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Gender Differences in Treatment of Severe Carotid Stenosis After TIA

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Abstract

Background and Purpose—Gender differences in carotid endarterectomy (CEA) rates after transient ischemic attack (TIA) are not well studied, though some reports suggest that eligible men are more likely to have CEA than women after stroke.

Methods—We retrospectively identified all patients diagnosed with TIA and ≥70% carotid stenosis on ultrasound in 2003-2004 from 19 emergency departments. Medical records were abstracted for clinical data, 90-day follow-up events including stroke, cardiovascular events or death, CEA within 6 months, and post-operative 30-day outcomes. We assessed gender as a predictor of CEA and its complications, adjusting for demographic and clinical variables, as well as time to CEA between groups.

Results—Of 299 patients identified, 47% were women. Women were older with higher presenting SBP and less likely to smoke or to have CAD or diabetes. Fewer women (36.4%) had CEA than men (53.8%) (p=0.004). Reasons for withholding surgical treatment were similar in women and men, and there were no differences in follow-up stroke, CV event, postoperative complications or death. Time to CEA was also significantly delayed in women.

Conclusions—Women with severe carotid stenosis and recent TIA are less likely to undergo CEA than men, and surgeries are more delayed.

Keywords

[8] Epidemiology; [49] Carotid Stenosis; [76] Carotid endarterectomy; [81] Transient Ischemic Attacks

Introduction

Carotid artery stenosis is responsible for 10-16% of all strokes.[1, 2] Carotid endarterectomy (CEA) decreases stroke risk in patients with severe (≥70% by ultrasound) extracranial internal carotid artery (ICA) stenosis, with a 12-17% absolute risk reduction over 2-3 years in symptomatic patients, and a 5% absolute risk reduction over 5 years in asymptomatic patients,

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compared to medical therapy.[3-5] Subgroup analyses of randomized trials showed that women benefit less from CEA than men, in large part due to an increased perioperative morbidity.[5-9] Other studies have challenged this finding, demonstrating similar perioperative complication rates and long-term benefits from CEA among men and women.[10-13] Current US guidelines recommend CEA for patients with symptomatic severe carotid stenosis who are appropriate surgical candidates, regardless of gender.[14] For asymptomatic severe carotid stenosis, guidelines are vague regarding the issue of sex, stating only that CEA is recommended in highly selected patients, guided by comorbidities, life expectancy and other individual factors.[15] Despite this, CEA is performed less often in women than men.[16]

Stroke risk is high after TIA, regardless of etiology. A subgroup analysis of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) found that subjects with hemispheric TIA and severe carotid stenosis treated medically had a 1-month stroke risk of 22%: approximately double that of all cause TIA.[17, 18] The little data regarding use of CEA for symptomatic carotid stenosis specifically in patients with TIA, suggests a benefit. In a combined subgroup analysis of two large trials of CEA in symptomatic carotid stenosis, 36% of cases presented with cerebral TIA. Among those presenting with TIA and severe symptomatic carotid stenosis, CEA was associated with a 15.4% absolute risk reduction of ipsilateral stroke within 5 years, compared with 17.7% in those presenting with stroke, a non-significant difference.[8] It is not clear whether perioperative risks truly differ between women and men, and even less clear in those patients presenting with TIA. Theoretically, risk should be lower in patients with TIA than in those with stroke, given the smaller amount of permanent brain injury with the index event. Illustrating this point, a recent large population-based cohort study found odds ratios of perioperative death or stroke of 1.81 and 2.40 respectively for patients presenting with TIA and stroke.[19]

Identifying gender disparities in care and determining their etiologies are crucial to improving quality of care for women with stroke and reducing future disease burden.[20] We sought to define the rate of CEA use in men and women after TIA, and if a difference exists, to evaluate possible explanations. We hypothesized that after TIA, women with severe carotid stenosis are treated with CEA less often than men, even after taking into account their clinical factors.

Methods

We performed a retrospective cohort study within Kaiser Permanente Medical Care Plan (KPMCP). KPMCP, an integrated healthcare system, provides care for 3.3 million members residing in northern California (~30% of the Northern California population). Although socioeconomic extremes are underrepresented in KPMCP, its member demographics are similar to the California population.[21] This study was approved by local institutional review boards.

Case Ascertainment and Data Abstraction

From January 1st 2003 to December 31st 2004, records of patients diagnosed with TIA by emergency department (ED) physicians in KPMCP were entered into an automated database. Patient records are linked to computerized inpatient and outpatient records, and ultrasound and other imaging reports. Online reports of carotid ultrasound performed within 6 months of the index TIA were reviewed by study neurologists and disease severity was recorded. The study included all those with severe ICA stenosis (70-99%) and a random sample of those without severe stenosis (0-69%). Only severe cases were included in these analyses.

A nurse medical record analyst reviewed medical records for all subjects. Using standardized abstraction forms, patient demographics, past medical history, TIA symptoms and onset, examination findings attributed to the TIA, initial ED heart rate and blood pressure, and

treatment plans were recorded. Subtypes of speech impairment and vision loss were not identified, given the difficulty of distinguishing dysarthria from aphasia, and monocular blindness from homonymous visual field deficits based on patient recollection. It was not possible to retrospectively identify which patients the evaluating physicians thought had TIA symptoms attributable to their severe carotid stenosis. We used presenting symptoms to distinguish those likely to have definite symptomatic stenoses, defined as symptoms of unilateral weakness and/or numbness contralateral to the side of the severe stenosis. Patients were followed for 90 days after presentation, identifying all strokes, TIAs, deaths and hospitalizations for cardiovascular events from computerized databases and medical records. Follow-up strokes were independently confirmed by two reviewing neurologists, and disagreements were resolved by a third neurologist, all of whom were blinded to whether the patient had severe carotid stenosis or not. We searched for performance of CEA within 6 months post-TIA. Post-op complications, including stroke, TIA, and death, were identified in the 30-day perioperative period after CEA. Any documented reasons for a patient not having surgery were collected, and were retrospectively grouped by a neurologist reviewer (SP) into 6 categories: no severe stenosis by follow up imaging, poor surgical candidate or not a surgical candidate (either due to comorbidities or lesion type), patient or family refusal, non-invasive follow up or medical management recommended, loss to follow-up, or late CEA done (>6 months after index TIA).

Statistical Analysis

Baseline demographics, medical history, type of presentation, average degree of stenosis, and likelihood of follow-up imaging were compared between men and women using chi-squared tests for nominal variables and t-tests for continuous variables. These covariates were then examined for potential Association with CEA in univariate analyses using generalized estimating equations (GEE) to account for clustering by hospital. Multivariable GEE models assessing the Association between gender and CEA were then adjusted for those variables significant at the α=0.20 level in univariate analyses.

In order to test for gender differences in time to CEA after TIA, stratified Kaplan-Meier estimates were calculated, with the log-rank test (Mantel-Haenszel) used to test the null hypothesis of no difference between men and women. Subjects were censored either at 6 months post-TIA, or at death if it occurred during this 6-month period. Cox proportional hazards models were used to evaluate potential predictors of time to CEA.

Rates of post-CEA outcomes, including stroke, TIA, cardiovascular events, or death within 90 days of the procedure were compared between men and women using t-tests. Among those patients who were not treated with CEA, gender differences in demographics, age, clinical presentation, and rates of follow-up stroke or TIA were compared using chi-squared tests for nominal variables and t-tests for continuous variables and proportions.

Results

Of 5,120 patients diagnosed with TIA during the study, 3156 (61.6%) had carotid ultrasound performed within 6 months of index event, and 299 patients were found to have 70-99% extracranial ICA stenosis. Of these, 143 (47.8%) were women. Characteristics of women and men are detailed in Table 1. Women were significantly older with higher systolic blood pressures, and men were more likely to have a history of coronary artery disease, diabetes and smoking.

During follow-up 52 women (36.4%) and 84 men (53.8%) had a CEA (OR 0.85, 95% CI 0.76-0.95, p=0.004), a difference that persisted after adjustment for other variables, including age, past medical history, number of TIAs prior to presentation, $ABCD^2$ score, average degree

of stenosis, unilateral symptoms, and definite symptomatic stenosis (OR 0.89, 95% CI 0.80-1.0, p=0.04). There were no differences in rate of follow up events, including stroke (11.9% vs. 9.0%, p=0.41), TIA (14.1% vs. 18.6%, p=0.30), cardiovascular events (3.5% vs. 3.9%, p=0.87), death (23.8% vs. 20.5%, p=0.50), or any vascular event or death (43.4% vs. 41.7%, p=0.77) within the 90-day follow up period. Only 1 patient (0.3%) had a carotid stent placed within 6 months of their index TIA.

Among those with severe disease but not treated with CEA, there were no significant differences between women and men in demographics, age or clinical presentation. During follow-up, there were similar rates of stroke (13.2% vs 6.9%, p=0.2), cardiovascular events (3.3% vs.2.8%, p=0.85) and death (30.8% vs. 27.8%, p=0.68), but men were more likely to have TIA (19.4% vs. 8.8%, p=0.05). These results were unchanged after adjusting for age. Of those who did not undergo CEA, 51.6% of women and 56.9% of men (p=0.50) had reasons documented for withholding surgical treatment (Table 2). There were no significant differences by gender in the types of reasons documented for withholding surgery (p=0.83).

In the patients with severe ICA disease who did have CEA, women were significantly older than men (74.4±8.3 years vs. 70.5±8.4 years, p=0.008) and were more likely to present with an $ABCD^2$ score ≥4 (92.3% vs. 79.8%, p=0.05). Men who had CEA were more likely to have coronary artery disease than women (39.3% vs. 15.4%, p=0.003). There were no differences in post-operative strokes, TIAs, MIs or death (Table 3). Of those with CEA, 16 women (30.8%) and 38 men (45.2%) had surgery within 2 weeks (p=0.09), and 79% of these surgeries were done during the initial TIA hospitalization. In survival analysis, women had a significantly longer time to CEA, with median time to CEA of 18 days for men and 35 days for women (p=0.03). This remained significant after adjusting for covariates (age, number of TIAs, history of CAD/stroke/CHF/cardiac disease, presentation with unilateral symptoms, $ABCD^2$≥4, definite symptomatic stenosis, and degree of carotid stenosis), by Cox Proportional Hazards Regression (women vs. men, HR 0.54, 0.36-0.83, p=0.004).

About half of both women and men had definite symptomatic carotid stenosis. In other subjects, reported symptoms did not clearly localize the TIA (i.e. confusion, dizziness, speech disturbance, vision loss, gait changes) so it was not possible to confirm that the carotid stenosis was responsible. Among those with definite symptomatic stenosis, 34 women (54.0%) and 52 men (62.7%) were treated with CEA (p=0.29). Time to CEA, however, remained significantly different between men and women with definite symptomatic stenosis, with a mean of 26 days for men, and 53 days for women (p=0.004).

Gender remained an independent predictor of receiving CEA after adjustment for other factors (OR 0.89, 0.80-0.99, p=0.04). Other independent predictors of CEA included age (OR 0.99, 0.99-1.0, p=0.002), number of TIAs at presentation (OR 1.01, 1.00-1.02, p=0.05), definite symptomatic stenosis (OR 1.22, 1.05-1.41, p=0.007) and mean degree of stenosis (OR 1.01, 1.00-1.01, p=0.007). Presentations with unilateral symptoms, presenting $ABCD^2$ score, past medical history of stroke or cardiac disease were not predictive of CEA.

Discussion

We found that women with severe carotid stenosis and TIA are less likely to be treated with CEA than men, independent of other clinical factors. There is little data for comparison, as prior studies mainly focused on cohorts of patients undergoing CEA, not patients with carotid stenosis.

Demographic differences did not explain the large disparity in CEA rates. However, rates were similar amongst men and women who clearly had symptomatic carotid stenosis, and women who did have CEA presented with higher risk TIAs then men. This suggests a higher threshold

for performing CEA on women. Although evidence suggests that earlier treatment leads to better outcome in symptomatic patients, we found that women treated with CEA were treated later than men, specifically in the group who were definitely symptomatic.[8, 14] Among those not treated with CEA, reasons given for withholding surgical treatment were similar. We found no gender differences in perioperative complications, which reflects recent data regarding risk associated with CEA.[10-13, 19, 22, 23]

Retrospective studies have reported more frequent CEA in men than women.[10] Two large population-based registries mirrored these findings, with a 2-fold higher overall rate of CEA in men, regardless of severity of disease or symptoms.[12, 24] In addition, all large randomized trials studying CEA similarly enrolled 2-3 times more men than women.[3-5, 7] This difference persists when studies divide cases into symptomatic or asymptomatic presentation and by degree of stenosis. Higher rates of carotid stenosis in men could explain the difference, but results of studies evaluating burden of carotid disease by gender vary.[25, 26 27, 28] Our study eliminated prevalence as a confounder by enrolling only patients with documented severe carotid stenosis. Half of these consecutively evaluated patients were women, suggesting that a true disparity exists in CEA utilization.

Physicians may be hesitant to offer CEA to women because large randomized trials suggested that women derive less benefit than men, both in symptomatic and asymptomatic carotid stenosis. This difference was, in large part, secondary to a higher risk of perioperative complications,[3-5, 7, 9] The discrepancy in risk and benefit is questionable given a large number of recent studies showing no difference in outcomes.[10, 12, 13, 23, 29] Guidelines suggest CEA by a surgeon with a perioperative morbidity and mortality of <6% for patients with symptomatic severe carotid stenosis, not differentiating by gender In contrast, gender is one of the patient-specific factors, suggested to be considered when deciding whether a patient with symptomatic moderate carotid stenosis should have CEA.[14] Guidelines for primary stroke prevention, however, are more vague, suggesting the use of prophylactic CEA in “highly selected patients” with high-grade stenosis, performed by surgeons with <3% morbidity and mortality rates. Recommendation for patient selection suggests an assessment of comorbidities, life expectancy and other individual factors.[15]

A recently published study from the Registry of the Canadian Stroke Network similarly found that women admitted with TIA or stroke were less likely then men with the same diagnoses to be treated with CEA.[30] They found that this difference no longer persisted after excluding patients with probable contraindications to surgery (nearly 50% of the patients), or when the analysis was restricted to those with documented severe carotid stenosis. Their study only consisted of 13.4% TIA patients, and excluded those discharged from the emergency department. Our study differs, in that all of our subjects presented with TIA, and despite all of them having documented severe carotid stenosis, we did find a gender difference in the use of CEA. We are unable to exclude all subjects with contraindications to surgery, but our inclusion of only TIAs excludes the possibility that any of our subjects would not have surgery due to a disabling stroke, which was included in their definition of “probable contraindications to surgery”. In contrast, 41% of their subjects were classified as having severe stroke, which makes it likely that this was a major portion of those excluded.

Recently, the efficacy and safety of carotid artery stenting (CAS) in comparison with CEA has been of interest in the treatment of carotid stenosis. So far, results are mixed.[31, 32] Recently reported results of CREST, a large trial of CAS versus CEA in both symptomatic and asymptomatic carotid stenosis, suggest no difference in outcomes after 2.5 years of follow up.[31] No significant gender differences in outcome with CAS, or in the outcomes of women undergoing CAS as compared to those undergoing CEA have been found.[13, 31, 33, 34] These results, while mainly subgroup analyses, suggest that CAS may be an option for treating carotid

stenosis in women, though the effectiveness of CAS as compared with CEA remains somewhat unclear. Only one patient in our study underwent CAS, and therefore, we are unable to evaluate this modality.

Other studies of utilization of care in women suggest that they are less confident than men in their decisions, are more likely to worry about risks of interventions and want additional information to guide them in decision making.[11] Women may be less likely to accept CEA when offered, but we were unable to determine if this was the case from our limited dataset.

This study is limited by retrospective data collection, which restricts what information can be obtained. We were unable to definitively distinguish between patients with symptomatic and asymptomatic carotid stenosis, in order to better differentiate in which group a gender disparity exists. It is possible that fewer women had symptomatic stenosis (i.e., their TIA was not localizable to territory of the carotid artery with severe stenosis), and therefore were not offered CEA as often, but our data suggest clear attributable symptoms in similar proportions of men and women. Since documentation of explanations for withholding surgery are not standard in medical records, they were documented in only half of subjects, limiting our ability to interpret reasons for the gender disparity. Finally, we used an ED diagnosis of TIA for subject entry, and some may have initially been inaccurately diagnosed with TIA. ED physicians have a high sensitivity and positive predictive value in diagnosing stroke and TIA[35], and our aim was to reflect current practice in the community setting, in which ED physicians play a large part in the diagnosis of TIA patients.[36]

Women have a higher lifetime risk of stroke and nearly 60,000 more strokes than men each year.[37] In order to reduce stroke burden and improve treatment, gender disparities and their causes must be identified so that practice can be changed when appropriate. Women with severe carotid stenosis are treated less often with CEA in the setting of TIA, but the reasons remain unclear. Future studies should collect more detailed information about the reasons women are not getting CEA, and examine outcomes of women with TIA and carotid stenosis treated with CEA.

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Table 1

Characteristics of Women and Men with TIA and Severe Carotid Stenosis

Variable	Women n=143	Men n=156	p-value
Demographics			
Mean Age (SD)	76.0 (8.8)	73.2 (9.1)	0.007
Caucasian, No. (%)	122 (85.3)	136 (87.2)	0.879
Past Medical History			
Hypertension, No. (%)	103 (72.0)	110 (70.5)	0.772
Atrial Fibrillation, No. (%)	19 (13.3)	20 (12.8)	0.905
Coronary Artery Disease, No. (%)	39 (27.3)	62 (39.7)	0.023
Stroke, No. (%)	39 (27.3)	30 (19.2)	0.099
Transient Ischemic Attack, No. (%)	18 (12.6)	30 (19.2)	0.118
Congestive Heart Failure, No. (%)	16 (11.2)	18 (11.5)	0.924
Peripheral Vascular Disease, No. (%)	14 (9.8)	16 (10.3)	0.879
Diabetes Mellitus, No. (%)	35 (24.5)	65 (41.7)	0.002
Cardiac Disease, No. (%)	23 (16.1)	34 (21.8)	0.209
Hypercholesterolemia, No. (%)	63 (44.1)	82 (52.6)	0.141
Current Cigarette Smoking, No. (%)	28 (19.6)	22 (14.6)	0.253
Past Cigarette Smoking, No. (%)	61 (77.2)	92 (91.1)	0.01
Treatment prior to TIA			
Antiplatelet, No. (%)	69 (48.3)	84 (53.9)	0.334
Oral Anticoagulation, No. (%)	11 (7.8)	15 (9.7)	0.556
Presentation			
Mean creatinine (SD)	1.01 (0.43)	1.32 (0.56)	<0.001
Mean Systolic Blood Pressure (SD)	165.5 (32.9)	155.6 (27.8)	0.005
Mean Diastolic Blood Pressure (SD)	76.7 (15.1)	76.5 (14.1)	0.922
Unilateral symptoms, No. (%)	100 (69.9)	102 (65.4)	0.402
Atypical symptoms, No. (%)	33 (23.1)	34 (21.8)	0.791
Mean Number of TIAs (SD)	1.87 (2.17)	2.21 (6.18)	0.537
Mean $ABCD^2$ score (SD)	4.76 (1.28)	4.68 (1.43)	0.631
$ABCD^2 \geq 4$, No. (%)	122 (85.3)	123 (78.9)	0.146
Definite symptomatic stenosis, No. (%)	63 (44.1)	83 (53.2)	0.114
Imaging and Treatment			
Mean highest degree of stenosis (SD)	80.8 (11.2)	83.2 (11.9)	0.072
Follow up imaging, No. (%)	76 (53.2)	81 (51.9)	0.832
Hospital Admission, No. (%)	44 (30.8)	59 (37.8)	0.2
Carotid Endarterectomy, No. (%)	52 (36.4)	84 (53.8)	0.002

Table 2

Reasons Given for Witholding Surgical Intervention

Reason	Women n=91	Men n=72	p-value
None, No. (%)	44 (48.4)	31 (43.1)	0.501
No severe stenosis on follow-up imaging, No. (%)	21 (23.1)	17 (23.6)	0.936
Poor surgical candidate or Not a surgical candidate, No. (%)	8 (8.8)	9 (12.5)	0.442
Patient or Family Refused, No. (%)	11 (12.1)	7 (9.7)	0.632
Non-invasive follow up or medical management recommended, No. (%)	5 (5.5)	6 (8.3)	0.473
Loss to follow-up, No. (%)	1 (1.1)	2 (2.8)	0.428
CEA done >6 months after TIA, No. (%)	1 (1.1)	0 (0)	0.372

Table 3

Post-operative Complications in Women and Men after CEA

Variable	Women n=52	Men n=84	p-value
Stroke, No. (%)	1 (1.9)	5 (6.0)	0.266
TIA, No. (%)	2 (3.9)	2 (2.4)	0.623
MI, No (%)	2 (3.9)	5 (6.0)	0.589
Death, No. (%)	0 (0)	0 (0)	N/A