SUPPLEMENTAL MATERIAL

Data S1. Supplemental Methods

Instrumental variable analysis methods

Rationale

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

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

Instrumental variable technique: perioperative results

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

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

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

Instrumental variable technique: one-year results

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

Proposed instrument

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

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

Instrument rationale

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

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

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

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

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

Limitations

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

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

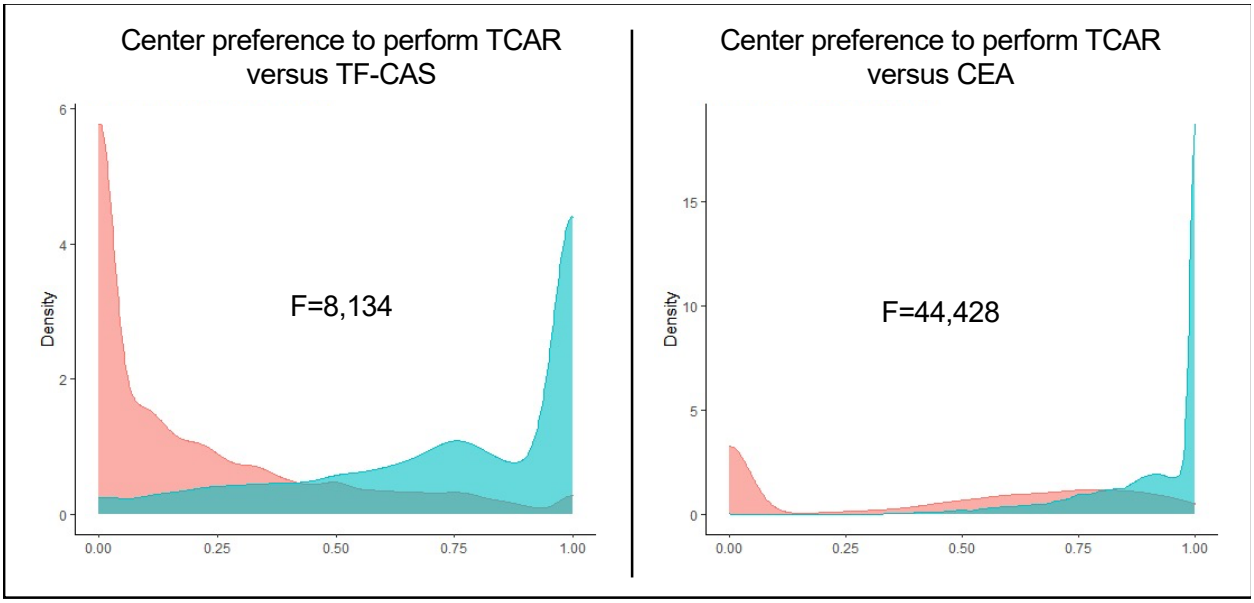
Table S1. Sensitivity analyses for perioperative stroke or death.

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

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

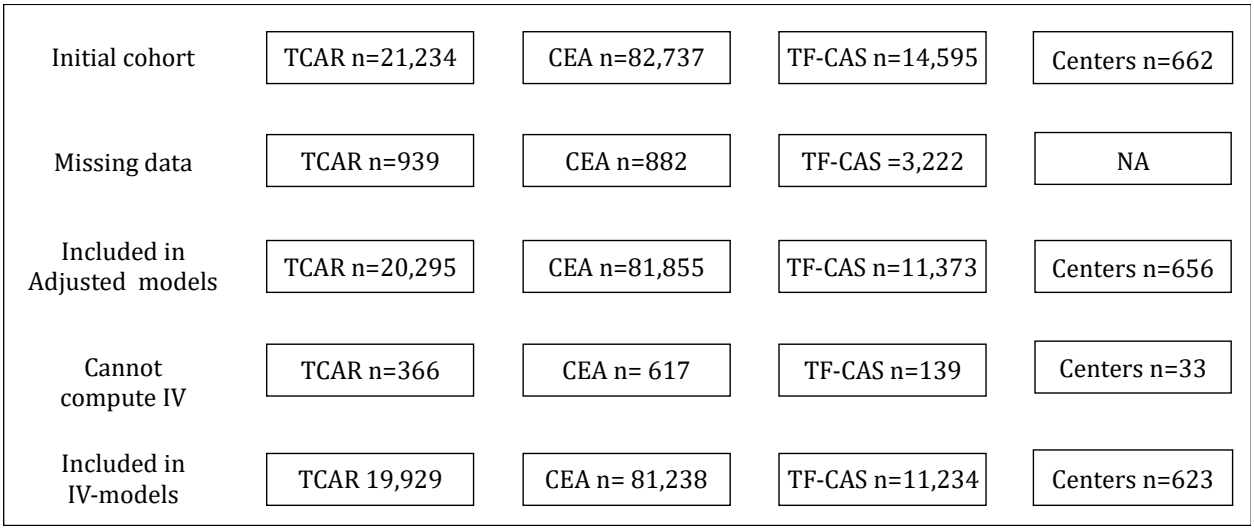
		Cox Regression		
	Current	**% stenosis as covariate Missing=3,744**	**+surgeon as random effect Missing=0**	**Surgeon and % stenosis Missing=3,744**
CEA	0.86 (0.79-0.94)	0.87 (0.80-0.96)	0.86 (0.78-0.95)	0.87 (0.79-0.96)
TF-CAS	1.38 (1.23-1.55)	1.39 (1.24-1.56)	1.42 (1.25-1.60)	1.41 (1.25-1.60)
		2SRI-Frailty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

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



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

Figure S2. Flow diagram of missing data.



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