Sex-Based Differences in Ten-Year Nationwide Outcomes of Carotid Revascularization

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BACKGROUND: We compared the rates of stroke, death, and/or MI between men and women, stratified by symptomatic status and procedure type (carotid endarterectomy [CEA] or carotid artery stent [CAS]).

STUDY DESIGN: Using the Nationwide Inpatient Sample, crude and propensity-matched rates of the composite end point of stroke/death/MI were estimated. Multivariable logistic regression was used to calculate the odds of stroke/death/MI associated with sex.

RESULTS: Between 2005 and 2015, there were 1,242,688 carotid interventions performed (1,083,912 CEA; 158,776 CAS; 515,789 [41.5%] were female patients). Symptomatic admissions comprised 11.3% of the cohort. In-hospital stroke/death/MI rates were more prevalent in men compared with women (4.2% vs 3.9%; $p < 0.01$). Subgroup analysis revealed symptomatic women vs men had higher rates of stroke after CEA (7.7% vs 6.2%; $p < 0.01$) and CAS (9.9% vs 7.6%; $p < 0.01$). Asymptomatic women experienced the same rates of stroke after either CEA (0.3% vs 0.3%; $p = 0.051$) or CAS (0.4% vs 0.5%; $p = 0.09$). Propensity-matched logistic regression revealed that symptomatic males vs females had lower odds of stroke after CEA (odds ratio [OR] 0.81; 95% CI 0.72 to 0.91) and CAS (OR 0.72; 95% CI 0.57 to 0.90). Asymptomatic men and women had similar odds of stroke after both CEA (OR 0.95; 95% CI 0.79 to 1.14) and CAS (OR 0.70; 95% CI 0.43 to 1.13).

CONCLUSIONS: This is the largest cohort study to date that demonstrates asymptomatic women undergoing CEA or CAS do not have a higher risk of perioperative stroke, death, or MI. Symptomatic men experience lower rates of stroke after CEA or CAS. (J Am Coll Surg 2019;229:38−47. © 2019 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

The surgical management of cerebrovascular disease in women remains a topic of debate. Recent data show that women have higher stroke incidence and tend to have more severe strokes.[1] Aspirin use in women results in greater reduction of stroke risk than in men.[2] Prospective randomized controlled trials of asymptomatic patients with carotid artery stenosis, including the Asymptomatic Carotid Atherosclerosis Study and the Asymptomatic Carotid Surgery Trial, show that women have higher rates of stroke and death than men after revascularization.[3,4] In asymptomatic women, it remains unclear whether there is actually a higher risk of stroke after revascularization, mainly due to a lack of statistical power in nested cohorts from these randomized trials. Experts debate the marginal benefit of carotid revascularization in asymptomatic women.

Within symptomatic patients, there are conflicting data. Subgroup analysis of the Carotid Revascularization

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Abbreviations and Acronyms

CAS = carotid artery stent
CEA = carotid endarterectomy
CREST = Carotid Revascularization Endarterectomy Versus Stenting Trial
HCUP = Healthcare Cost and Utilization Project
MAE = major adverse event
NIS = Nationwide Inpatient Sample
OR = odds ratio

Endarterectomy Versus Stenting Trial (CREST) and subsequent retrospective studies on sex-related differences in in-hospital outcomes after carotid revascularization found that women, especially those with symptomatic disease, have higher rates of adverse outcomes after carotid artery stenosis and suggest that carotid endarterectomy (CEA) might be preferred in women compared with carotid artery stenting (CAS).[5-12] In contrast, others have found no differences in postoperative complications in symptomatic men vs women.[13,14]

To fill the gap in knowledge, we sought to evaluate the risk of stroke after carotid revascularization. Using a nationally representative inpatient database and a propensity score-matched analysis, we aimed to quantify the independent association between sex and the likelihood of perioperative complications, stratified by symptom status and procedure type (CEA or CAS), and document sex-specific temporal trends in relative use of CEA vs CAS.

METHODS

We conducted a serial cross-sectional analysis using data from the National Inpatient Sample (NIS), part of a family of databases developed for the Healthcare Cost and Utilization Project (HCUP). The NIS is the largest publicly available all-payer inpatient healthcare database in the US. It contains unweighted data from more than 7 million hospital admissions each year. When weighted, it estimates more than 35 million hospitalizations nationally. Before 2012, the NIS was created using a 2-stage sampling strategy that first selected a sample of hospitals and then all hospitalizations from selected hospitals; beginning in 2012, a sample of hospitalizations was selected from all hospitals participating in HCUP. In both designs, the resultant database contains a 20% sample of hospitalizations from nonfederal US community hospitals that is considered nationally representative. All inpatient discharges after carotid revascularization taking place between January 1, 2005 and September 30, 2015 were initially eligible for inclusion; the fourth quarter of 2015 was excluded to remove extraneous influence on study findings due to the transition ICD-9-CM to ICD-10-CM, which occurred October 1, 2015.[15] Due to the publicly available, de-identified nature of the NIS, this study was deemed exempt by the Baylor College of Medicine IRB (IRB00000077). Our methodological standards were consistent with Agency for Healthcare Research and Quality recommendations for the use of the NIS.[16]

Patient data

Currently, each hospitalization record in the NIS contains a primary ICD-9-CM diagnosis code and up to 29 secondary diagnoses, as well as a principal ICD-9-based procedure code and up to 14 secondary procedures. We identified all adult (18 years of age and older) admissions with a diagnosis code for carotid artery stenosis, as well as a procedure code indicative of carotid revascularization for CAS using CAS or CEA. Symptomatic carotid artery stenosis was differentiated from asymptomatic based on the presence of 1 or more diagnosis codes indicative of amaurosis fugax, transient ischemic attack, or stroke.[17,18] Additional preoperative characteristics, including age, sex, race/ethnicity, and comorbidities (hypertension, hyperlipidemia, coronary artery disease, diabetes mellitus, congestive heart failure, COPD, chronic kidney disease, and end-stage renal disease) were collected. All ICD-9-CM diagnosis and procedure codes used are listed in Table 1.

Non-clinical variables were collected, including the year of admission, primary payer status, median household income, timing of discharge (weekday or weekend), hospital bed size, hospital region, and hospital type. These variables have standardized definitions within HCUP. Primary payer status is separated into government, private, and other. Median household income of residents in the patient's ZIP code was divided into quartiles. HCUP designates hospital sizes as small, medium, and large. Hospital regions include Northeast, Midwest, South, and West. The hospital-type variable separates rural vs urban hospitals and then substratifies the urban group into teaching and non-teaching hospitals.

The outcomes of interest were postoperative cerebrovascular infarction or hemorrhage, postoperative MI, and in-hospital death. To more fully capture acute inpatient MI, postoperative MI included both acute MI and other cardiac complications. These 3 outcomes were analyzed individually and also as a major adverse event (MAE) composite.

Statistical analysis

We used descriptive statistics to investigate sex differences in the distribution of selected clinical and sociodemographic characteristics, and used the Rao-Scott

Table 1. ICD-9-CM Procedure and Diagnosis Codes

Diagnosis or procedure	ICD-9-CM code
Determination of the study population	
Carotid artery stenosis	
Occlusion and stenosis of carotid artery without mention of cerebral infarct	433.10
Occlusion and stenosis of carotid artery with cerebral infarct	433.11
Occlusion and stenosis of multiple and bilateral precerebral arteries without mention of cerebral infarct	433.30
Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarct	433.31
Procedure	
Carotid endarterectomy	38.12
Carotid artery stent	00.63
Outcome	
Iatrogenic cerebrovascular infarction or hemorrhage	997.02
Acute MI	410
Cardiac complications, not elsewhere classified	997.1
Condition reflecting symptomatic carotid artery stenosis	
Amaurosis fugax	
Transient retinal arterial occlusion	362.34
Transient visual loss	368.12
Transient ischemic attack	
Unspecified transient cerebral ischemia	435.9
Transient paralysis of limb	781.4
Stroke	
Occlusion and stenosis of unspecified precerebral artery with cerebral infarction	433.91
Cerebral thrombosis with cerebral infarction	434.01
Cerebral embolism with cerebral infarction	434.11
Cerebral artery occlusion, unspecified with cerebral infarction	434.91
Comorbidity	
Hypertension	
Essential hypertension	401
Hypertensive heart disease	402
Hypertensive chronic kidney disease	403
Hypertensive heart and chronic kidney disease	404
Secondary hypertension	405
Disorder of lipid metabolism	272
Diabetes mellitus	250—250.9
Other forms of chronic ischemic heart disease	414—414.9
Heart failure	428—428.9
Chronic obstructive pulmonary disease	
Bronchitis	490
Chronic bronchitis	491
Emphysema	492
Asthma	493
Bronchiectasis	494
Extrinsic allergic alveolitis	495
Chronic airway obstruction, not elsewhere classified	496
Coal workers' pneumoconiosis	500
Asbestosis	501
Pneumoconiosis due to other silica or silicates	502
Pneumoconiosis due to other inorganic dust	503
Pneumoconiosis due to inhalation of other dust	504
Pneumoconiosis, unspecified	505
Chronic respiratory conditions due to fumes and vapors	506.4
Chronic kidney disease	
Chronic glomerulonephritis	582—582.9
Nephritis and nephropathy not specified as acute or chronic	583—583.8
Chronic kidney disease	585
Renal failure, unspecified	586
Disorder resulting from impaired renal function	588—588.9
End-stage renal disease	585.6

modified chi-square test to determine the statistical significance of differences between men and women hospitalized to receive revascularization for carotid artery stenosis. We calculated the unadjusted proportion of hospitalizations experiencing each of the primary study outcomes, stratified by carotid artery stenosis subtype, revascularization procedure, and sex. Then, for each of the 4 possible cohorts based on carotid artery stenosis subtype and revascularization procedure—namely, asymptomatic patient admissions who underwent CAS, asymptomatic patient admissions who underwent CEA, symptomatic patient admissions who underwent CAS, and symptomatic patient admissions who underwent CEA—our primary aim was to estimate the association between sex and MAEs after revascularization.

We used 2 approaches to removing the effects of potential confounders and isolating the independent contribution of sex. First, we used traditional covariate-adjusted, survey-weighted, unconditional logistic regression models on the entire study population to calculate adjusted odds ratio (OR) and 95% CI representing the associations of interest. Selection of confounders was based on data availability, the scientific literature, and empirical bivariate analyses, and included year, race/ethnicity, ZIP code level median income, primary payer, weekday/weekend admission, chronic comorbidities (hypertension, lipid disorders of metabolism, diabetes, congestive heart failure, chronic ischemic heart disease, COPD, chronic kidney disease/end-stage renal disease), hospital region, size, and type.

Second, to adjust for potential confounding and selection biases, we performed a propensity score-matched analysis. For each cohort, we first using a logistic regression model with the confounders mentioned to predict the adjusted probability of being female, the propensity score. We then we matched men and women in a 1:1 fashion using a greedy 8-to-1 digit-matching algorithm.[19] We assessed the success of the propensity-matching algorithm by comparing the distribution of sociodemographic and clinical characteristics between men and women in the matched sample. We then used conditional logistic regression on the propensity score-matched samples to estimate measures of association for the 4 cohorts.

Last, we explored the annual proportion of all procedures for carotid artery stenosis that were CEA vs CAS to identify any temporal shifts in revascularization approach. Statistical analyses were performed with SAS, version 9.4 (SAS Institute). We assumed a 5% type I error rate for all hypothesis tests (2-sided). Because the NIS sampling design changed during the study period, HCUP-supplied NIS Trends files were used to ensure that discharge weights and data elements were defined consistently over time.

RESULTS

This analysis included data on an estimated 1.2 million hospitalizations, during which carotid revascularization was performed for carotid artery stenosis. Of these, 87.2% were CEA and 12.8% were CAS. Demographic and clinical characteristics for the sample, stratified by sex, are depicted in Table 2. Women comprised 41.5% of the cohort. Overall, 11.3% of patients had symptomatic disease. Median age was 71.2 years (interquartile range 64.3 to 77.4 years). The 3 most common comorbidities in the cohort were hypertension (80.4%), followed by hyperlipidemia (58.0%) and coronary artery disease (44.2%). Women were slightly more likely than men to receive CEA vs CAS (88.1% vs 86.6%; $p < 0.01$), and had slightly higher rates of hypertension, congestive heart failure, and COPD. Men were more likely to have symptomatic disease than women (11.8% vs 10.7%; $p < 0.01$), and had slightly higher rates of hyperlipidemia and chronic kidney disease, and substantially higher rates of coronary artery disease (49.3% vs 37.0%; $p < 0.01$).

The unadjusted rates of stroke, in-hospital mortality, MI, and the composite MAE end point are presented in Table 3. In the total cohort, the rate of acute MI, stroke, and in-hospital mortality were 2.9%, 1.1%, and 0.5%, respectively. The overall rate of MAEs was 4.1%. Regardless of sex or procedure type, symptomatic patients had substantially higher rates of all study outcomes. Within each procedure type-symptom status subgroup, there were several statistically significant differences in outcomes rates between men and women. Symptomatic

Table 2. Distribution of Selected Patient Characteristics among Inpatient Discharges for Revascularization for Carotid Artery Stenosis, by Sex, United States, 2005 to 2015

Characteristic	Overall	Men	Women	p Value*
Procedure, %				
Carotid endarterectomy	87.2	86.6	88.1	<0.01
Carotid artery stent	12.8	13.4	11.9	<0.01
Symptomatic carotid stenosis, %	11.3	11.8	10.7	<0.01
Age, y, median (IQR)	71.2 (64.3–77.4)	71.1 (64.2–77.2)	71.3 (64.3–77.8)	<0.01
Comorbidity, %				
Hypertension	80.4	79.4	81.9	<0.01
Hyperlipidemia	58.0	58.3	57.5	<0.01
Diabetes mellitus	32.2	32.1	32.2	0.73
Coronary artery disease	44.2	49.3	37.0	<0.01
Congestive heart failure	8.0	7.9	8.3	<0.01
COPD	18.0	17.3	19.1	<0.01
Chronic kidney disease	8.9	9.6	7.8	<0.01
End-stage renal disease	1.0	1.0	1.0	0.60

*The p value from a Rao-Scott modified chi-square test assessing sex differences in the proportion of patients with each characteristic. For age, the p value is from a Wilcoxon rank sum test.
IQR, interquartile range.

Table 3. Rates of Major Adverse Events among Inpatient Discharges for Revascularization for Carotid Artery Stenosis, by Sex, Procedure Type, and Symptom Status, US, 2005 to 2015

	Carotid artery stent						Carotid endarterectomy					
	Symptomatic			Asymptomatic			Symptomatic			Asymptomatic		
Outcome	Men, %	Women, %	p Value*	Men, %	Women, %	p Value*	Men, %	Women, %	p Value*	Men, %	Women, %	p Value*
Stroke	7.6	9.9	<0.01	0.4	0.5	0.09	6.2	7.7	<0.01	0.3	0.3	0.051
Acute MI	5.5	4.9	0.30	3.3	2.9	0.12	3.4	3.4	0.77	2.9	2.4	<0.01
In-hospital mortality	4.1	4.4	0.65	0.4	0.3	0.15	1.4	1.7	0.10	0.3	0.2	0.08
Major adverse event†	15.7	17.1	0.20	3.8	3.4	0.14	9.8	11.3	<0.01	3.3	2.8	<0.01

*p Value from a Rao-Scott modified chi-square test assessing sex differences in the proportion of patients with each end point.
†A major adverse event constituted a composite variable reflecting one or more of the other outcomes (stroke, acute MI, in-hospital mortality).

women who underwent CAS had higher rates of stroke compared with symptomatic men (9.9% vs 7.6%; $p < 0.01$). Similarly, symptomatic women who underwent CEA had higher rates of stroke compared with symptomatic men (7.7% vs 6.2%; $p < 0.01$) and of MAEs (11.3% vs 9.8%; $p < 0.01$). However, asymptomatic women vs asymptomatic men who underwent CEA had lower rates of MAEs (2.8% vs 3.3%; $p < 0.01$) and acute MI (2.4% vs 2.9%; $p < 0.01$).

Propensity score matching worked well in creating similar distributions of sociodemographic and clinical characteristics between men and women in matched samples (eTables 1, 2, 3, and 4). Traditional covariate-adjusted logistic regression on the entire study population and propensity score-matched analysis on the pair-matched population yielded extremely similar ORs estimating the association between sex and MAEs in each procedure type and symptom status subgroup (Fig. 1A).

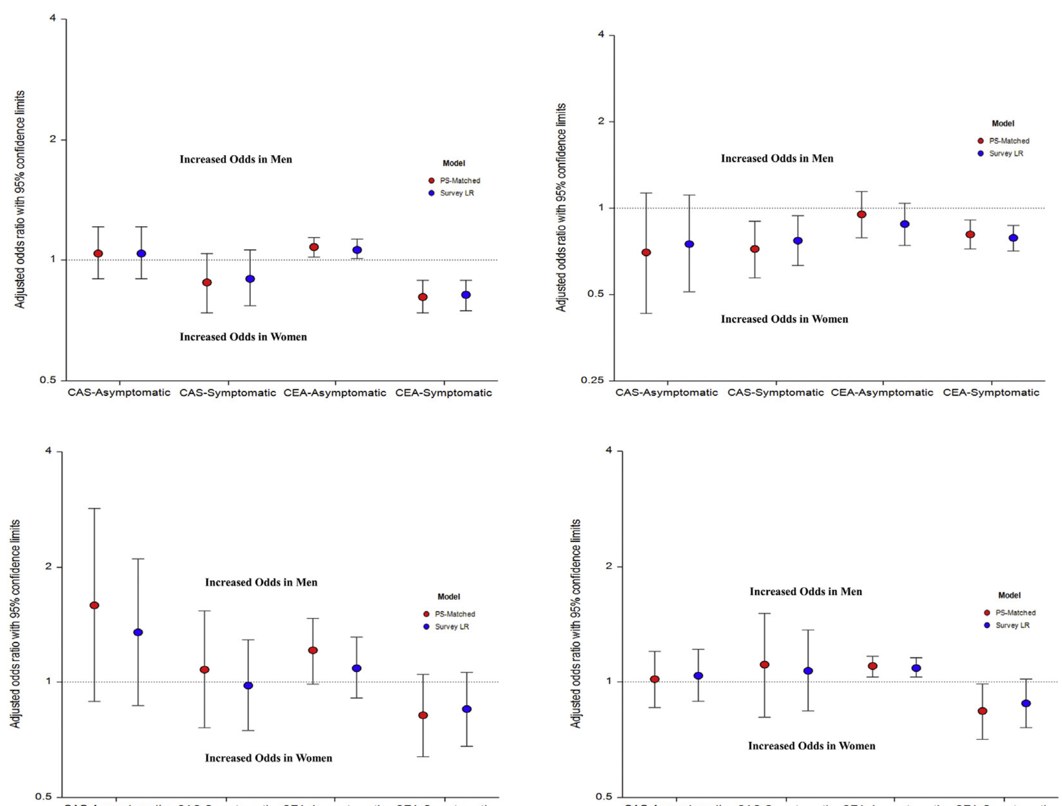

Figure 1. Odds of outcomes for men vs women. (A) Major adverse event; (B) stroke; (C) death; (D) cardiac. CAS, carotid artery stent; CEA, carotid endarterectomy; LR, logistic regression; PS, propensity score.

After CAS, regardless of symptom status, there was no difference in the odds of MAEs between men and women. Asymptomatic men had a small (6% to 8%) increased odds of MAEs compared with women. In contrast, symptomatic men had nearly 20% decreased odds of stroke/death/MI compared with asymptomatic women. When analyzing each adverse end point separately (Table 4), among asymptomatic patients undergoing CEA, men had 10% increased odds of acute MI, and among symptomatic patients undergoing CEA, it was women who had increased odds of both acute MI and stroke (Figs. 1B, 1D). Symptomatic women undergoing CAS also had increased odds of stroke compared with symptomatic men undergoing CAS.

Figure 2 illustrates temporal trends in carotid revascularization procedures performed, stratified by sex and procedure type. During the study period, the overall proportion of procedures that were CAS increased. The increase was most pronounced among symptomatic patients, nearly doubling from 11.3% to 22.3% ($p < 0.01$) in women, and 12.6% to 24.6% ($p < 0.01$) in men. Among asymptomatic patients, the increase was

Table 4. Adjusted Odds Ratios and 95% CIs Representing the Association between Sex and Surgical Outcomes among Inpatient Discharges for Revascularization for Carotid Artery Stenosis, Stratified by Procedure Type and Symptom Status in the US, 2005 to 2015

Outcome, procedure, symptom status	Model 1, OR (95% CI)*	Model 2, OR (95% CI)†
Stroke		
CAS		
Asymptomatic	0.75 (0.51, 1.11)	0.70 (0.43, 1.13)
Symptomatic	0.77 (0.63, 0.94)‡	0.72 (0.57, 0.90)‡
CEA		
Asymptomatic	0.88 (0.74, 1.04)	0.95 (0.79, 1.14)
Symptomatic	0.79 (0.71, 0.87)‡	0.81 (0.72, 0.91)‡
In-hospital death		
CAS		
Asymptomatic	1.35 (0.87, 2.10)	1.59 (0.89, 2.85)
Symptomatic	0.98 (0.75, 1.29)	1.08 (0.76, 1.54)
CEA		
Asymptomatic	1.09 (0.91, 1.31)	1.21 (0.99, 1.47)
Symptomatic	0.85 (0.68, 1.06)	0.82 (0.64, 1.05)
Acute MI		
CAS		
Asymptomatic	1.04 (0.89, 1.22)	1.02 (0.86, 1.20)
Symptomatic	1.07 (0.84, 1.37)	1.11 (0.81, 1.51)
CEA		
Asymptomatic	1.09 (1.03, 1.16)‡	1.10 (1.03, 1.17)‡
Symptomatic	0.88 (0.76, 1.02)	0.84 (0.71, 0.99)‡
Major adverse event§		
CAS		
Asymptomatic	1.04 (0.90, 1.21)	1.04 (0.90, 1.21)
Symptomatic	0.90 (0.77, 1.06)	0.88 (0.74, 1.04)
CEA		
Asymptomatic	1.06 (1.01, 1.13)‡	1.08 (1.02, 1.14)‡
Symptomatic	0.82 (0.75, 0.89)‡	0.81 (0.74, 0.89)‡

*Model 1 was a covariate-adjusted model including all inpatient discharges for revascularization for carotid artery stenosis within the subgroup specified, and adjusting for year, race/ethnicity, ZIP-code level median income, primary payer, weekday/weekend admission, chronic comorbidities (hypertension, lipid disorders of metabolism, diabetes, congestive heart failure, chronic ischemic heart disease, COPD, chronic kidney disease/end-stage renal disease), hospital region, size, and type.
†Model 2 was a propensity score-matched conditional logistic regression model.
‡Statistically significant.
§A major adverse event constituted a composite variable reflecting 1 or more of the other outcomes (stroke, acute MI, in-hospital mortality).
CAS, carotid artery stent; CEA, carotid endarterectomy; OR, odds ratio.

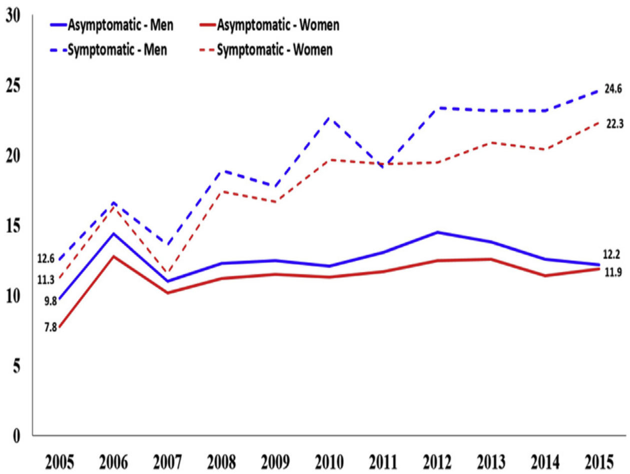

Figure 2. Temporal trends in carotid revascularization procedures performed, stratified by sex and procedure type.

lesser in magnitude and without significant changes from 2007 to 2015.

DISCUSSION

Based on the analysis of more than 1.2 million hospitalizations for carotid revascularization in a decade, the risks of postoperative adverse events in women with asymptomatic carotid artery stenosis were not significantly different than the risks in men. After CEA, men had a higher risk of MI and overall MAEs. Symptomatic women, however, experienced increased perioperative risk of stroke after CEA, and especially after CAS. These findings were consistent across all models, including propensity matching. Over time, the proportion of CEA performed declined relative to CAS.

Our data dispel the previously held belief that women are at increased risk of perioperative stroke and/or death after carotid revascularization. Our study surmounts the main limitations of the earlier literature, namely, the lack of statistical power to evaluate females appropriately, and the lack of real-world, modern outcomes. Our study is the largest, propensity-matched, real-world cohort of subjects undergoing carotid revascularizations; type 2 error could not have influenced our findings, in contrast to previous studies. In addition, our series spans the most recent decade. Differences that might have been present 20 to 30 years ago in the Asymptomatic Carotid Atherosclerosis Study and the Asymptomatic Carotid Surgery Trial might have been mitigated over time by iterative improvements in the technical execution of carotid revascularizations in women, and improved penetrance of optimal medical management.

The majority of carotid revascularizations performed in the earlier decade were for asymptomatic disease. Although mostly safe, the appropriateness of carotid revascularization for asymptomatic stenoses remains unclear. Appropriateness for carotid intervention is particularly prescient, as the proportion of elderly patients continues to increase within the US. Our study does not determine whether the risk to benefit ratio favors carotid revascularization in asymptomatic men or women, as there was not a control arm of patients undergoing medical management only. This will require additional study with appropriate female representation, hopefully within CREST-2.

Several studies have documented worse outcomes after CAS than CEA in women. In a subset analysis of CREST, women had an 84% increased hazard of periprocedural events compared with women undergoing CEA.[5] Retrospective series found that women had an increased risk of stroke/death after CAS compared with men.[7,12] However, our data contradict previous authors' results in this regard. Our results reflect real-world outcomes, which might explain the differences between our results and the prespecified analysis of the CREST trial.[6] The large sample size and national representation of patients within our study confers on it the added merit of being more generalizable with respect to the observed association between sex and type of carotid revascularization (CAS vs CEA).

Our data did find 2 significant disparities based on sex. Symptomatic women in our cohort, both in the crude and propensity-matched analysis, consistently had worse outcomes relative to males. This is particularly concerning because multiple earlier studies have shown that women bear a disproportionate burden of morbidity and mortality after stroke. The fact that the disparity persists after propensity matching suggests an intrinsically female biologic factor, as the propensity model mitigated differences based on medical or socioeconomic variables. Additional prospective randomized cohorts might help to corroborate these findings and optimize care for this particularly high-risk cohort. However, given the strength our results in the context of the current literature,[5-12] we recommend preferentially performing CEA for symptomatic women instead of CAS.

Second, men in our cohort had higher rates of postoperative MI than women. Traditionally, the cardiovascular benefits of estrogen and differences in stressors associated with sex roles have been touted as reasons for the delayed presentation of coronary artery disease in women.[20] Estrogen has been shown to have an anti-inflammatory effect on atherosclerotic plaques, resulting in plaque stabilization,[21] though this has been reported inconsistently in the literature. Additional sex-based studies are needed to understand the mechanism for increased MI in men after carotid revascularization to better improve outcomes in this cohort.

During our study period, the proportion of CEA performed relative to CAS declined. Other studies using NIS or Medicare databases also demonstrated that the rates of CEA were decreasing over time, and CAS use increased over time. As CEA remained a larger proportion of the total carotid revascularizations performed, the overall rate of carotid revascularization declined.[10,22,23] Trend analysis revealed an increase in patient age and comorbidities over time.[10] This likely represents the transition from CEA to CAS, especially the substitution of poor CEA candidates to CAS and addition of patients who were not previously offered surgical therapy who now have the option of CAS.

This study is limited mainly by its cross-sectional design and the known restrictions imposed by an administrative hospital discharge database. As the NIS contains only a sample of inpatient records, without the ability to link hospitalizations for the same patient over time, data on adverse events that occurred after discharge cannot be ascertained. In contrast to carotid revascularization, medical management of carotid artery stenosis is often performed as an outpatient, therefore, we were unable to compare outcomes after carotid revascularization to a nonoperatively managed cohort. In addition, identification of the study population, study outcomes, procedures, and comorbidities were identified using ICD-9-CM codes that have suboptimal accuracy; therefore, some misclassification is possible, though coding practices are unlikely to be significantly different between men and women. Reliance on these codes and lack of sensitivity for certain conditions, however, might have resulted in an overestimation of the degree to which procedures are performed in asymptomatic patients. This is plausibly evidenced by the near 90% of the study population classified as having asymptomatic disease, an estimate that is greater than the prevalence reported previously.[24] We also did not examine the role of physician volume or specialty on sex-stratified outcomes, as this had been studied previously by other authors. In addition, after propensity matching, there were no differences when stratified by sex and symptoms type with respect to hospital size or hospital region where the procedures were performed. Despite these limitations, significant strengths of the study stem from the standardized compilation of more than 10 years of nationally representative data and use of propensity score matching to reduce selection and confounding biases and estimate differences between men and women undergoing revascularization procedures for carotid artery stenosis on the likelihood of severe postsurgical events.

CONCLUSIONS

To date, this is the largest cohort study examining the relationship between sex and adverse outcomes after carotid revascularization during the most recent decade. In asymptomatic patients, carotid revascularization, either CEA or CAS, does not portend a higher risk of adverse outcomes in women than in men. Symptomatic women have higher odds of perioperative stroke than men after both CEA and CAS. Overall, women are not at increased risk of events based on procedural type. Prospective risk-stratified registries will be required to continually monitor outcomes after carotid revascularization to ensure that sex disparities are ascertained accurately, and mitigated by clinicians and researchers.

Author Contributions

Study conception and design: Mayor, Montero-Baker, Mills, Chung

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Analysis and interpretation of data: Mayor, Salemi, Dongarwar, Salihu, Chung

Drafting of manuscript: Mayor, Salemi, Dongarwar, Montero-Baker, Mills, Chung

Critical revision: Mayor, Salemi, Salihu, Montero-Baker, Mills, Chung

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Discussion

DR M ASHRAF MANSOUR (Grand Rapids, MI): Dr Mayor and colleagues queried the National Inpatient Sample (NIS) for carotid interventions between 2005 and 2015. They stopped collecting data after October 2015 because we switched to ICD-10 and they were afraid of contaminating their data. They found more than 1,242,000 patients in this database. These patients received either carotid endarterectomy or stent. Roughly 41.5% were women. Interestingly, only 11.3% were symptomatic. Their studies showed the highest rate of stroke in their patients was in symptomatic women having a carotid stent, followed by symptomatic women having an endarterectomy. I have several questions that are unlikely to be answered by querying this large database. For instance, why are we operating or intervening on so many asymptomatic patients? In our hospital, 25% to 30% of patients are symptomatic. Is this a good use of our precious resources? Are we making a positive impact on the quality of life of our population? Also, in one of the tables in the study, there were men and women in the 18- to 39-year-old age group who underwent carotid stenting. Really? Why?

Do you have any information on the specialties of physicians performing carotid stenting and the proportion of cardiologists, radiologists, and surgeons performing them? The rate of stroke in symptomatic women is so high, 9.9%, to be accurate. Should you be making a stronger statement like symptomatic women should not have a stent except in very rare circumstances? Can you please comment? I am encouraged by your reported stroke rate in asymptomatic patients in both men and women, which is under 0.5%, but it is still very concerning that the rates of mortality and major adverse events in this patient population are 0.4% and 4%, respectively. Do you have any recommendation on who should be performing these procedures? Specifically, should carotid interventions be regionalized?

DR JAYER CHUNG (Houston, TX): Who is doing the carotid artery interventions? This has been explored in a previous study done by one of my colleagues. He examined which specialties performed the carotid artery stenting procedure specifically. In the NIS, there is not a specific variable that distinguishes which specialists performed a given procedure. In order to distinguish who is a cardiologist, for instance, you have to find people who are also doing carotid artery stents and coronary percutaneous interventions, and define these as cardiologists. Those that are cardiac surgeons, by contrast, are defined by those who perform both carotid artery interventions and coronary artery bypass grafting. It is somewhat inaccurate. What they were finding is that the carotid artery stenting procedures that are done by cardiologists actually have somewhat inferior outcomes; so as to not overlap with my colleagues' previous work, we did not specifically investigate the role of the operator's specialty in our study.

Should we be performing carotid artery stenting in females, since we do have a very high stroke rate? There are 2 points I would make about this. One is that the NIS does tend to underestimate the number of symptomatic women. Therefore, the symptomatic women you are seeing are the most symptomatic with the most comorbidities. This may slightly exaggerate the stroke risk in the symptomatic women. Second, in the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the stroke risk in symptomatic carotid artery stenosis $>$ 70% is 26% in the medically managed arm, which decreased to 9% after carotid endarterectomy. The benefit was seen regardless of sex. For this subgroup,

eTable 1. Demographic, Socioeconomic, and Medical Risk Factors Pre- and Post-Propensity Score Matching for Men and Women Who Underwent Carotid Artery Stenting for Asymptomatic Carotid Disease

	Pre-matching, %			Post-matching, %		
Variable	**Male (n = 80,247)**	**Female (n = 51,804)**	**p Value**	**Male (n = 51,626)**	**Female (n = 51,648)**	**p Value**
Age						
18–39 y	0.1	0.3	<0.01	0.2	0.2	0.55
40–49 y	1.3	2.0	<0.01	1.7	1.9	0.25
50–59 y	10.1	10.9	0.04	10.6	10.9	0.51
60–69 y	30.7	29.5	0.05	29.5	29.6	0.93
70–79 y	38.3	35.4	<0.01	36.2	35.5	0.30
80+ y	19.5	22.0	<0.01	21.8	22.0	0.73
Comorbidity						
Hypertension	76.0	78.5	<0.01	78.7	78.6	0.87
Hyperlipidemia	61.3	60.5	0.17	60.2	60.6	0.63
Diabetes mellitus	32.3	32.5	0.65	31.9	32.6	0.32
Coronary artery disease	58.2	47.3	<0.01	47.6	47.4	0.86
Congestive heart failure	11.3	11.6	0.45	10.8	11.6	0.05
COPD	17.4	20.0	<0.01	19.1	20.0	0.13
Chronic kidney disease	11.5	9.6	<0.01	8.9	9.6	0.06
End-stage renal disease	1.3	1.4	0.77	1.1	1.4	0.07
Median household income						
Lowest	26.2	28.4	<0.01	28.3	28.4	0.89
Second	26.7	26.7	0.97	26.7	26.6	0.93
Third	24.5	24.3	0.66	24.7	24.3	0.51
Highest	20.4	18.9	<0.01	18.8	19.0	0.80
Missing	2.2	1.8	0.01	1.6	1.8	0.19
Primary payer						
Government	76.5	78.9	<0.01	79.5	79.0	0.41
Private	19.7	18.0	<0.01	17.8	18.0	0.75
Other	3.8	3.0	0.01	2.7	3.0	0.25
Year						
2005–2008	40.2	40.4	0.83	40.2	40.4	0.82
2009–2012	37.4	37.6	0.82	37.2	37.6	0.62
2013–2015	22.3	22.0	0.59	22.6	22.0	0.38

eTable 2. Demographic, Socioeconomic, and Medical Risk Factors Pre- and Post-Propensity Score Matching for Men and Women Who Underwent Carotid Artery Stenting for Symptomatic Carotid Disease

	Pre-matching, %			Post-matching, %		
Variable	**Male (n = 16,908)**	**Female (n = 9,817)**	**p Value**	**Male (n = 9,789)**	**Female (n = 9,773)**	**p Value**
Age						
18−39 y	0.5	1.5	<0.01	0.8	1.0	0.48
40−49 y	2.9	4.8	<0.01	4.3	4.8	0.44
50−59 y	15.3	14.1	0.20	14.0	14.1	0.92
60−69 y	30.3	28.4	0.14	28.8	28.6	0.88
70−79 y	31.0	29.6	0.26	29.9	29.7	0.89
80+ y	19.8	21.7	0.10	22.2	21.8	0.72
Comorbidity						
Hypertension	78.2	80.0	0.12	81.0	80.0	0.43
Hyperlipidemia	60.5	58.6	0.15	59.3	58.7	0.65
Diabetes mellitus	33.0	35.0	0.13	34.8	35.0	0.94
Coronary artery disease	42.5	35.0	<0.01	35.5	35.2	0.80
Congestive heart failure	12.2	13.9	0.07	11.7	13.9	0.04
COPD	16.4	18.0	0.13	16.0	18.1	0.08
Chronic kidney disease	13.4	11.2	0.02	10.2	11.2	0.34
End-stage renal disease	1.2	1.5	0.41	0.9	1.5	0.06
Median household income						
Lowest	28.1	29.8	0.16	29.8	29.9	0.95
Second	26.5	27.8	0.30	28.5	27.8	0.62
Third	23.5	22.0	0.22	21.2	22.0	0.54
Highest	19.7	18.4	0.25	18.7	18.4	0.78
Missing	2.2	2.0	0.62	1.7	1.9	0.74
Primary payer						
Government	69.7	75.7	<0.01	77.9	75.7	0.11
Private	23.1	18.6	<0.01	17.0	18.5	0.20
Other	7.1	5.8	0.06	5.2	5.8	0.38
Year						
2005−2008	27.4	29.8	0.06	30.3	29.9	0.79
2009−2012	38.3	38.1	0.88	36.8	38.0	0.44
2013−2015	34.4	32.1	0.09	32.9	32.1	0.58

eTable 3. Demographic, Socioeconomic, and Medical Risk Factors Pre- and Post-Propensity Score Matching for Men and Women Who Underwent Carotid Endarterectomy for Asymptomatic Carotid Disease

Variable	Pre-matching, %			Post-matching, %		
	Male (n = 560,998)	Female (n = 408,655)	p Value	Male (n = 406,017)	Female (n = 405,691)	p Value
Age						
18–39 y	0.0	0.1	0.03	0.1	0.1	0.98
40–49 y	1.2	1.6	<0.01	1.4	1.5	0.06
50–59 y	10.4	10.1	0.07	10.2	10.1	0.56
60–69 y	30.2	29.3	<0.01	29.6	29.4	0.38
70–79 y	39.1	38.1	<0.01	38.6	38.3	0.30
80+ y	19.1	20.1	<0.01	20.3	20.7	0.03
Comorbidity						
Hypertension	79.7	82.3	<0.01	81.8	82.2	0.03
Hyperlipidemia	57.5	56.8	<0.01	56.4	56.8	0.08
Diabetes mellitus	32.2	32.1	0.49	32.3	32.0	0.17
Coronary artery disease	49.5	36.6	<0.01	37.0	36.8	0.51
Congestive heart failure	7.1	7.6	<0.01	7.1	7.3	0.20
COPD	17.3	19.0	<0.01	18.4	18.8	0.06
Chronic kidney disease	9.1	7.3	<0.01	7.4	7.3	0.56
End-stage renal disease	1.0	0.9	0.27	0.8	0.9	0.17
Median household income						
Lowest	24.9	27.1	<0.01	26.9	26.9	0.98
Second	20.8	29.3	<0.01	29.1	29.3	0.61
Third	24.9	24.0	<0.01	24.2	24.1	0.73
Highest	20.2	17.8	<0.01	18.0	17.9	0.56
Missing	2.0	1.8	<0.01	1.8	1.8	0.33
Primary payer						
Government	74.9	78.5	<0.01	78.3	78.4	0.53
Private	22.2	18.6	<0.01	18.9	18.7	0.29
Other	2.9	2.9	0.83	2.8	2.9	0.34
Year						
2005–2008	42.7	43.6	<0.01	43.5	43.6	0.75
2009–2012	35.8	35.9	0.89	35.8	35.8	0.75
2013–2015	21.5	20.5	<0.01	20.7	20.6	0.41

eTable 4. Demographic, Socioeconomic, and Medical Risk Factors Pre- and Post-Propensity Score Matching for Men and Women Who Underwent Carotid Endarterectomy for Symptomatic Carotid Disease

	Pre-matching, %			Post-matching, %		
Variable	**Male (n = 68,746)**	**Female (n = 45,513)**	**p Value**	**Male (n = 45,408)**	**Female (n = 45,378)**	**p Value**
Age						
18–39 y	0.2	0.3	0.32	0.3	0.3	0.85
40–49 y	2.4	3.5	<0.01	3.1	3.3	0.52
50–59 y	14.2	13.6	0.21	12.9	13.7	0.13
60–69 y	29.5	27.9	<0.01	28.2	28.0	0.70
70–79 y	34.5	32.6	<0.01	33.9	32.7	0.10
80+ y	19.2	22.1	<0.01	21.7	22.1	0.43
Comorbidity						
Hypertension	80.8	82.4	<0.01	82.8	82.4	0.44
Hyperlipidemia	60.8	59.9	0.15	60.2	59.9	0.72
Diabetes mellitus	31.3	32.8	0.02	32.3	32.7	0.58
Coronary artery disease	39.2	30.0	<0.01	30.1	30.1	0.98
Congestive heart failure	8.8	9.5	0.06	8.6	9.5	0.03
COPD	16.9	19.7	<0.01	19.0	19.6	0.29
Chronic kidney disease	11.3	9.7	<0.01	9.0	9.7	0.10
End-stage renal disease	0.9	1.1	0.26	0.8	1.0	0.14
Median household income						
Lowest	24.8	27.8	<0.01	27.9	27.6	0.71
Second	27.5	28.1	0.36	27.7	28.1	0.57
Third	25.1	24.3	0.19	24.6	24.4	0.70
Highest	20.3	18.0	<0.01	18.0	18.0	0.96
Missing	2.3	1.9	0.03	1.8	1.9	0.66
Primary payer						
Government	70.4	74.5	<0.01	75.3	74.4	0.21
Private	24.0	20.2	<0.01	19.8	20.2	0.47
Other	5.5	5.3	0.51	4.9	5.3	0.22
Year						
2005–2008	36.8	38.7	<0.01	38.6	38.7	0.90
2009–2012	35.9	35.3	0.43	35.4	35.4	0.99
2013–2015	27.4	25.9	0.02	26.1	26.0	0.90