SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Carotid Stent

Device Trade Name: ENROUTE® Transcarotid Stent System

Device Procode: NIM

Applicant's Name and Address: Silk Road Medical, Inc.
1213 Innsbruck Drive
Sunnyvale, CA 94089

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P140026/S016

Date of FDA Notice of Approval: April 28, 2022

The original PMA (P140026) for the ENROUTE® Transcarotid Stent System was approved on May 18, 2015 and is indicated for use in conjunction with the ENROUTE Transcarotid Neuroprotection System (NPS) for the treatment of patients at high risk for adverse events from carotid endarterectomy who require carotid revascularization and meet the criteria outlined below.

1. Patients with neurological symptoms and ≥ 50% stenosis of the common or internal carotid artery by ultrasound or angiogram OR patients without neurological symptoms and ≥ 80% stenosis of the common or internal carotid artery by ultrasound or angiogram, AND
2. Patients must have a vessel diameter of 4-9mm at the target lesion, AND
3. Carotid bifurcation is located at minimum 5 cm above the clavicle to allow for placement of the ENROUTE Transcarotid NPS.

The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for the ENROUTE® Transcarotid Stent System to include patients at standard risk for adverse events from carotid endarterectomy.

II. INDICATIONS FOR USE

The ENROUTE® Transcarotid Stent System used in conjunction with the ENROUTE Transcarotid Neuroprotection System (NPS) is indicated for the treatment of patients at high and standard risk for adverse events from carotid endarterectomy who require carotid revascularization and meet the criteria outlined below:

	High Risk	Standard Risk
With neurological symptoms	≥ 50% stenosis of the common or internal carotid artery by ultrasound or angiogram	≥ 70% stenosis of the common or internal carotid artery by ultrasound or ≥ 50% stenosis of the common or internal carotid artery by angiogram
Without neurological symptoms	≥ 80% stenosis of the common or internal carotid artery by ultrasound or angiogram	≥ 70% stenosis of the common or internal carotid artery by ultrasound or ≥ 60% stenosis of the common or internal carotid artery by angiogram
Reference vessel diameter	Must be within 4.0 mm – 9.0 mm at the target lesion	
Carotid bifurcation location	Minimum 5 cm above the clavicle to allow for placement of the ENROUTE Transcarotid NPS	

III. CONTRAINDICATIONS

Use of the ENROUTE® Transcarotid Stent System is contraindicated in the following patients:

1. Patients in whom antiplatelet and/or anticoagulation therapy is contraindicated.
2. Patients in whom the ENROUTE® Transcarotid NPS is unable to be placed.
3. Patients with uncorrected bleeding disorders.
4. Patients with known allergies to nitinol.
5. Lesions in the ostium of the common carotid artery.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the ENROUTE® Transcarotid Stent System labeling.

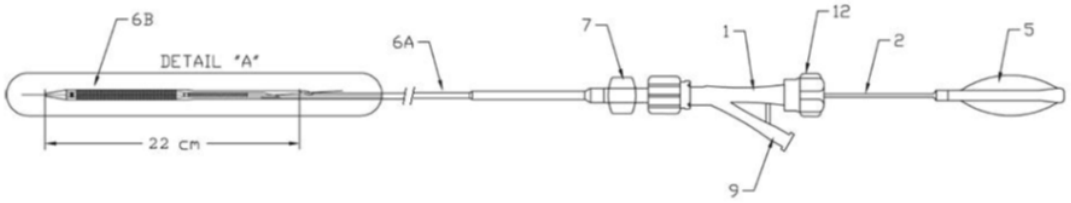
V. DEVICE DESCRIPTION

The SRM ENROUTE® Transcarotid Stent System for standard surgical risk patients is identical to that approved under P140026 for high surgical risk patients.

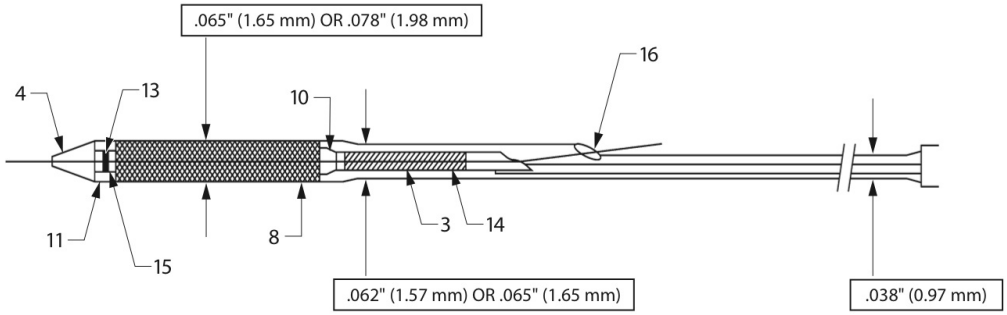
The SRM ENROUTE® Transcarotid Stent System consists of a nitinol self-expanding stent preloaded on a .065 inch (1.65 mm) or .078 inch (1.98 mm) sheathed delivery system. The delivery system consists mainly of an inner shaft and an outer sheath with radiopaque markers, and a Tuohy Borst valve. The distal inner shaft consists of a support member and

wire lumen. The proximal portion of the support member is comprised of a hub connected to a stainless steel wire and hypotube and distally of a stainless steel coil. The wire lumen originates distally in a catheter tip and terminates proximally at a guidewire exit port located mid-shaft and designed to accept a .014" (0.36 mm) guidewire. The outer sheath has a proximal shaft and distal outer sheath with a nominal working length of 57 cm. The self-expanding stent is constrained within the space between the inner shaft and the distal outer sheath, located between distal and proximal stent markers on the inner shaft. The stent expands to its unconstrained diameter when released from the deployment catheter into the vessel. Upon deployment, the stent forms an open lattice and pushes outward on the luminal surface, helping to maintain the patency of the vessel. Due to the self-expanding behavior of nitinol, the stents are indicated for placement into vessels that are 1-2 mm smaller in diameter than the unconstrained diameter of the stent. Device depictions and components are provided in Figure 1.

Figure 1: ENROUTE® Transcarotid Stent System



DETAIL "A":



Item	Description
1	Tuohy Borst valve
2	Hypotube
3	Coil
4	Catheter inner shaft tip
5	Inner shaft hub
6A	Proximal shaft
6B	Distal outer sheath
7	Outer shaft Luer hub
8	Pod housing crimped stent
9	Tuohy Borst Y-connection
10	Proximal inner shaft marker (stop) marks trailing end of stent
11	Outer sheath radiopaque marker
12	Proximal valve end
13	Distal inner shaft stent marker
14	Coil sleeve
15	Wire lumen
16	Guidewire exit port

Table 1 lists the stent configurations. Due to the self-expanding behavior of nitinol, the stents are indicated for placement into vessels that are 1-2mm smaller in diameter than the unconstrained diameter of the stent.

Table 1: Silk Road ENROUTE® Transcarotid Stent System Catalog Numbers

Catalog Number	Unconstrained Stent Dimensions Diameter x Length (mm)	Crossing Profile
SR-0520-CS	5 x 20	5F (.078", 1.98mm)
SR-0530-CS	5 x 30	5F (.078", 1.98mm)
SR-0540-CS	5 x 40	5F (.078", 1.98mm)
SR-0620-CS	6 x 20	5F (.078", 1.98mm)
SR-0630-CS	6 x 30	5F (.078", 1.98mm)
SR-0640-CS	6 x 40	5F (.078", 1.98mm)
SR-0720-CS	7 x 20	5F (.078", 1.98mm)
SR-0730-CS	7 x 30	5F (.078", 1.98mm)
SR-0740-CS	7 x 40	5F (.078", 1.98mm)
SR-0820-CS	8 x 20	5F (.078", 1.98mm)
SR-0830-CS	8 x 30	5F (.078", 1.98mm)
SR-0840-CS	8 x 40	5F (.078", 1.98mm)
SR-0920-CS	9 x 20	6F (.087", 2.21mm)
SR-0930-CS	9 x 30	6F (.087", 2.21mm)
SR-0940-CS	9 x 40	6F (.087", 2.21mm)
SR-1020-CS	10 x 20	6F (.087", 2.21mm)
SR-1030-CS	10 x 30	6F (.087", 2.21mm)
SR-1040-CS	10 x 40	6F (.087", 2.21mm)

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternatives to stenting for the correction of carotid artery disease include surgery, medical therapy, or a combination of both. The primary treatment used to prevent stroke in patients with significant carotid artery disease is surgery (endarterectomy) to remove plaque from the affected artery. Medical therapy includes use of antiplatelet and/or anticoagulant medicine, as well as antihypertensive and antilipidemic drugs as indicated. Antiplatelet drugs include aspirin, Plavix® (clopidogrel), or Ticlid® (ticlopidine). Anticoagulants include Coumadin® (warfarin). Medical therapy can also include modification of lifestyle risk factors for stroke, such as cigarette smoking and alcohol use. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The ENROUTE® Transcarotid Stent System has been commercially available in the United States since June 2015. As of December 2021, 57,895 stents have been distributed within the United States. The ENROUTE® Transcarotid Stent System (initially marketed as the KOBI Transcervical Carotid Stent System in Europe) has been on the market in the following countries since August 2013:

- United Kingdom
- Belgium
- France
- Germany

- Hungary
- The Netherlands
- Spain
- Switzerland

As of December 2021, 536 stents have been distributed outside the United States (OUS). The ENROUTE® Transcarotid Stent System that is marketed OUS does not include risk stratification of patients in the labeling (i.e. patient risk status is not defined in the labeling).

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- Air embolism
- Allergic/anaphylactoid reaction
- Aneurysm
- Angina/coronary ischemia
- Arrhythmia (including bradycardia, possibly requiring need for a temporary or permanent pacemaker)
- Arterial dissection
- Arterial occlusion/restenosis of the treated vessel
- Arterial occlusion/thrombus, at puncture site
- Arterial occlusion/thrombus, remote from puncture site
- Arteriovenous fistula
- Bacteremia or septicemia
- Cerebral edema
- Death
- Embolization, arterial
- Embolization, stent
- Emergent repeat hospital intervention
- Fever
- Gastrointestinal disorders
- GI bleeding from anticoagulation/antiplatelet medication
- Hallucination
- Hematoma bleed, access site
- Hematoma bleed, remote site
- Hemorrhage
- Hyperperfusion syndrome
- Hypotension/hypertension
- Hyomagnesaemia
- Hypophoshatemia
- Infection
- Intimal injury/dissection
- Ischemia/infarction of tissue/organ
- Local infection and pain at insertion site

- Malposition (failure to deliver the stent to the intended site)
- Myocardial infarction
- Nausea
- Oxygen saturation decrease
- Pain
- Pseudoaneurysm
- Renal failure
- Respiratory infection
- Restenosis of the vessel (> 50% obstruction)
- Rhinorrhea
- Seizure
- Severe unilateral headache
- Stent migration
- Stent thrombosis
- Stroke
- Transient ischemic attack
- Transient intolerance to reverse flow
- Urinary tract infection
- Vasospasm
- Venous occlusion/thrombosis, at puncture site
- Venous occlusion/thrombosis, remote from puncture site
- Vessel rupture, dissection, perforation
- Vomiting
- Wheezing

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

Because the ENROUTE® Transcarotid Stent System for standard surgical risk patients is identical to the ENROUTE® Transcarotid Stent System approved for high surgical risk patients, non-clinical and pre-clinical testing was leveraged from the P140026 approval for high surgical risk subjects. Please reference the P140026 SSED for additional detail on the preclinical testing that supported the approval.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant utilized real-world data (RWD) housed within the Society for Vascular Surgery Vascular Quality Initiative (SVS VQI) to conduct analyses presented to support the standard risk approval. The analyses establish real-world evidence (RWE) to provide reasonable assurance of the safety and effectiveness of the ENROUTE® Transcarotid Stent System in standard surgical risk patients during transcarotid artery revascularization (TCAR) procedures. Reasonable assurance of safety and effectiveness was demonstrated through an analysis of patient-level data from the carotid artery stenting (CAS) and carotid endarterectomy (CEA) registries of the SVS VQI.

The TCAR Surveillance Project (TSP) was initiated in 2016 by the Society for Vascular Surgery Vascular Quality Initiative (SVS VQI) to obtain more data about real-world outcomes of TCAR in patients deemed high surgical risk for CEA as performed by centers participating in the SVS VQI. As of January 2021, 565 centers have contributed almost 28,000 TCAR cases to the CAS registry.

A. Study Design

Patients deemed to be at standard risk for adverse events from CEA were analyzed in a propensity score matched analysis to provide RWE. Outcomes include major adverse events (death/stroke/myocardial infarction) through 30 days and ipsilateral stroke from 31 days through 365 days. The outcomes are presented as a composite endpoint. Propensity score matching and data analyses were conducted on behalf of the sponsor by a third party that is unaffiliated with the sponsor.

All standard risk CEA and TCAR patients that underwent the procedure from August 8, 2016 through September 2, 2020 that were entered into the SVS VQI CAS and CEA registries were considered for inclusion. The analysis was conducted with data through September 2, 2020.

1. Clinical Inclusion and Exclusion Criteria

Patients included in this analysis were consecutively entered into the SVS VQI. TCAR patients were treated with the ENROUTE® Transcarotid Stent System (ENROUTE Stent) in conjunction with the ENROUTE® Transcarotid Neuroprotection System (ENROUTE NPS). Only patients deemed to be at standard risk for adverse events from CEA were included.

In the TSP, the following patients are considered high surgical risk (HSR):

Anatomic High-Risk Inclusion Criteria:

- Contralateral carotid artery occlusion
- Tandem stenoses in the internal carotid artery >70% diameter reducing
- High cervical carotid artery stenosis above the C2 vertebra
- Restenosis after prior ipsilateral carotid endarterectomy
- Hostile neck including but not limited to prior neck irradiation, prior radical neck dissection, stoma presence or cervical spine immobility

Clinical High-Risk Inclusion Criteria:

- Patient is ≥ 75 years of age
- Patient has ≥ 2-vessel coronary artery disease and history of angina
- Patient has a history of unstable angina or Canadian Cardiovascular Society (CCS) angina class 3 or 4
- Patient has congestive heart failure (CHF) - New York Heart Association (NYHA) Functional Class III or IV

- Patient has known severe left ventricular dysfunction with left ventricular ejection fraction (LVEF) <30%
- Patient has had a myocardial infarction < 6 weeks prior to procedure
- Patient has severe pulmonary disease (COPD) with either forced expiratory volume (FEV1) <50% predicted or chronic oxygen therapy or resting partial pressure of oxygen (PO2) of <= 60 mmHg (on room air) or is on home oxygen
- Patient has permanent contralateral laryngeal nerve injury
- Patient has chronic renal insufficiency (serum creatinine > 2.5 mg/dL) or is on dialysis
- Patient has need for open heart or other major operation within 30 days of carotid treatment

Hence, patients that present without any of these HSR anatomic or clinical features would be considered standard surgical risk (SSR) except for age ≥75 years. While CMS considers age ≥75 years to be a high-risk criterion, the sponsor has altered the age threshold for patients included in this analysis to patients age <80 years. This aligns with other standard risk trials such as ACT-1 (Ref. 1) which excluded patients <80 years and the CREST study (Ref. 2) which had no upper age limit. In the FDA analysis from the CREST study, octogenarians accounted for only 10.2% of enrollment in the transfemoral carotid artery stenting (TFCAS) arm (Ref. 3). In the lead-in phase of CREST (Ref. 4), the incidence of death or stroke within 30 days in octogenarians was 12.12%. This was significantly higher than the incidence of death or stroke within 30 days in non-octogenarians (3.23%; p<0.0001) and is the reason for establishing the threshold in this analysis at <80 years.

Patients excluded from these analyses are as follows:

- Tandem, traumatic or dissection lesions
- More than one stented lesion
- CEA with concomitant procedures
- TCAR patients treated with another manufacturer's stent

2. Follow-up Schedule

Patients deemed to be at standard risk for adverse events from CEA were analyzed in a propensity score matched analysis. Outcomes include Major Adverse Events (MAE; death/stroke/myocardial infarction) through 30 days and ipsilateral stroke from 31 days through 365 days.

3. Clinical Endpoints

The composite primary endpoint to establish reasonable assurance of the safety and effectiveness of the subject device is death/stroke/myocardial infarction through 30 days and ipsilateral stroke from day 31 through day 365.

The objective of the analysis is to determine if TCAR is non-inferior to CEA based on the primary endpoint definition. The null hypothesis and alternative hypothesis are presented below.

Ho: $\pi_{TCAR} - \pi_{CEA} \geq$ non-inferiority margin (%)
Ha: $\pi_{TCAR} - \pi_{CEA} <$ non-inferiority margin (%)

Where π_{TCAR} represents the percentage of TCAR patients who experience the composite primary endpoint, π_{CEA} represents the percentage of CEA patients who experience the composite primary endpoint, and non-inferiority margin (%) refers to the pre-specified non-inferiority margin.

A non-inferiority margin of 5% was chosen.

The cumulative incidence of the endpoint was estimated among the matched population using Kaplan Meier methods. Statistical inference was performed using the bootstrap method.

Other procedural and outcome measures were also assessed including the following:

Secondary Endpoints

- Outcomes by Gender
- Outcomes by Age (<65 and ≥65)
- Cranial Nerve Injury, in-hospital

Observational Endpoints

- Outcomes by Race
- Outcomes by Ethnicity
- Stroke, in-hospital
- Death, in-hospital
- Myocardial Infarction (MI), in-hospital
- Stroke/Death/MI, in-hospital
- Access Site Complication
- Hematoma/bleeding
- Postoperative stenosis/occlusion
- Pseudoanuerysm
- Return to Operating Room

B. Accountability of PMA Cohort

All CEA and TCAR patients that underwent the procedure from August 8, 2016 through September 2, 2020 who were entered into the SVS VQI CAS and CEA registries were considered for inclusion. A total of 44,743 CEA patients and 5,066 TCAR patients over the aforementioned period were available for the analyses. After matching CEA and TCAR patients in a 3:1 ratio, 15,198 CEA patients and 5,066 TCAR patients who received the ENROUTE stent were available for the analyses.

This includes 2,988 CEA patients with 1-year follow-up and 996 TCAR patients treated with the ENROUTE stent with 1-year follow-up that were analyzed.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for standard surgical risk carotid artery stenting study performed in the US.

Demographics and Baseline Characteristics (All Matched Patients)

Table 2 provides a tabulation of the baseline demographics for all matched CEA and TCAR patients. Three CEA patients were matched to each TCAR patient (3:1 nearest neighbor, no caliper). There were no TCAR patients treated with the ENROUTE Stent that were excluded from matching. Key demographic parameters were similar between the matched cohorts: symptom status, age, gender, congestive heart failure, COPD, dialysis, smoking, hypertension, kidney function, coronary artery disease and percent stenosis. TCAR patients had a slightly higher mean body mass index based on the arithmetic mean, and a slightly higher incidence of mild coronary artery disease, but neither was considered clinically significant. The median BMI differed by 0.5 (kg/m^2) between TCAR and CEA. The incidence of severe stenosis (>70%) was 91.3% and 90.2% for the CEA and TCAR cohorts, respectively.

Table 2: Demographics and Baseline Characteristics after Matching (All Patients)

	Total	Treatment Modality		
		CEA	TCAR	
	n = 20264	n = 15198	n = 5066	Std Diff (%)
Presenting Symptom Status				1.5
Stroke	6187 (30.5%)	4619 (30.4%)	1568 (31.0%)	
Cortical TIA	2435 (12.0%)	1823 (12.0%)	612 (12.1%)	
Retinal TIA	838 (4.1%)	630 (4.1%)	208 (4.1%)	
Unknown Stroke Severity	1516 (7.5%)	1135 (7.5%)	381 (7.5%)	
Asymptomatic	9288 (45.8%)	6991 (46.0%)	2297 (45.3%)	
Age				3.1
Mean ± SD	70.22 ± 6.72	70.17 ± 6.66	70.38 ± 6.88	
Median (IQR)	72.00 (66.00, 76.00)	71.00 (66.00, 75.00)	72.00 (66.00, 76.00)	
Age ≥65	16360 (80.7%)	12285 (80.8%)	4075 (80.4%)	1.0
Male	12943 (63.9%)	9684 (63.7%)	3259 (64.3%)	1.3
Caucasian	18211 (89.9%)	13670 (89.9%)	4541 (89.6%)	1.0
Race				1.7
American Indian or Alaskan Native	95 (0.5%)	70 (0.5%)	25 (0.5%)	
Asian	160 (0.8%)	122 (0.8%)	38 (0.8%)	
Black or African American	1149 (5.7%)	854 (5.6%)	295 (5.8%)	
	17 (0.1%)	12 (0.1%)	5 (0.1%)	
Native Hawaiian or other Pacific Islander	18211 (89.9%)	13670 (89.9%)	4541 (89.6%)	
White	41 (0.2%)	29 (0.2%)	12 (0.2%)	
More than 1 race	591 (2.9%)	441 (2.9%)	150 (3.0%)	
Unknown / Other				
Body Mass Index				5.6
Mean ± SD	28.79 ± 8.14	28.68 ± 7.95	29.14 ± 8.68	
Median (IQR)	28.25 (25.01, 32.04)	28.17 (24.98, 31.93)	28.44 (25.09, 32.42)	
Hispanic or Latino	944 (4.7%)	712 (4.7%)	232 (4.6%)	0.5
None vs mild CAD (i.e., without unstable angina or MI within 6 months)	9020 (44.5%)	6657 (43.8%)	2363 (46.6%)	5.7
None vs. Asymptomatic/Mild CHF	2277 (11.2%)	1683 (11.1%)	594 (11.7%)	2.0
None vs mild COPD (i.e., not on home oxygen)	4377 (21.6%)	3273 (21.5%)	1104 (21.8%)	0.6

	Total	Treatment Modality		
	n = 20264	CEA n = 15198	TCAR n = 5066	Std Diff (%)
Dialysis	0 (0.0%)	0 (0.0%)	0 (0.0%)	
ASA Class				1.7
1	112 (0.6%)	84 (0.6%)	28 (0.6%)	
2	748 (3.7%)	562 (3.7%)	186 (3.7%)	
3	14631 (72.2%)	10999 (72.4%)	3632 (71.7%)	
4 or 5	4773 (23.6%)	3553 (23.4%)	1220 (24.1%)	
Smoking				0.9
None	5220 (25.8%)	3904 (25.7%)	1316 (26.0%)	
Prior	10130 (50.0%)	7615 (50.1%)	2515 (49.6%)	
Current	4914 (24.2%)	3679 (24.2%)	1235 (24.4%)	
Hypertension	18184 (89.7%)	13635 (89.7%)	4549 (89.8%)	0.3
Diabetes				1.5
None	12177 (60.1%)	9158 (60.3%)	3019 (59.6%)	
Diet	993 (4.9%)	738 (4.9%)	255 (5.0%)	
Non-Insulin	4098 (20.2%)	3068 (20.2%)	1030 (20.3%)	
Insulin/medication dependent	2996 (14.8%)	2234 (14.7%)	762 (15.0%)	
Prior CABG	3991 (19.7%)	3012 (19.8%)	979 (19.3%)	1.2
Prior PCI	5097 (25.2%)	3827 (25.2%)	1270 (25.1%)	0.3
Creatinine mg/dl				1.5
Mean ± SD	1.03 ± 0.32	1.03 ± 0.32	1.04 ± 0.32	
Median (IQR)	0.98 (0.80, 1.20)	0.98 (0.80, 1.20)	0.99 (0.80, 1.20)	
GFR				1.9
Mean ± SD	75.29 ± 18.60	75.38 ± 18.64	75.03 ± 18.48	
Median (IQR)	79.44 (61.76, 88.92)	79.65 (61.91, 89.03)	78.64 (61.56, 88.48)	
GFR<60	4614 (22.8%)	3448 (22.7%)	1166 (23.0%)	0.8
Pre-admission Living Status				0.4
Home	20018 (98.8%)	15014 (98.8%)	5004 (98.8%)	
Nursing home	220 (1.1%)	164 (1.1%)	56 (1.1%)	
Homeless	26 (0.1%)	20 (0.1%)	6 (0.1%)	
Percent Lesion Stenosis				4.0
> 50%	1257 (6.2%)	907 (6.0%)	350 (6.9%)	
> 60%	560 (2.8%)	417 (2.7%)	143 (2.8%)	
> 70%	2610 (12.9%)	1949 (12.8%)	661 (13.0%)	
> 80%	15837 (78.2%)	11925 (78.5%)	3912 (77.2%)	

Procedure Information (All Matched Patients)

Table 3 provides a tabulation of the procedure information for all matched CEA and TCAR patients by treatment modality. The use of general anesthesia was higher in the CEA cohort. The use of pre-operative P2Y12 antagonists was higher in the TCAR patients which is expected in accordance with multi-society, treatment guidelines following CAS procedures. Mean procedure times were longer for CEA than TCAR (117.30 min vs 72.50 min respectively). The use of dual antiplatelet therapy was higher in the TCAR cohort, which is expected in accordance with multi-society, treatment guidelines following CAS procedures.

Table 3: Procedure Information after Matching (All Patients)

	Total	Treatment modality		
		CEA	TCAR	
	n = 20264	n = 15198	n = 5066	Std Diff (%)
Lesion Laterality				0.4
Right	10468 (51.7%)	7843 (51.6%)	2625 (51.8%)	
Left	9796 (48.3%)	7355 (48.4%)	2441 (48.2%)	
Lesion Length (mm)				
Mean ± SD	25.46 ± 11.51	Not Reported	25.46 ± 11.51	N/A
Median (IQR)	25.00 (18.00, 30.00)		25.00 (18.00, 30.00)	
Missing			605	
General Anesthesia Use	18387 (90.7%)	14203 (93.5%)	4184 (82.6%)	33.9
Pre-op P2Y12 Antagonist				117.6
None	9305 (45.9%)	8716 (57.3%)	589 (11.6%)	
Clopidogrel	10010 (49.4%)	5737 (37.7%)	4273 (84.3%)	
Prasugrel	99 (0.5%)	56 (0.4%)	43 (0.8%)	
Ticagrelor	1 (0.0%)	1 (0.0%)	0 (0.0%)	
Other P2Y12 Inhibitor	238 (1.2%)	116 (0.8%)	122 (2.4%)	
No, for Medical Reason	34 (0.2%)	28 (0.2%)	6 (0.1%)	
Non-compliant	542 (2.7%)	517 (3.4%)	25 (0.5%)	
Aggrenox	32 (0.2%)	27 (0.2%)	5 (0.1%)	
Missing	3 (0.0%)	0 (0.0%)	3 (0.1%)	
Pre-op Statin	18190 (89.8%)	13627 (89.7%)	4563 (90.1%)	1.4
Pre-op ASA	18406 (90.8%)	13803 (90.8%)	4603 (90.9%)	0.1
Medication Loading				
None	2957 (59.0%)	Not Applicable	2957 (59.0%)	N/A
ASA or P2YI2 antagonist	846 (16.9%)		846 (16.9%)	
Statin	138 (2.8%)		138 (2.8%)	
Both	1072 (21.4%)		1072 (21.4%)	
Missing			53	
Pre-op Chronic Anticoagulant	2319 (11.4%)	1722 (11.3%)	597 (11.8%)	1.4
Prophylactic Anti-bradyarrhythmic	2669 (53.1%)	Not Applicable	2669 (53.1%)	N/A
Missing			39	
Pre-dilatation	965 (19.1%)	Not Applicable	965 (19.1%)	N/A
Missing			13	
Number of stents placed				
1	4783 (94.4%)	Not Applicable	4783 (94.4%)	N/A
2	283 (5.6%)		283 (5.6%)	
Missing				
Contrast Volume (mL)				
Mean ± SD	31.20 ± 22.19	Not Applicable	31.20 ± 22.19	N/A
Median (IQR)	25.00 (18.00, 40.00)		25.00 (18.00, 40.00)	
Missing			155	
Total Procedure Time				57.2
Mean ± SD	106.13 ± 66.49	117.30 ± 44.43	72.50 ± 101.40	
Median (IQR)	98.00 (73.00, 129.00)	110.00 (87.00, 139.00)	65.00 (52.00, 84.00)	
Missing	58	29	29	

Demographics and Baseline Characteristics (Patients with 1-Year Follow-Up)

Table 4 provides a tabulation of the baseline demographics for matched CEA and TCAR patients with 1-year follow-up. For the composite endpoint analysis, there were 2,988 CEA patients and 996 TCAR patients with 1-year follow-up. Key demographic parameters were similar between the matched cohorts: symptom status, age, gender, congestive heart failure, COPD, smoking, hypertension, dialysis, kidney function, coronary artery disease and percent stenosis. Body mass index and the

incidence of mild coronary artery disease were similar in patients with 1-year follow-up. The incidence of severe stenosis (>70%) was 91.5% and 91.1% for the CEA and TCAR cohorts respectively. There were differences in the procedural variables that are likely due to variations in the treatment modalities.

Table 4: Demographics and Baseline Characteristics after Matching (Patients with 1-Year Follow-Up)

	Total	Treatment Modality		
	n = 3984	CEA n = 2988	TCAR n = 996	Std Diff (%)
Presenting Symptom Status				2.6
Stroke	1211 (30.4%)	904 (30.3%)	307 (30.8%)	
Cortical TIA	479 (12.0%)	360 (12.0%)	119 (11.9%)	
Retinal TIA	159 (4.0%)	117 (3.9%)	42 (4.2%)	
Unknown Stroke Severity	205 (5.1%)	152 (5.1%)	53 (5.3%)	
Asymptomatic	1930 (48.4%)	1455 (48.7%)	475 (47.7%)	
Age				1.0
Mean ± SD	70.69 ± 6.46	70.70 ± 6.37	70.64 ± 6.72	
Median (IQR)	72.00 (67.00, 76.00)	72.00 (67.00, 76.00)	72.00 (66.00, 76.00)	
Age ≥65	3307 (83.0%)	2491 (83.4%)	816 (81.9%)	3.8
Male	2629 (66.0%)	1971 (66.0%)	658 (66.1%)	0.2
Caucasian	3564 (89.5%)	2673 (89.5%)	891 (89.5%)	0.0
Race				3.6
American Indian or Alaskan Native	26 (0.7%)	18 (0.6%)	8 (0.8%)	
Asian	38 (1.0%)	28 (0.9%)	10 (1.0%)	
Black or African American	201 (5.0%)	151 (5.1%)	50 (5.0%)	
	7 (0.2%)	5 (0.2%)	2 (0.2%)	
Native Hawaiian or other Pacific Islander	3564 (89.5%)	2673 (89.5%)	891 (89.5%)	
White	17 (0.4%)	12 (0.4%)	5 (0.5%)	
More than 1 race	131 (3.3%)	101 (3.4%)	30 (3.0%)	
Unknown / Other				
Body Mass Index				0.3
Mean ± SD	29.01 ± 7.46	29.02 ± 5.89	28.99 ± 10.88	
Median (IQR)	28.41 (25.31, 32.26)	28.37 (25.28, 32.19)	28.73 (25.41, 32.60)	
Hispanic or Latino	183 (4.6%)	136 (4.6%)	47 (4.7%)	0.8
None vs mild CAD (i.e., without unstable angina or MI within 6 months)	1793 (45.0%)	1341 (44.9%)	452 (45.4%)	1.0
None vs. Asymptomatic/Mild CHF	503 (12.6%)	377 (12.6%)	126 (12.7%)	0.1
None vs mild COPD (i.e., not on home oxygen)	917 (23.0%)	685 (22.9%)	232 (23.3%)	0.9
Dialysis	0 (0.0%)	0 (0.0%)	0 (0.0%)	N/A
ASA Class				1.8
1	14 (0.4%)	10 (0.3%)	4 (0.4%)	
2	160 (4.0%)	118 (3.9%)	42 (4.2%)	
3	2710 (68.0%)	2033 (68.0%)	677 (68.0%)	
4 or 5	1100 (27.6%)	827 (27.7%)	273 (27.4%)	

	Total	Treatment Modality		
	n = 3984	CEA n = 2988	TCAR n = 996	Std Diff (%)
Smoking				2.3
None	922 (23.1%)	694 (23.2%)	228 (22.9%)	
Prior	2111 (53.0%)	1575 (52.7%)	536 (53.8%)	
Current	951 (23.9%)	719 (24.1%)	232 (23.3%)	
Hypertension	3611 (90.6%)	2711 (90.7%)	900 (90.4%)	1.3
Diabetes				2.1
None	2360 (59.2%)	1776 (59.4%)	584 (58.6%)	
Diet	160 (4.0%)	118 (3.9%)	42 (4.2%)	
Non Insulin	842 (21.1%)	631 (21.1%)	211 (21.2%)	
Insulin/medication dependent	622 (15.6%)	463 (15.5%)	159 (16.0%)	
Prior CABG	794 (19.9%)	591 (19.8%)	203 (20.4%)	1.5
Prior PCI	1021 (25.6%)	769 (25.7%)	252 (25.3%)	1.0
Creatinine mg/dl				1.7
Mean ± SD	1.04 ± 0.32	1.04 ± 0.33	1.04 ± 0.31	
Median (IQR)	0.99 (0.81, 1.20)	0.99 (0.81, 1.20)	0.99 (0.81, 1.20)	
GFR				1.6
Mean ± SD	74.41 ± 18.46	74.34 ± 18.53	74.63 ± 18.27	
Median (IQR)	78.12 (60.50, 88.07)	78.10 (60.50, 88.07)	78.20 (60.54, 88.18)	
GFR<60	964 (24.2%)	728 (24.4%)	236 (23.7%)	1.6
Pre-admission Living Status				2.0
Home	3938 (98.8%)	2955 (98.9%)	983 (98.7%)	
Nursing home	43 (1.1%)	31 (1.0%)	12 (1.2%)	
Homeless	3 (0.1%)	2 (0.1%)	1 (0.1%)	
Dual antiplatelet therapy	1744 (43.8%)	947 (31.7%)	797 (80.0%)	111.4
Percent Lesion Stenosis				2.8
> 50%	220 (5.5%)	163 (5.5%)	57 (5.7%)	
> 60%	121 (3.0%)	90 (3.0%)	31 (3.1%)	
> 70%	434 (10.9%)	320 (10.7%)	114 (11.4%)	
> 80%	3209 (80.5%)	2415 (80.8%)	794 (79.7%)	

Procedure Information (Patients with 1-Year Follow-Up)

Table 5 provides a tabulation of the procedure information for matched CEA and TCAR patients with 1-year follow-up by treatment modality. The use of general anesthesia was higher in the CEA cohort. The use of pre-operative P2Y12 antagonists was higher in the TCAR patients which is expected in accordance with multi-society, treatment guidelines following CAS procedures. Mean procedure times were longer for CEA than TCAR (118.56 min vs 74.18 min respectively). The use of dual antiplatelet therapy was higher in the TCAR cohort which is expected in accordance with multi-society, treatment guidelines following CAS procedures.

Table 5: Procedure Information after Matching (Patients with 1-Year Follow-Up)

	Total	Treatment Modality		
	n = 3984	CEA n = 2988	TCAR n = 996	Std Diff (%)
Lesion Laterality Right Left	 1984 (49.8%) 2000 (50.2%)	 1489 (49.8%) 1499 (50.2%)	 495 (49.7%) 501 (50.3%)	0.3
Lesion Length (mm) Mean ± SD Median (IQR) Missing	 24.96 ± 12.03 22.00 (17.00, 30.00) 3094	Not Reported	 24.96 ± 12.03 22.00 (17.00, 30.00) 106	N/A
General Anesthesia Use	3623 (90.9%)	2803 (93.8%)	820 (82.3%)	36.0
Pre-op P2Y12 Antagonist None Clopidogrel Prasugrel Ticagrelor Other P2Y12 Inhibitor No, for Medical Reason Non-compliant Aggrenox	 1901 (47.7%) 1885 (47.3%) 20 (0.5%) 32 (0.8%) 8 (0.2%) 131 (3.3%) 6 (0.2%) 1 (0.0%)	 1779 (59.5%) 1048 (35.1%) 7 (0.2%) 20 (0.7%) 4 (0.1%) 124 (4.1%) 6 (0.2%) 0 (0.0%)	 122 (12.2%) 837 (84.0%) 13 (1.3%) 12 (1.2%) 4 (0.4%) 7 (0.7%) 0 (0.0%) 1 (0.1%)	123.3
Pre-op Statin	3513 (88.2%)	2629 (88.0%)	884 (88.8%)	2.4
Pre-op ASA	3583 (89.9%)	2682 (89.8%)	901 (90.5%)	2.4
Medication Loading None ASA or P2YI2 antagonist Statin Both Missing	 608 (61.7%) 169 (17.1%) 33 (3.3%) 176 (17.8%)	Not Applicable	 608 (61.7%) 169 (17.1%) 33 (3.3%) 176 (17.8%) 10	N/A
Pre-op Chronic Anticoagulant	561 (14.1%)	424 (14.2%)	137 (13.8%)	1.3
Prophylactic Anti-bradyarrhythmic Missing	469 (47.4%)	Not Applicable	469 (47.4%) 6	N/A
Pre-dilatation Missing	163 (16.4%)	Not Applicable	163 (16.4%) 2	N/A
Number of stents placed 1 2 Missing	 949 (95.3%) 47 (4.7%)	Not Applicable	 949 (95.3%) 47 (4.7%) 0	N/A
contrast Mean ± SD Median (IQR) Missing	 36.19 ± 23.22 30.00 (20.00, 45.00)	Not Applicable	 36.19 ± 23.22 30.00 (20.00, 45.00) 35	N/A
Total Procedure Time Mean ± SD Median (IQR) Missing	 107.51 ± 45.65 100.00 (75.00, 130.00) 7	 118.56 ± 45.08 111.00 (88.00, 140.00) 1	 74.18 ± 27.58 69.50 (55.00, 88.00) 6	118.8
Post-dilation (Stent 1) Missing	574 (57.9%)	Not Applicable	574 (57.9%) 4	N/A

	Total	Treatment Modality		
	n = 3984	CEA n = 2988	TCAR n = 996	Std Diff (%)
Post-dilation (Stent 2) Missing	25 (54.3%)	Not Applicable	25 (54.3%) 950	N/A
Percent Lesion Stenosis > 50% > 60% > 70% > 80%	 220 (5.5%) 121 (3.0%) 434 (10.9%) 3209 (80.5%)	 163 (5.5%) 90 (3.0%) 320 (10.7%) 2415 (80.8%)	 57 (5.7%) 31 (3.1%) 114 (11.4%) 794 (79.7%)	2.8

D. Safety and Effectiveness Results

1. Composite Endpoint Analysis

There were two analysis populations generated to compare the propensity score matched results between CEA and TCAR to evaluate the safety and effectiveness profile of the ENROUTE® Transcarotid Stent System (ENROUTE Stent) relative to CEA; all matched patients and patients with 1-year follow-up.

Results Based on All Matched Patients

All TCAR patients were treated with the ENROUTE Stent used in conjunction with the ENROUTE Transcarotid Neuroprotection System (ENROUTE NPS). The CEA and TCAR cohorts were propensity score matched (3:1 nearest neighbor, no caliper). There were no TCAR patients excluded from the matching (i.e., all standard surgical risk TCAR patients who received the ENROUTE stent from the SVS VQI were included in the analysis). The primary endpoint is a composite of death/stroke/ myocardial infarction through 30 days and ipsilateral stroke from day 31 to day 365 (365 days minus 45 days).

The estimates generated for comparison of the individual outcomes between CEA and TCAR were derived using a right-censored approach for patients who did not experience the event of interest. The Kaplan-Meier (K-M) approach provides adjusted estimates based on the number of patients that remain at risk of experiencing the event. This risk-based approach is appropriate when dealing with longitudinal data where the duration of follow-up varies across patients and clinical sites. From the K-M analysis, the estimate of the rate at a specific time can be determined.

The first analysis population includes all TCAR patients (n=5,066) and three (3) matched CEA patients for every TCAR patient (n=15,198). Outcomes using Kaplan-Meier estimates are presented in Table 6 and Figure 2.

Table 6: Endpoint Analysis (All Matched Patients)

Outcome	K-M Estimate for TCAR	K-M Estimate for CEA	Bootstrap 95% Confidence interval (TCAR-CEA)
30 Day Death/Stroke/MI* + 1yr Ipsilateral stroke	2.93%	2.62%	-0.38%, 1.08%
30 Day Stroke	1.40%	1.12%	
30 Day Death	0.34%	0.38%	
30 Day Death/Stroke	1.62%	1.42%	
30 Day Death/Stroke/MI*	2.00%	2.01%	
1yr Ipsilateral Stroke	1.40%	1.08%	

*MI is reported in-hospital as the CEA registry of the SVS VQI does not track MI past discharge whereas the CAS registry does.

There were no differences in the composite endpoint or components of the composite endpoint between the CEA and TCAR cohorts. To establish non-inferiority relative to the pre-specified non-inferiority margin of 5%, the upper bound of the 2-sided 95% confidence interval of the difference (TCAR minus CEA) for the composite endpoint was calculated. The results presented in Figure 2 are drawn directly from Table 6 and demonstrates that the upper bound of the confidence interval of the difference for the composite endpoint is firmly below the 5% non-inferiority margin. The observed difference in the composite endpoint between the TCAR and CEA cohorts was 0.14% with an upper 95% confidence limit of 0.81% (within the pre-specified non-inferiority margin of 5%). Based on these results, TCAR using the ENROUTE Stent in conjunction the ENROUTE NPS is non-inferior to CEA in the standard surgical risk patient population.

Figure 2 Graphical Representation of the Non-Inferiority Analysis (All Matched Patients)

(Difference in the Event Rates [TCAR minus CEA] from the Kaplan-Meier Estimates with the 95% Confidence Interval

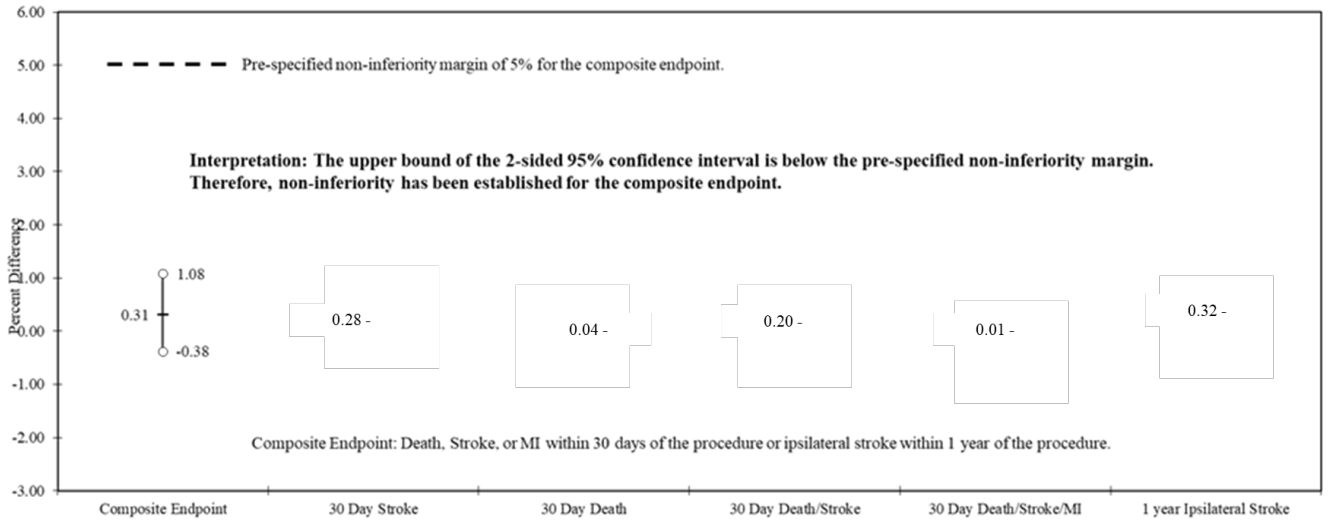
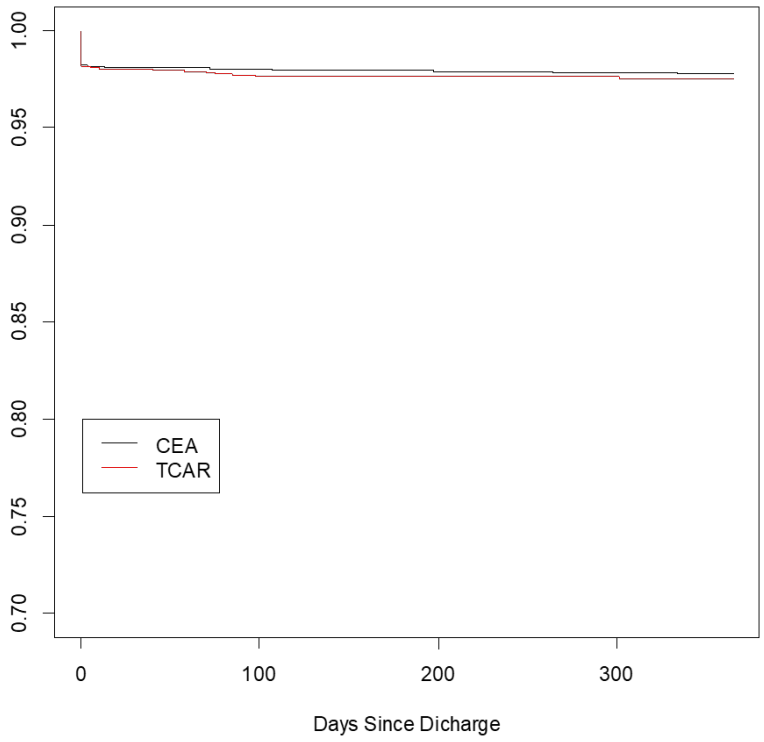


Figure 3 shows the Kaplan-Meier estimate of the freedom from the composite endpoint event for all matched patients.

Figure 3 Freedom from Composite Endpoint Event Through 1 Year (All Matched Patients)



Patients with 1-Year Follow-Up

The second analysis population includes TCAR patients with 1-year follow-up (n=996) and three (3) matched CEA patients with 1-year follow-up for every TCAR patient (n=2,988).

Table 7: Endpoint Analysis (Matched Patients with 1-Year Follow-Up)

Outcome	K-M Estimate for TCAR	K-M Estimate for CEA	Bootstrap 95% Confidence interval (TCAR-CEA)
30 Day Death*/Stroke/MI** + 1yr Ipsilateral Stroke	2.31%	2.18%	-0.95%, 1.15%

*By definition, the 1-year follow-up cohort had to survive ≥320 days to be included in this analysis because a patient is only included in the 1-year cohort exclusive of a 30-day periprocedural death.
** MI is reported as in-hospital. The CEA registry of the SVS VQI does not track MI past discharge whereas the CAS registry does.

There was no difference in the 1-year endpoint between the CEA and TCAR cohorts. To establish non-inferiority relative to the pre-specified non-inferiority margin of 5%, the upper bound of the 2-sided 95% confidence interval of the difference (TCAR minus CEA) for the composite endpoint was calculated. Supplemented by an analysis of the 1-year component of the composite endpoint in CEA and TCAR patients with

1-year follow-up, TCAR using the ENROUTE Stent in conjunction the ENROUTE NPS is non-inferior to CEA in the standard surgical risk patient population.

2. Other Endpoint Analyses

Procedural Outcomes

Table 8 presents other outcome and procedural measures from all matched TCAR and CEA patients. Certain procedural variables that are captured in the CAS registry of the SVS VQI are not captured in the CEA registry. Conversely, certain procedural variables that are captured in the CEA registry of the SVS VQI are not captured in the CAS registry. Those variables are presented as "Not Reported."

Table 8: Other Outcomes and Procedural Measures (All Matched Patients)

	Total	**Treatment Modality**		
		CEA	**TCAR**	**TCAR-CEA, difference**
	n = 20264	**n = 15198**	**n = 5066**	
Stroke, in-hospital	226 (1.12%)	158 (1.04%)	68 (1.34%)	-0.30%
Death, in-hospital	27 (0.13%)	18 (0.12%)	9 (0.18%)	-0.06%
Myocardial Infarction (MI), in-hospital	127 (0.63%)	102 (0.67%)	25 (0.49%)	0.18%
Stroke/Death/MI, in-hospital	353 (1.74%)	260 (1.71%)	93 (1.84%)	-0.13%
Cranial Nerve Injury, in-hospital	423 (2.09%)	408 (2.68%)	15 (0.30%)	2.39%
Access Site Complication No Yes Missing	 4915 (97.06%) 149 (2.94%)	Not Reported	 4915 (97.06%) 149 (2.94%) 2	N/A
Hematoma/bleeding None Medical Treatment Interventional Treatment Surgical Treatment Missing	 4930 (97.35%) 84 (1.66%) 6 (0.12%) 44 (0.87%)	Not Reported	 4930 (97.35%) 84 (1.66%) 6 (0.12%) 44 (0.87%) 2	N/A
Postoperative stenosis/occlusion None Medical Treatment Interventional Treatment Surgical Treatment Missing	 5058 (99.88%) 2 (0.04%) 1 (0.02%) 3 (0.06%)	Not Reported	 5058 (99.88%) 2 (0.04%) 1 (0.02%) 3 (0.06%) 2	N/A
Pseudoanuerysm No Moderate, thrombin injection Missing	 5062 (99.96%) 2 (0.04%)	Not Reported	 5062 (99.96%) 2 (0.04%) 2	N/A
Return to Operating Room No Yes, bleeding Yes, neurologic Yes, both bleeding/neurologic Yes, other CEA incision Yes, other Missing	 14916 (98.16%) 161 (1.06%) 37 (0.24%) 3 (0.02%) 7 (0.05%) 71 (0.47%) 5069	 14916 (98.16%) 161 (1.06%) 37 (0.24%) 3 (0.02%) 7 (0.05%) 71 (0.47%) 3	Not Reported	N/A

As shown in Table 8, the incidence of in-hospital stroke, in-hospital death or in-hospital MI were similar for CEA and TCAR. The incidence of the in-hospital composite of stroke/death/MI was similar for CEA and TCAR. TCAR had a lower

incidence of in-hospital cranial nerve injury than CEA (0.30% vs 2.68% respectively).

The incidence of access site complications for TCAR was 2.94%. There was no equivalent variable for CEA in the SVS VQI. The ROADSTER study supported approval of the high surgical risk indication approved in P140026. For reference, the incidence of access site complications requiring intervention in the ROADSTER study was 2.3% (K143072). The incidence of hematoma/bleeding for TCAR was 2.70%; the incidence of those requiring interventional or surgical treatment was 0.99%. There was no equivalent variable for CEA in the SVS VQI. For reference, the incidence of wound hematoma requiring intervention in the ROADSTER study was 2.3%. The incidence of postoperative stenosis/occlusion for TCAR was 0.12%; the incidence of those requiring interventional or surgical treatment was 0.08%. There was no equivalent variable for CEA. For reference, the incidence of stenosis/ occlusion in the ROADSTER study was 1.0%. The incidence of pseudoaneurysm for TCAR was 0.04%; both incidents were treated with thrombin injection. There was no equivalent variable for CEA in the SVS VQI. For reference, there were no reports of pseudoaneurysm in the ROADSTER study. For CEA, the incidence of a return to the operating room was 1.84% (bleeding/neurologic/incision/other). There was no equivalent variable for TCAR in the SVS VQI. These events are similar to those in the ROADSTER study and are expected of this device type.

Supplemental Analysis (all subjects eligible for 1-year follow-up)

At the request of FDA, the sponsor conducted a supplemental analysis on all patients that were 1-year follow-up eligible. This combined all patients with documented 1-year follow-up who had their procedure on or before September 2, 2019 (one year prior to database lock), plus all patients without documented 1-year follow-up who had their procedure on or before September 2, 2019 (one year prior to database lock). The following table shows the number of TCAR patients in this population that were subsequently matched to CEA patients 3:1.

Table 9: TCAR Patients Included in Supplemental Analysis

	Patients with Documented 1-Year Follow-Up*	**Patients without Documented 1-Year Follow-Up**	**Total Number of TCAR Patients Available for Matching**
TCAR Patients	983*	1979*	2962*

*Had their procedure on or before Sept 2, 2019 (one year prior to database lock), thus 1-year follow-up eligible.

After matching, 2,962 TCAR patients were matched to 8,886 CEA patients. Table 10 shows the post-matching data for the TCAR and CEA cohorts in the supplemental analysis population.

Table 10: All CEA and TCAR Patients in Supplemental Analysis Population After Matching
(3:1 nearest neighbor, no caliper)

	Total	Modality		
	n = 11848	CEA n = 8886	TCAR n = 2962	Std Diff (%)
Symptomatic Status				1.0
1 Stroke	3572 (30.1%)	2678 (30.1%)	894 (30.2%)	
2 Cortical TIA	1486 (12.5%)	1121 (12.6%)	365 (12.3%)	
3 Retinal TIA	459 (3.9%)	343 (3.9%)	116 (3.9%)	
4 Unknown severity	903 (7.6%)	674 (7.6%)	229 (7.7%)	
5 Asymptomatic	5428 (45.8%)	4070 (45.8%)	1358 (45.8%)	
Age				1.0
Mean ± SD	70.39 ± 6.61	70.38 ± 6.51	70.44 ± 6.87	
Median (IQR)	72.00 (66.00, 76.00)	72.00 (66.00, 76.00)	72.00 (66.00, 76.00)	
Age>=65	9634 (81.3%)	7240 (81.5%)	2394 (80.8%)	1.7
Male	7687 (64.9%)	5777 (65.0%)	1910 (64.5%)	1.1
Caucasian	10630 (89.7%)	7986 (89.9%)	2644 (89.3%)	2.0
Race				3.4
1 American Indian or Alaskan Native	65 (0.5%)	44 (0.5%)	21 (0.7%)	
2 Asian	93 (0.8%)	71 (0.8%)	22 (0.7%)	
3 Black or African American	683 (5.8%)	508 (5.7%)	175 (5.9%)	
4 Native Hawaiian or other Pacific Islander	17 (0.1%)	13 (0.1%)	4 (0.1%)	
5 White	10630 (89.7%)	7986 (89.9%)	2644 (89.3%)	
6 More than 1 race	28 (0.2%)	20 (0.2%)	8 (0.3%)	
7 Unknown / Other	332 (2.8%)	244 (2.7%)	88 (3.0%)	
Body Mass Index				4.5
Mean ± SD	28.78 ± 10.05	28.67 ± 10.01	29.13 ± 10.16	
Median (IQR)	28.33 (25.00, 32.13)	28.28 (24.98, 32.04)	28.52 (25.05, 32.34)	
Hispanic or Latino	527 (4.4%)	385 (4.3%)	142 (4.8%)	2.2
Any CAD	5444 (45.9%)	4071 (45.8%)	1373 (46.4%)	1.1
Prior CHF	1427 (12.0%)	1065 (12.0%)	362 (12.2%)	0.7
COPD	2591 (21.9%)	1936 (21.8%)	655 (22.1%)	0.8
Dialysis	0 (0.0%)	0 (0.0%)	0 (0.0%)	
ASA Class				1.2
1	83 (0.7%)	61 (0.7%)	22 (0.7%)	
2	524 (4.4%)	391 (4.4%)	133 (4.5%)	
3	8374 (70.7%)	6291 (70.8%)	2083 (70.3%)	
4	2867 (24.2%)	2143 (24.1%)	724 (24.4%)	
Smoking				0.7
0 None	2985 (25.2%)	2236 (25.2%)	749 (25.3%)	
1 Prior	5895 (49.8%)	4417 (49.7%)	1478 (49.9%)	
2 Current	2968 (25.1%)	2233 (25.1%)	735 (24.8%)	
Hypertension	10743 (90.7%)	8064 (90.7%)	2679 (90.4%)	1.0

	Total	Modality		Std Diff (%)
	n = 11848	CEA n = 8886	TCAR n = 2962	
Diabetes				1.7
0 None	7071 (59.7%)	5318 (59.8%)	1753 (59.2%)	
1 Diet	490 (4.1%)	363 (4.1%)	127 (4.3%)	
2 Non Insulin	2438 (20.6%)	1828 (20.6%)	610 (20.6%)	
3 Insulin	1849 (15.6%)	1377 (15.5%)	472 (15.9%)	
Prior CABG	2232 (18.8%)	1678 (18.9%)	554 (18.7%)	0.5
Prior PCI	2962 (25.0%)	2225 (25.0%)	737 (24.9%)	0.4
Creatinine mg/dl				1.0
Mean ± SD	1.04 ± 0.32	1.04 ± 0.32	1.04 ± 0.31	
Median (IQR)	0.99 (0.81, 1.20)	0.99 (0.81, 1.20)	1.00 (0.81, 1.20)	
Glomerular filtration rate (GFR)				1.4
Mean ± SD	74.97 ± 18.33	75.03 ± 18.36	74.77 ± 18.24	
Median (IQR)	78.54 (61.69, 88.43)	78.71 (61.76, 88.62)	78.18 (61.13, 88.00)	
GFR<60	2703 (22.8%)	2017 (22.7%)	686 (23.2%)	1.1
General Anesthesia	10729 (90.6%)	8314 (93.6%)	2415 (81.5%)	37.1
Pre-op P2Y12 Antagonist				117.5
0 None	5521 (46.6%)	5157 (58.0%)	364 (12.3%)	
1 Clopidogrel	5754 (48.6%)	3264 (36.7%)	2490 (84.1%)	
2 Prasugrel	61 (0.5%)	36 (0.4%)	25 (0.8%)	
4 Ticagrelor	121 (1.0%)	68 (0.8%)	53 (1.8%)	
5 Other P2Y12 Inhibitor	16 (0.1%)	10 (0.1%)	6 (0.2%)	
6 No, for Medical Reason	350 (3.0%)	333 (3.7%)	17 (0.6%)	
7 Non-compliant	22 (0.2%)	18 (0.2%)	4 (0.1%)	
9	3 (0.0%)	0 (0.0%)	3 (0.1%)	
Pre-op Statin	10710 (90.4%)	8034 (90.4%)	2676 (90.3%)	0.2
Pre-op ASA	10659 (90.0%)	7993 (90.0%)	2666 (90.0%)	0.2
Pre-op Anticoagulation	1448 (12.2%)	1086 (12.2%)	362 (12.2%)	0.0
Total Procedure Time				120.0
Mean ± SD	105.77 ± 44.94	116.89 ± 43.66	72.21 ± 29.39	
Median (IQR)	98.00 (74.00, 129.00)	110.00 (87.00, 138.00)	66.00 (53.00, 85.50)	
Missing	41	19	22	
Pre-admission Living Status				1.3
1 Home	11709 (98.8%)	8785 (98.9%)	2924 (98.7%)	
2 Nursing home	128 (1.1%)	93 (1.0%)	35 (1.2%)	
3 Homeless	11 (0.1%)	8 (0.1%)	3 (0.1%)	
DAPT	5374 (45.4%)	3016 (33.9%)	2358 (79.6%)	103.9
% Stenosis				2.9
2 > 50%	756 (6.4%)	553 (6.2%)	203 (6.9%)	
3 > 60%	390 (3.3%)	298 (3.4%)	92 (3.1%)	
4 > 70%	1443 (12.2%)	1078 (12.1%)	365 (12.3%)	
5 > 80%	9259 (78.1%)	6957 (78.3%)	2302 (77.7%)	

After matching, the baseline covariates are well balanced between the TCAR and CEA cohorts. TCAR patients had a higher mean Body Mass Index. For procedural

variables after matching, TCAR patients were still more likely to be treated under local anesthesia as well as being more likely to be treated with pre-operative P2Y12 antagonists. The use of pre-operative P2Y12 antagonists is expected in accordance with multi-society, treatment guidelines following CAS procedures. Mean total procedure time for TCAR was lower than CEA.

Table 11 shows the primary endpoint results in the supplemental analysis population (composite of D/S/MI at 30 days plus 1-year ipsilateral stroke) as well as the components of the composite endpoint.

Table 11: Primary Endpoint Results for All Matched Patients in the Supplemental Analysis Population

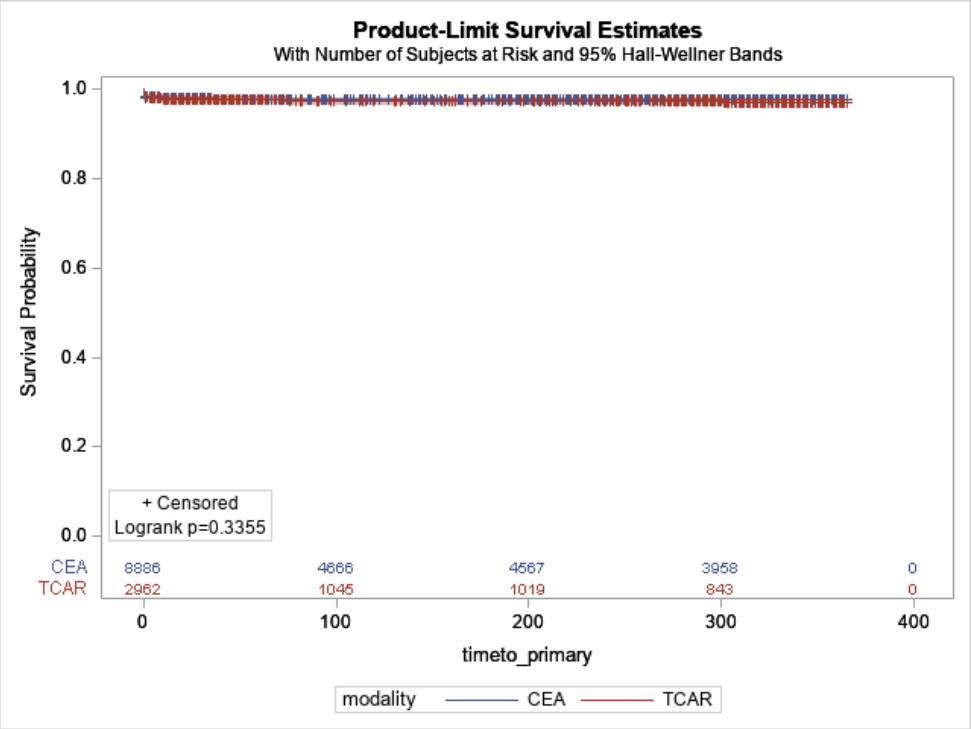
Outcome	KM Estimate for TCAR N=2962	KM Estimate for CEA N=8886	Bootstrap 95% Confidence interval (TCAR minus CEA)
30 Day Stroke	1.55%	1.13%	
30 Day Death	0.34%	0.41%	
30 Day Death/Stroke	1.79%	1.45%	
30 Day Death/Stroke/MI*	2.20%	2.05%	
Primary Endpoint: 30 Day Death/Stroke/MI* and 1-Year Ipsilateral Stroke	2.96%	2.56%	-0.43%, 1.24%

*MI is reported as in-hospital. The CEA registry of the SVS VQI does not track MI past discharge whereas the CAS registry does.

There were no statistically significant differences in the composite endpoint or the components of the composite endpoint between the TCAR and CEA cohorts. To establish non-inferiority relative to the pre-specified non-inferiority margin of 5%, the upper bound of the 2-sided 95% confidence interval of the difference (TCAR minus CEA) for the composite endpoint was calculated. The observed difference in the composite endpoint between the TCAR and CEA cohorts was 0.4% with an upper 95% confidence limit of 1.24% (within the pre-specified non-inferiority margin of 5%). Based on these results, TCAR using the ENROUTE Stent in conjunction the ENROUTE NPS is non-inferior to CEA in standard surgical risk patients included in the supplemental analysis population.

The following figure shows the Kaplan-Meier estimate of the freedom from the composite endpoint event (time-to-event) for all matched patients in the supplementary analysis population.

Figure 4: Product-Limit Survival Estimates for the Supplemental Analysis Population



3. Subgroup Analyses

The following subgroups were evaluated for potential association with outcomes:

- Age <65 vs ≥65
- Gender (male vs female)
- Caucasian vs non-Caucasian
- Hispanic vs non-Hispanic

To evaluate the individual subgroups, a test for interaction between the proportion of patients who met the primary endpoint was calculated for each individual subgroup factor. Given that a pre-specified threshold for determining significant interaction was not pre-determined, probability values were calculated. This demonstrated that there was no interaction for gender, race or ethnicity.

The age of the patient (<65 vs. ≥65) had an interaction term <0.1 and was investigated further. The hazard ratio by age group revealed that the upper limit of the 2-sided 95% confidence interval was 2.76 for patients <65 years of age and 1.27 for patients ≥65 years of age. While the outcomes by age stratification showed some interaction, the upper bounds were below the pre-specified non-inferiority margin of 5%.

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 1 investigator. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory Systems Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM CLINICAL STUDIES

A. Effectiveness Conclusions

The results from analyses using patient-level data from the SVS VQI demonstrate reasonable assurance of effectiveness for the ENROUTE® Transcarotid Stent System for use in standard surgical risk subjects with carotid artery disease. Effectiveness of the device was analyzed by evaluating the composite primary endpoint of death, stroke and myocardial infarction through 30 days and one-year ipsilateral stroke. These analyses demonstrated that TCAR with the ENROUTE® Transcarotid Stent System used in conjunction with ENROUTE Neuroprotection System is non-inferior to carotid endarterectomy by 5% when used to treat patients at standard risk for complications from CEA.

B. Safety Conclusions

The risks of the device are based on data collected in a clinical study conducted to support PMA approval as described above including procedural information for both procedures. These data show that the TCAR procedure with the ENROUTE® Transcarotid Stent System is non-inferior to CEA relative to the primary endpoint (death/stroke/myocardial infarction through 30 days plus ipsilateral stroke from day 31 through day 365). Furthermore, the Kaplan-Meier estimates (time-to-event analysis) were similar for TCAR and CEA for the primary endpoint. These analyses provide reasonable assurance of the safety and effectiveness of the TCAR procedure with the ENROUTE® Transcarotid Stent System in the standard surgical risk population.

For other observational clinical outcomes, the incidence of in-hospital stroke, in-hospital death and in-hospital MI were similar for CEA and TCAR. The incidence of the composite of stroke/death/MI in-hospital was similar for CEA and TCAR. TCAR had a lower incidence of in-hospital cranial nerve injury (a well characterized surgical complication) compared to CEA (0.30% vs 2.68% respectively).

The incidence of access site complications for TCAR (both procedure and device related) was 2.94%. This is comparable to the incidence of access site complications in prior clinical studies of TCAR. The incidence of hematoma/bleeding for TCAR was 2.70%; the incidence of those requiring interventional or surgical treatment (defined as serious) was 0.99%. Serious events of this nature are treated and resolved prior to hospital discharge. The incidence of serious wound hematomas requiring intervention in this clinical study was lower than in prior studies of TCAR.

The incidence of postoperative stenosis/occlusion for TCAR was 0.12%; the incidence of those requiring interventional or surgical treatment (defined as serious) was 0.08%. These are device-related complications and are well characterized in CAS. Post-operative stenosis or occlusion can manifest during the initial hospitalization or after discharge. The incidence of postoperative stenosis/occlusion in this clinical study was lower than in prior clinical studies of TCAR.

The incidence of pseudoaneurysm requiring intervention (defined as serious) for TCAR was 0.04%. Such events can manifest during the initial hospitalization or after discharge. These events can be either device or procedure related. The incidence in this clinical study is comparable to prior clinical studies of TCAR.

C. Benefit-Risk Conclusions

Reasonable assurance of the safety and effectiveness of TCAR with the ENROUTE® Transcarotid Stent System in standard surgical risk patients has been demonstrated through a non-inferiority analysis with a pre-specified non-inferiority margin compared to CEA in standard surgical risk patients. Low rates of major adverse clinical events (death, stroke and myocardial infarction) which are events that can occur during any carotid artery interventional modality were seen for both TCAR and CEA. As a prophylactic procedure largely targeted to prevent the occurrence or recurrence of neurological events related to carotid artery stenosis, the chosen endpoints are clinically meaningful and have been used in multiple clinical trials of carotid interventions. The incidence of serious and non-serious device and procedure related adverse events is low and is comparable to similar FDA-approved devices and prior studies of TCAR. Therefore, the benefits of TCAR with the ENROUTE® Transcarotid Stent System in standard surgical risk patients outweigh the associated device or procedural risks.

The probable benefits and risks of the device are based on clinical data collected from the SVS VQI and also leveraged from the non-clinical testing and clinical study conducted to support the original PMA approval. The ENROUTE® Transcarotid Stent

System used in conjunction with the ENROUTE® Transcarotid Neuroprotection System offers similar benefits compared to carotid endarterectomy. The benefits and risks of the ENROUTE® Transcarotid Stent System are similar to those for carotid endarterectomy with a reduction of the risk of cranial nerve injury.

Since complication rates in carotid stenting procedures are known to correlate with the experience of the operator, the sponsor plans to mitigate these risks through physician training.

1. Patient Perspective

   This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above, the data support that for the treatment of patients at standard risk for adverse events from carotid endarterectomy who require carotid revascularization, the probable benefits of the ENROUTE® Transcarotid Stent System used in conjunction with the ENROUTE® Transcarotid Neuroprotection System (NPS) outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Two analyses demonstrated that TCAR is statistically non-inferior to CEA when performed using the ENROUTE® Transcarotid Stent System in conjunction with the ENROUTE® Transcarotid Neuroprotection System to treat standard surgical risk subjects with disease in the internal carotid artery. Both periprocedural and one-year outcomes have established the safety and effectiveness of the ENROUTE® Transcarotid Stent System for this supplemental pre-market approval application.

XIII. CDRH DECISION

CDRH issued an approval order on April 28, 2022. The final conditions of approval cited in the approval order are described below.

The sponsor agreed to conduct a study as follows:

The ROADSTER 3 Study is an open label, single arm, multi-center post-approval study to evaluate real world usage of the ENROUTE® TSS and the ENROUTE Transcarotid NPS for the treatment of patients at standard risk for adverse events from carotid endarterectomy who require carotid revascularization and who are eligible for treatment with these devices. A maximum of 400 patients will be enrolled in up to 60 sites in the United States and up to 5 sites in the European Union according to the protocol (SRM–2022–01) provided via email dated March 2, 2022. Patients will be followed at 30 days (±7 days), 6 months/180 days (±30 days), and 1 year/365 days (±45 days).

The primary endpoint is the hierarchical composite of Major Adverse Events (MAEs) defined as any death, stroke, or myocardial infarction (MI) within 30 days of the index procedure and ipsilateral stroke within 31 days to 365 days of the index procedure.

Key secondary endpoints are:

- Incidence of cranial nerve injury within 30 days of the index procedure
- Stroke within 30 days of the index procedure
- Death within 30 days of the index procedure
- MI within 30 days of the index procedure
- Stroke/Death/MI within 30 days of the index procedure
- Ipsilateral stroke at 1 year

Additional secondary endpoints are:

- Persistent cranial nerve injury at 6 months and 1 year
- Rate of cardiac death within 30 days of the index procedure
- Rate of neurological death within 30 days of the index procedure
- Rate of hierarchical ipsilateral stroke, death, and MI within 30 days of the index procedure
- Cardiac death at 1 year of patients who experienced an MI within 30 days of the index procedure
- Access site complications (arterial/venous)
- Hematoma/bleeding complications (arterial/venous access site)
- Rate of stent thrombosis or occlusion within 30 days of the index procedure
- Rate of dissection within 30 days of the index procedure (during index procedure or a reintervention procedure)

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

1. Rosenfield, et al. Randomized Trial of Stent versus Surgery for Asymptomatic Carotid Stenosis. *N Engl J Med*. 2016 Mar 17;374(11):1011-20.

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4. Hobson RW 2nd, et al. Carotid artery stenting is associated with increased complications in octogenarians: 30-day stroke and death rates in the CREST lead-in phase. *J Vasc Surg*. 2004 Dec;40(6):1106-11.