common carotid arteries, likely you'll have no problem crossing the arch, so in your experience, (and it's not something that you may be able to answer today)—with this approach, who gets excluded, by secondary group gender and ethnicity assessments? Do you have a sense of the male-to-female ratio in that 25% that don't meet the device IFU criteria? And in the design of the very much needed level 1 evidence randomized trial that we are all advocating for, how would you propose getting around this challenge of really understanding who's getting excluded from first-generation TCAR technology, and how are we going to design the technology for the future so that is equally available to men and women and ethnicities with smaller caliber common carotid arteries?

This was a critical question we had to ask at the advent of aortic endograft, showing that women were being excluded from the early EVAR clinical trials by a disproportionally higher number (compared to men) and we, the vascular surgeon community, pushed the industry to what needed to happen so that women would not be excluded, by redesigning devices to be smaller profile and more flexible, thus meeting the needs of the majority of women with small caliber iliac arteries.

Thank you.

Response From Mahmoud Malas

Thank you Dr. Velazquez for these important questions. It is possible that we are underestimating the percentage of patients not meeting the anatomical inclusion criteria of TCAR, especially women and other ethnicities. I think if you are treating very high-risk patients with significant disease burden, probably that percentage is higher. I strongly believe that we need to design endovascular solutions to fit women's anatomy instead of utilizing devices designed for men in women vessels and then blaming women's anatomy for worse outcomes. However, it is important to mention that the current outcomes of TCAR are similar between men and women and across different races in our own prior studies. I again emphasize that a well-designed RCT that is inclusive of women and minority is overdue. We have working on funding for over a year. The main challenge that we are facing is the ongoing CREST II trial and the fact that our neurology colleagues at NIH feel strongly against any carotid revascularization procedure and especially in asymptomatic patients.

Thank you.