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Sex Differences in Carotid Endarterectomy Outcomes Results From the Ontario Carotid Endarterectomy Registry

Moira K. Kapral, MD, MSc, FRCPC; Hua Wang, PhD; Peter C. Austin, PhD; Jiming Fang, PhD; Daryl Kucey, MD, MSc, MPH, FRCSC; Beverley Bowyer, RN; Jack V. Tu, MD, PhD, FRCPC; for the Participants in the Ontario Carotid Endarterectomy Registry

- **Background and Purpose**—The existing literature provides conflicting evidence on surgical risks of carotid endarterectomy in women compared with men. We used data from a large population-based carotid surgery registry to determine whether sex differences exist in the risk of perioperative complications from carotid endarterectomy.
- *Methods*—We analyzed data from the Ontario Carotid Endarterectomy Registry, which contains data on all patients who underwent carotid endarterectomy in the province of Ontario between 1994 and 1997. We compared the risk of death or stroke at 30 days in women and men and used multivariate analyses to adjust for age, comorbid conditions, and surgical factors. Secondary analyses compared the risks of death and/or stroke in women and men at 2 years after surgery.
- *Results*—The study sample consisted of 6038 patients (35% women). The risks of perioperative stroke or death were not significantly different in women compared with men (adjusted hazard ratio, 1.10; 95% CI, 0.90 to 1.35). The combined risk of stroke or death at 2 years after surgery was also similar in women and men (adjusted hazard ratio, 1.05; 95% CI, 0.92 to 1.21). However, women were more likely to have a stroke (adjusted hazard ratio, 1.26; 95% CI, 1.05 to 1.51) and less likely to die (adjusted hazard ratio, 0.82; 95% CI, 0.68 to 0.99) within 2 years after surgery.
- *Conclusions*—Perioperative complication rates from carotid endarterectomy are similar in women and men. Women should not be discouraged from carotid endarterectomy solely on the basis of surgical risks. (*Stroke*. 2003;34:1124-1125.)

Key Words: carotid endarterectomy ■ perioperative complications ■ sex ■ stroke

Carotid endarterectomy can prevent strokes in individuals who have moderate to severe symptomatic carotid stenosis.^{1–3} Like any major surgical procedure, however, endarterectomy can cause serious perioperative complications. The overall effectiveness of carotid surgery is a balance between the short-term perioperative risks and long-term benefits. It has been postulated that women may be at an increased risk of surgical complications from carotid endarterectomy and that risk this could negate the overall benefit of the procedure in women, especially in subgroups at lower risk of stroke with medical therapy.^{4–6}

The existing literature provides conflicting evidence on the risks of carotid surgery in women compared with men. Some studies suggest higher perioperative complication rates in women,^{4–10} but others have found no difference in surgical risks for women and men.^{3,11–24} Many of the previous studies were limited by either a lack of adjustment for other impor-

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tant prognostic factors or a relatively small sample size, leaving them underpowered to detect important differences. Other studies included only patients participating in clinical trials, thus limiting their generalizability to the typical endarterectomy population; used administrative data with little clinical information and the potential for undercoding of complications and comorbidity; or did not include outcomes occurring after hospital discharge.

We undertook a study to further evaluate sex differences in perioperative complications from carotid endarterectomy. We used data from the Ontario Carotid Endarterectomy Registry, which is a population-based registry of endarterectomies performed in the province of Ontario, Canada. We compared the risks of perioperative stroke and death in women and men,

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From the Institute for Clinical Evaluative Sciences (M.K.K., H.W., J.F., P.C.A., D.S.K, J.V.T.); Division of General Internal Medicine and Clinical Epidemiology and Women's Health Program, University Health Network (M.K.K); Clinical Epidemiology and Health Care Research Program and Division of General Internal Medicine, Sunnybrook and Women's College Health Sciences Centre (J.V.T.); Department of Medicine, University of Toronto (M.K.K., D.K., J.V.T.); Division of Vascular Surgery, Sunnybrook and Women's College Health Sciences Centre, University of Toronto (D.S.K.); and Department of Public Health Sciences, University of Toronto (M.K.K., P.C.A., D.K., J.V.T.), Toronto, Ontario, Canada.

Participating hospitals and surgeons in the Ontario Carotid Endarterectomy Registry are listed in the Appendix, which can be found online at http://stroke.ahajournals.org.

Reprint requests to Dr Moira K. Kapral, Toronto General Hospital, 200 Elizabeth St, ENG-246, Toronto, Ontario, Canada M5G 2C4. E-mail moira.kapral@uhn.on.ca

TABLE 1.	Baseline Char	acteristics of	f Patients	in the	Ontario
Carotid En	darterectomy F	Registry			

	Men	Women	
n (%)	3942 (65)	2096 (35)	*
Mean age, y	68	68	
Income quintile,† %			
1 (low)	22	22	
2	24	24	
3	22	21	
4	18	18	
5 (high)	14	15	
Symptomatic before surgery, %	70	69	
Carotid stenosis (ipsilateral), %			
Mild	2	1	
Moderate	10	9	
Severe or occlusion	85	86	
Unavailable	4	4	
Contralateral occlusion	10	6	*
Hypertension, %	61	71	*
Diabetes mellitus, %	23	23	
Hyperlipidemia, %	35	37	
Smoking (ever), %	76	63	*
Atrial fibrillation, %	6	4	
Coronary artery disease, %	37	33	*
Peripheral vascular disease, %	28	25	*
Charlson comorbidity index score $<\!\!1,\%$	55	59	*

*P<0.05.

†Income quintile corresponds to the median personal income of residents in each of 493 Forward Sortation Areas in Ontario on the basis of 1996 Canada Census data.

with adjustment for age and other prognostic factors. In addition, through linkages with administrative data from the Canadian Institute for Health Information (CIHI) hospital discharge database and the Ontario Registered Persons Database, we compared 30-day and 2-year rates of death or stroke in women and men.

Methods

Data Sources

The Ontario Carotid Endarterectomy Registry includes data on all patients who underwent isolated carotid endarterectomy in the province of Ontario, Canada, between January 1, 1994, and December 31, 1997. A total of 6116 patients were identified from the CIHI hospital discharge database through the use of the Canadian Classification of Procedure code 50.12. By law in Ontario, all separations (discharges, transfers, deaths) from acute care hospitals are included in the CIHI database. Patients who underwent coronary artery bypass grafting on the same admission or who had a length of stay >365days were excluded, leaving 6,038 patients in the registry. Chart reviews and data abstraction were performed by 2 experienced neurology research nurses. The registry database contains detailed clinical data, including patient sociodemographics and comorbidity, symptom status, degree of carotid stenosis, type of surgery and anesthesia, and in-hospital surgical complications. Variable definitions (eg, symptom status) were similar to those used in the North American Symptomatic Carotid Endarterectomy Trial.1

TABLE 2. Hospital and Surgical Variables in Men and Women in the Ontario Carotid Endarterectomy Registry

	Men, %	Women, %	
Hospital volume high (\geq 25/y)	91	91	
Teaching hospital	62	61	
Surgeon			
Neurosurgeon	45	42	*
Vascular surgeon	52	54	
Cardiovascular surgeon	3	4	
Surgeon volume high (\geq 12/y)	82	81	
General anesthesia	91	91	
Patch	16	19	*
Shunt	29	29	
Emergency/urgent surgery	7	5	*
Surgery on left carotid artery	50	52	
Participating in NASCET	2	1	
Participating in ACE	8	6	*

NASCET indicates North American Symptomatic Carotid Endarterectomy Trial; ACE, Aspirin and Carotid Endarterectomy Trial.

*P<0.05.

Through record linkage, the CIHI database also provided data on readmissions for stroke within 30 days and 2 years of surgery. Validation studies of the CIHI database have established an accuracy rate of 90% for the diagnosis of stroke based on *International Classification of Diseases*, ninth revision, codes 431, 434, and 436.²⁵ Data on 30-day and 2-year mortality, regardless of place of death, were obtained from the Ontario Registered Persons Database.

Statistical Analysis

The primary outcome measure was the combined risk of death or stroke within 30 days of surgery in women compared with men, with secondary outcomes of death alone, stroke alone, length of stay, and discharge destination, as well as death or stroke at 2 years. Descriptive statistics were conducted to provide information on characteristics of patients, hospitals, and surgeons, as well as crude outcomes for women and men. Cox proportional-hazards models were developed to determine the relationship of sex to stroke and death over the 30-day postoperative period and the 2-year follow-up period through the use of a competing risks analysis and with adjustment for age, comorbid conditions, symptom status, and surgical, hospital, and physician characteristics. Variables were selected on the basis of backward stepwise regression and comparison of the $-2 \log$ likelihoods of the Cox proportional-hazards model. A value of P < 0.05was considered statistically significant in the analyses. However, patient sex was forced into the multivariate models regardless of statistical significance. SAS (version 8.02) was used for all data analyses.

Results

During the study time frame, a total of 6038 patients (35% women) underwent carotid endarterectomy. Men and women had the same average age, 68 years, at the time of surgery. Baseline characteristics of men and women were similar, except that women were less likely to have a history of coronary artery or peripheral vascular disease and more likely to have a history of hypertension (Table 1). Overall, comorbid illness was slightly less common in women than in men, as reflected by a Charlson comorbidity index score of 0 (59% of women versus 55% of men, P=0.0142). There were no significant sex differences in symptom status before surgery,

 TABLE 3.
 Outcomes After Carotid Endarterectomy in Women and Men

	Men (n=3942), n (%)	Women (n=2096), n (%)	Adjusted Hazard Ratio (95% Cl)*
Death or stroke within 30 d	231 (5.9)	130 (6.2)	1.10
			(0.90–1.35)
Death within 30 d	69 (1.8)	25 (1.2)	0.74
			(0.46–1.17)
Nonfatal stroke within 30 d	167 (4.2)	105 (5.0)	1.21
			(0.97–1.50)
Death or stroke within 2 y	604 (15.3)	315 (15.0)	1.05
			(0.92–1.21)
Death within 2 y	383 (9.7)	165 (7.9)†	0.82†
			(0.68–0.99)
Stroke within 2 y	311 (8.5)	195 (9.9)	1.26†
			(1.05–1.51)

*Adjusted for age, comorbid illness, contralateral carotid artery occlusion, previous stroke or transient ischemic attack, and surgeon type.

†P<0.05 for male/female comparison.

degree of carotid stenosis, hospital type, anesthesia, or side of surgery (Table 2).

The risks of perioperative stroke or death were not significantly different in women compared with men (6.2% versus 5.9%, P=0.28), even after adjustment for age, comorbidity, and surgical variables (adjusted hazard ratio, 1.10; 95% CI, 0.90 to 1.35; P=0.53) (Table 3). The risk of perioperative stroke or death was 7.3% in patients with previous stroke or transient ischemic attack, 3.9% in those with a history of amaurosis fugax, and 4.7% in asymptomatic patients. There were no significant sex differences in the combined outcome of death or stroke at 2 years after surgery (adjusted hazard ratio, 1.05; 95% CI, 0.92 to 1.21) (Table 3 and the Figure). However, within 2 years of surgery, the risk of death alone was lower in women than in men (7.9% versus 9.7%; P < 0.05; adjusted hazard ratio, 0.82; 95% CI, 0.68 to 0.99), whereas the risk of stroke alone was higher in women (9.9% versus 8.5%; adjusted hazard ratio, 1.26; 95% CI, 1.05 to 1.51).



Adjusted 2-year stroke-free survival curves for men and women. Difference between survival curves is not significant.

Discussion

We found no significant sex differences in the risks of perioperative stroke or death and no significant difference in the combined outcome of stroke or death at 2 years. However, women were more likely to experience recurrent stroke and were less likely to die in the 2 years after surgery. These data represent the largest published population-based series of consecutive patients undergoing carotid surgery in a "realworld" setting and are strengthened by the linkages to administrative data that allow the determination of postdischarge stroke and death risks.

These findings are consistent with several previous studies that have failed to find any sex gradient in the perioperative risks of carotid surgery and contribute to a growing body of literature suggesting that carotid endarterectomy is equally safe in women and men.^{12–21,23,24,26} However, other studies, including some of the major randomized trials of carotid endarterectomy, have documented higher perioperative complication rates in women, reminiscent of those seen in women undergoing coronary artery bypass surgery.^{4–10} In particular, women in the European Carotid Surgery Trial and the Asymptomatic Carotid Surgery Trial appeared to have higher risks of perioperative complications, whereas those in the moderate (50% to 69%) stenosis arm of the North American Symptomatic Carotid Endarterectomy Trial did not appear to benefit from surgery.²⁻⁴ Selection criteria for these randomized controlled trials may explain the discrepant findings.

Potential explanations for higher surgical risks in women include the older age of onset of cerebrovascular disease in women, when comorbid illness can increase operative complication rates.²⁷ In addition, as has been seen in the setting of coronary artery disease, women may have smaller blood vessels that can present technical obstacles to successful surgery.²⁸ Although we cannot comment on the relative size of carotid arteries in women and men in our registry, age and comorbidity were not significantly increased in women compared with men; indeed, women tended to have less comorbid illness than men. In addition, there were no significant sex differences in other potential prognostic variables such as degree of carotid stenosis or symptom status before surgery.

Our finding of higher long-term stroke rates in women treated with carotid endarterectomy has not been documented consistently in the existing literature, with several previous studies finding no sex differences in long-term postoperative stroke rates.^{20,24,29,30} However, a small study found an increased risk of ipsilateral stroke at 34 months in women compared with men,26 and other studies have documented higher rates of operative site thrombosis and asymptomatic late restenosis in women, again raising the possibility that sex differences in the size or anatomy of carotid vessels may influence surgical outcomes.^{21–23} Alternatively, higher late stroke admission rates in women might be unrelated to the carotid surgery and instead may be explained by factors such a higher risk of hypertensive lacunar stroke or variations in stroke admission thresholds for women and men. Our administrative data do not contain sufficient clinical detail to evaluate these hypotheses. Higher long-term postoperative stroke rates in women would be a concern if they negated the overall benefit of carotid endarterectomy, and we were unable to address this issue given the lack of a medical control arm in our study. However, it is reassuring that the clinical trials of carotid endarterectomy confirm the superiority of surgical over medical therapy for both women and men with severe carotid artery stenosis.^{3,31,32}

Some study limitations merit comment. Because we do not have a comparison group of medically treated patients with carotid stenosis, we cannot compare the overall effectiveness of carotid surgery with medical therapy in women and men. In addition, we cannot comment on sex differences in access to surgery. Other studies have raised the possibility of underuse of carotid endarterectomy in women, given the low rates of surgery in women relative to men.^{33,34} The low proportion of women (\approx 30%) undergoing carotid surgery is a consistent finding across many studies and may or may not reflect the underlying prevalence of carotid stenosis in women and men.^{34–39} Our finding that women and men had the same average age at the time of surgery, despite the older age of onset of cerebrovascular disease in women, could reflect decreased use of carotid endarterectomy in older women.

It is notable that the perioperative stroke or death rates observed in this study (7.3% and 4.7% for symptomatic and asymptomatic patients, respectively) are higher than those recommended from the results of clinical trials.⁴⁰ During the registry time frame, 9% of procedures were performed at low-volume institutions, and 18% were done by low-volume surgeons. Although our study does not evaluate the effect of hospital and surgeon volume on endarterectomy outcomes, this might in theory have led to higher-than-expected complication rates. These findings illustrate the challenges that exist in applying the results of clinical trials to typical clinical settings.

The selection of patients for carotid endarterectomy will always involve careful consideration of the risks and benefits for each individual patient, including not only sex-specific perioperative complication rates but also surgeon- and institutionspecific complication rates, as well as the expected stroke risks without surgery. Our results from a large, representative database provide strong evidence that sex is not a significant determinant of perioperative complication rates. Accordingly, women should not be discouraged from carotid endarterectomy solely on the basis of the surgical risks.

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Editorial Comment

Female Sex: A Questionable Risk Factor for Carotid Endarterectomy

The misconception that clinical manifestations of cardiovascular disease are a much more significant problem among male patients is hard to eliminate, supported by the higher incidence of cardiac, cerebrovascular, and peripheral arterial diseases in men than in women.¹

Our understanding of cerebrovascular disease in women is hampered by a paucity of studies including an adequate number of female patients. Most studies are heavily biased toward the male sex. The efficacy of aspirin in primary and secondary stroke prevention trials has been demonstrated almost exclusively in men.² Men were also the majority of the population recruited in the major clinical trials on symptomatic (North American Symptomatic Carotid Endarterectomy Trial [NASCET] and European Carotid Surgery Trial [ECST])^{3,4} and asymptomatic (Asymptomatic Carotid Atherosclerosis Study [ACAS]) carotid stenoses,⁵ and no women were enrolled in the Veteran Administration trials.6,7 Unfortunately, neither the original report from the NASCET nor the one from ECST analyzed data specifically by sex. Although the superiority of carotid endarterectomy (CEA) over the best medical management in protecting against stroke for selected symptomatic and asymptomatic patients with carotid lesions was well demonstrated,^{3–7} post-hoc analyses,^{8,9} along with several reviews and large single-center studies, have prompted a reevaluation of the role of CEA in women.^{10–14}

The NASCET results did not distinguish, however, between men and women with regard to perioperative risk in patients with severe stenosis,³ and they showed no apparent benefit from CEA in women with moderate stenosis.⁸ Furthermore ACAS investigators found a slightly higher, albeit statistically insignificant, perioperative stroke and/or death rate in women (3.6% versus 1.7%), that probably meant an estimated 5-year relative risk reduction for ipsilateral stroke of just 17% in women compared with 66% in men.⁵ On the other hand, several other studies specifically focusing on sex-related differences in perioperative stroke and death rates failed to find any such differences in the perioperative risks of CEA, suggesting that CEA is equally safe in men and women.^{15–21}

In the accompanying article, Kapral et al analyze the findings on sex-related differences in perioperative outcome emerging from an impressive population-based series of 6038 consecutive patients undergoing CEA in a real-world setting over a 4-year period, ie, more than 4 and 3 times the number of patients enrolled in the surgical arm of NASCET and ECST, respectively, and nearly 4 times the entire population of the ACAS.3-5 Women accounted for more than one third of the whole surgically treated population of the NASCET.³ The baseline characteristics of men and women were similar, except that the women were less likely to have a history of coronary artery or peripheral vascular disease and more likely to have a history of hypertension; there were no significant sex differences in the preoperative symptom status, degree of carotid stenosis, need for shunting, or type of anesthesia. Sex did not affect the risk of perioperative stroke or death in symptomatic and asymptomatic patients. In addition, women were more likely to have a stroke and less likely to die within 2 years of CEA.

This study is interesting for several reasons. First, given that the role of CEA in the management of women with symptomatic, and especially asymptomatic, carotid stenoses remains debatable, any additional information on this issue is welcome. This is particularly relevant at a time when some are advocating carotid angioplasty and stenting as a less invasive and potentially less risky treatment of carotid disease in symptomatic and asymptomatic patients.

Second, women had a slightly higher incidence, albeit statistically insignificant, of adverse events (6.2% versus 5.9%), confirming a trend observed in large randomized trials and real-world clinical experience, possibly due to the sample

of women being smaller than that of the men (2096, 35% versus 3942, 65%). The reported overall crude perioperative complication rates (7.3% and 4.7% for symptomatic and asymptomatic patients, respectively) also exceeded the recommended upper limits for perioperative risk and mortality rates supporting the beneficial effects of CEA in symptomatic and asymptomatic patients.²² This potential drawback of the study could be explained by the fact that 9% of the CEAs were performed at low-volume (albeit teaching) institutions and 18% by low-volume surgeons, leading to higher-thanexpected complication rates and revealing the challenge in translating the efficacy demonstrated in clinical trials (CEA performed in an ideal scenario of selected patients and selected surgeons) into typical clinical setting effectiveness. However, it would be interesting to know the incidence of perioperative stroke and death relating to urgent CEA procedures and the frequency of perioperative thrombosis of the endarterectomized vessel, all matters relating to the surgeon's expertise rather than to the patient's baseline characteristics.

Third, patch closure of the internal carotid artery was statistically more frequent among women. This is important, especially if we consider that in the ACAS only a few women were patched selectively, and results such as those reported in the ACAS have clearly affected medical practice. However, because the data were reviewed retrospectively and the decision to use a patch was subjective, and because the study was not designed specifically to address the association between the type of arteriotomy closure and perioperative neurologic morbidity, we can only speculate as to the reasons behind this and the implications in the comparison of outcome between the two sexes.

Finally, the intriguing finding of a higher incidence of late stroke in women is unexplained. Because no information is available in the study regarding the characteristics of late stroke (ie, ischemic or hemorrhagic, fatal or nonfatal, cardioembolic or lacunar, ipsilateral or contralateral to the operated side) and given the higher incidence of lacunar strokes in the female population in general²³ and the higher incidence of hypertension in the women in the study, one might expect to find a higher incidence of lacunar cerebral infarctions in this group. Lacunae are caused by an intrinsic disease of the single perforating branch artery that supplies the infarct (either lipohyalinosis or atheromatous branch disease), however, so they are unrelated to the surgical procedure. Moreover, lacunar strokes have a relatively good prognosis, and this could account for the lower late mortality rate in women than in men.

The results from this study strongly support the hypothesis that female sex is not a risk factor for perioperative stroke and death after CEA. I am also convinced that the outcome of CEA is affected exclusively by the surgeon and his technique, which demands a meticulous performance, expert intraoperative judgment, optimal anesthesiologic management, and appropriate patient selection.

Enzo Ballotta, MD, Guest Editor Section of Vascular Surgery Department of Medical and Surgical Sciences University of Padua School of Medicine Padua, Italy

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