Lower Rates of Intervention for Symptomatic Carotid Stenosis in Women Than in Men Reflect Differences in Disease Incidence
A Population-Based Study

Lars Marquardt, MD; Jack F. Fairhead, MRCS; Peter M. Rothwell, PhD

**Background and Purpose**—Although there is little sex difference in the age-specific incidence of transient ischemic attack (TIA) and stroke, substantially more men than women undergo endarterectomy/stenting for symptomatic carotid stenosis. Sexism in referral for investigation or intervention has been proposed as an explanation; however, a lower incidence of carotid disease in women or reluctance to undergo intervention might also be responsible.

**Methods**—We determined the sex-specific incidence of symptomatic carotid stenosis and subsequent endarterectomy/stenting from 2002 to 2009 in consecutive patients with TIA or nondisabling ischemic stroke in the Oxford Vascular Study. We studied equivalent data from routine clinical practices in the wider Oxfordshire population.

**Results**—There was no sex difference in age-specific referral rates for carotid imaging in the Oxford Vascular Study (n=616; age-adjusted relative rate [RR] for males vs females=1.08; 95% CI, 0.79 to 1.46; P=0.64). However, rates of 50% to 99% symptomatic carotid stenosis were higher in men (RR=1.89; 95% CI, 1.31 to 2.71; P=0.0005). The same was seen in imaged patients (n=575) in the wider Oxfordshire population (RR=1.82; 95% CI, 1.31 to 2.53; P=0.003) and in pooled data (RR=1.87; 95% CI, 1.32 to 2.64; P=0.0003). Rates of symptomatic carotid occlusion were also higher in men in both populations (RR=3.19; 95% CI, 1.95 to 5.23; P<0.0001). Consequently, although men were more likely to undergo carotid intervention (RR=1.98; 95% CI, 1.43 to 2.75; P<0.0001), the proportion of patients with 50% to 99% symptomatic carotid stenosis who received intervention was similar for men and women (odds ratio=1.13; 95% CI, 0.57 to 2.25; P=0.72).

**Conclusion**—Lower rates of intervention for 50% to 99% symptomatic carotid stenosis in women can be explained by sex differences in population-based incidence. We found no evidence of any investigation or intervention bias. (Stroke. 2010;41:16-20.)

**Key Words:** stroke ■ carotid stenosis ■ TIA ■ carotid endarterectomy ■ epidemiology

On average, women benefit less from carotid endarterectomy for symptomatic stenosis than men,1 partly because of a marginally higher operative risk of stroke and/or death and a lower risk of stroke with medical treatment alone.2 However, women do still benefit from endarterectomy for 70% to 99% stenosis1 and may actually benefit more than men if surgery is performed soon after the presenting event.3 However, although the incidence of ischemic stroke and transient ischemic attack (TIA) is only slightly higher in men than in women,4,5 data from clinical trials and routine practice consistently show that substantially fewer carotid endarterectomies for symptomatic stenosis are performed in women than in men.1,6-10 Although there is some evidence of underinvestigation of women with stroke8-10 and with coronary events,11,12 it remains uncertain to what extent any such bias accounts for the sex difference in carotid endarterectomy rates or whether the differences in incidence of symptomatic carotid disease or a reluctance among women to undergo investigation or invasive treatment also contribute. Population-based studies have shown a lower prevalence of asymptomatic carotid stenosis in women than in men11,14 and lower rates of symptomatic occlusion,15 but there are no published studies of the prevalence of symptomatic stenosis. In the absence of any previous similar studies, we performed 2 population-based studies of the investigation, incidence, and treatment of symptomatic carotid stenosis and sought to establish whether lower rates of endarterectomy for symptomatic stenosis in women were due to underinvestigation, a lower incidence of operable stenosis, or underreferral for surgery.

**Subjects and Methods**

We determined age- and sex-specific rates of referral for carotid imaging and incidence of symptomatic 50% to 99% carotid stenosis, acute symptomatic occlusion, and carotid endarterectomy in the Oxford Vascular Study (OXVASC) population (midstudy esti-
mate=91 105), which comprises all individuals registered with 9 primary care practices within Oxfordshire. We used data from the first 7 years of the study (April 1, 2002, to March 31, 2009). OXVASC methods have been published elsewhere.14,16,17 In brief, multiple overlapping methods of “hot” pursuit were used to achieve near-complete ascertainment of all individuals with TIA or stroke. These included a daily, urgent open-access neurovascular clinic; daily assessment of admissions to the medical, stroke, neurology, and other relevant wards; and daily searches of the local A&E (emergency room) attendance register. To not miss patients who presented late, were referred to other services, or were traveling, we also performed monthly computerized searches of family doctor diagnostic coding, hospital discharge codes, and all cranial and carotid imaging studies performed in local hospitals. Case ascertainment has been shown to be nearly complete for both TIA and stroke,17 and 99% of patients and/or relatives consented to being interviewed and examined. Patients were followed up face to face at 30 days, 6 months, 1 year, 2 years, and 5 years by a study nurse or physician.

Carotid ultrasonography was performed by an experienced vascular technician using an ATL Ultramark HDI 5000 scanner. A few patients underwent contrast-enhanced magnetic resonance angiography (Philips Achieva 1.5-T scanner with a neurovascular coil) instead of carotid ultrasonography. Stenosis was classified by the NASCET method of measurement of carotid stenosis.18

We also studied age- and sex-specific incidences of symptomatic 50% to 99% carotid stenosis, occlusion, and endarterectomy in routine clinical practice in the wider Oxfordshire population (non-OXVASC Oxfordshire Primary Care Trusts [NOPCT]; n=589 900) for 1 year (April 1, 2002, to March 31, 2003). The NOPCT population comprised all individuals registered with the remaining 78 primary care practices making up the Oxfordshire Primary Care Trusts. Virtually all individuals in the UK are registered with a primary care practice, and general practice–registered populations are very similar to actual populations.

In the NOPCT population, we identified all patients who underwent carotid imaging during the study period for a new ischemic cerebral or retinal event by screening all referrals for carotid ultrasonography, magnetic resonance angiography, computed tomography angiography, and conventional angiography in the 4 relevant centers in Oxfordshire. We also contacted centers in surrounding counties to ascertain cases imaged out of the NOPCT region. Reports, referral forms, and attendance records at each imaging center were searched and the following data were collected: age, sex, general practice, reason for referral, vascular territory, source of referral, and dates and results of carotid imaging. All patients in whom it was clear from the referral form that the reason for carotid imaging was not an ischemic cerebral or retinal event (eg, screening before coronary artery bypass surgery, follow-up after endarterectomy, etc) or when the indication for carotid imaging was unclear were excluded.

To test the completeness of the NOPCT search strategy, the same strategy was also used to identify patients who had undergone carotid imaging in the OXVASC population during the same time period, for which data on all carotid imaging had also been collected prospectively and separately.

Analysis
Analysis was restricted to patients undergoing carotid imaging for the first time during each study period and to patients with a carotid territory TIA or ischemic stroke during the 6 months before imaging. In OXVASC, the analysis was further restricted to patients with a carotid territory TIA or ischemic stroke during the 6 months before imaging. In OXVASC, only 575 patients (296 male, 279 female) underwent carotid imaging. Reasons for nonimaging were nonattendance (n=31), another event or death before the investigation (n=7), no request for imaging (n=3), and uncertain (n=5).

Case ascertainment for the NOPCT population has been reported previously.20 In brief, 575 patients (296 male, 279 female) underwent carotid imaging after a definite carotid territory TIA or stroke. Likely completeness of ascertainment of imaged patients by the retrospective search strategy used in the NOPCT population was assessed by comparison of the same process with the prospectively collected data in the OXVASC population. Only 9 (1.2%) OXVASC patients were not identified by the retrospective search strategy, suggesting that case ascertainment in NOPCT was high. No patients were identified by retrospective methods but not by the OXVASC methods.

In the OXVASC population, there was no sex difference in population rates of carotid imaging for symptomatic carotid stenosis (age-adjusted relative rate [RR] for males vs females=1.08; 95% CI, 0.79 to 1.46; P=0.64; Figure 1a). There was also no significant sex difference in the crude proportions of patients with recent carotid territory TIA or

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Results
The age/sex profiles of the 2 study populations are reported in the Table. During the 7 years of case ascertainment in OXVASC, 662 patients (323 male, 339 female) had a carotid territory TIA or nondisabling stroke (National Institutes of Health Stroke Scale score ≤5), of whom 616 (93%; 289 male, 327 female) underwent carotid imaging. Reasons for nonimaging were nonattendance (n=31), another event or death before the investigation (n=7), no request for imaging (n=3), and uncertain (n=5).
nondisabling stroke who were imaged (89% male, 96% female), irrespective of age (Figure 1b). However, the incidence of 50% to 99% recently symptomatic stenosis was higher in men: RR = 1.89 (95% CI, 1.31 to 2.71; \(P = 0.0005\)). The same excess incidence of 50% to 99% recently symptomatic carotid stenosis in men was also present in the NOPCT population (RR = 1.82; 95% CI, 1.31 to 2.53; \(P = 0.003\)) and in the pooled analysis of both cohorts (RR = 1.87; 95% CI, 1.32 to 2.64; \(P = 0.003\)). In a pooled analysis stratified by severity of stenosis, the higher incidence in men was nonsignificant for 50% to 69% stenosis (RR = 1.47; 95% CI, 0.85 to 2.55; \(P = 0.17\); Figure 2a) but was marked for 70% to 99% stenosis (RR = 2.44; 95% CI, 1.51 to 3.93; \(P = 0.0002\); Figure 2b). There was also a higher incidence of acute symptomatic carotid occlusion in men (pooled RR = 3.19; 95% CI, 1.95 to 5.23; \(P < 0.0001\); Figure 2c).

Figure 3 shows the distribution of symptomatic carotid stenosis in 10% bands in men and women. Stenoses tended to be more severe in men (ranking test, \(P < 0.0001\)), with a clear female excess at stenosis <40% and a clear male excess at stenosis ≥70%.

The proportions of patients with 50% to 69% symptomatic carotid stenosis who received carotid endarterectomy or stenting were 16% for OXVASC and 25% for NOPCT. The respective proportions for 70% to 99% stenosis were 89% and 91%. There were no differences in these rates by sex in either population separately or in the pooled analysis. The pooled age-adjusted odds ratio for intervention in men versus women with 50% to 99% symptomatic carotid stenosis was 1.13 (95% CI, 0.57 to 2.25; \(P = 0.72\)). However, given the higher incidence of symptomatic stenosis in men, the rates of carotid endarterectomy per 1000 population for 50% to 99% carotid stenosis were higher in men: OXVASC RR = 2.40 (95% CI, 1.77 to 3.25; \(P < 0.0001\)); NOPCT RR = 1.64 (95% CI, 1.02 to 2.63; \(P = 0.039\)); and pooled analysis RR = 1.98 (95% CI, 1.43 to 2.75; \(P < 0.0001\); Figure 4).

**Discussion**

The prevalence of asymptomatic carotid stenosis is greater in men than in women,\(^{21,13}\) but there have been no population-based studies of age- and sex-specific incidences of symptomatic stenosis. Consequently, it has not been possible to interpret the widespread observation that substantially more...
interventions are performed for symptomatic carotid stenosis in men than in women. In the first-ever population-based study of sex differences in rates of carotid imaging, incidence of symptomatic stenosis, and rates of intervention in patients with recent TIA or stroke, we found no evidence of any systematic underinvestigation or undertreatment of carotid disease in women. However, we did find clear evidence of a lower incidence of 50% to 99% symptomatic carotid stenosis in women than in men, which appeared to account completely for the sex difference in rates of intervention in our study populations.

Women accounted for 41% (95% CI, 31.3 to 51.7) of patients with 50% to 99% symptomatic carotid stenosis in our pooled population, which is not significantly different from the proportion in studies of patients undergoing endarterectomy for symptomatic carotid stenosis in routine clinical practice (36.2% women; 95% CI, 35.6 to 36.7).2 However, the proportion of women with 50% to 99% stenosis in the major trials of carotid endarterectomy for symptomatic carotid stenosis was slightly lower (30.6%; 95% CI, 28.9 to 32.3),1 perhaps because of the greater disinclination of women than men to agree to be randomized in clinical trials22 or because of the tendency of trials to recruit younger patients, at which stage the sex difference in incidence of symptomatic carotid disease is particularly marked.

The sex difference in incidence of symptomatic carotid disease in our populations is consistent with observations on the prevalence of asymptomatic carotid stenosis and with sex differences in the incidence of acute vascular events attributable to large-artery atherosclerosis in the coronary and peripheral vascular territories.4 A recent autopsy study of stroke patients also showed that the prevalence of proximal extracranial carotid stenosis was higher in men than in women (23.6% vs 14.9%, \( P = 0.038 \)).23 The population-based Northern Manhattan Stroke Study found that the prevalence of asymptomatic nonstenosing carotid artery atherosclerosis was similar in men and women in a multiethnic population.24,25 One small retrospective study of patients referred to a vascular laboratory for carotid imaging after TIA or stroke reported similar incidence rates for 50% to 99% symptomatic carotid stenosis in men and women, but no data were available on sex-specific rates of carotid TIA and stroke in the underlying population or in the proportion of men versus women referred for imaging.26 We found that the sex difference in incidence of symptomatic carotid disease increased with the severity of disease, ranging from little difference at 50% to 69% stenosis to a >3-fold male excess of symptomatic carotid occlusion.

Although we believe that the results of our study are reliable, there are a number of methodologic issues that merit discussion. First, the recruitment periods in our 2 populations were not completely congruent. However, where direct comparison was possible, the findings in the 2 populations were remarkably similar. Second, our study was based on UK populations only. It is possible that incidence rates of symptomatic carotid stenosis might differ in other countries or regions and that rates of intervention may not be exactly comparable. Third, we did not have data on the number of patients presenting to medical attention with carotid territory TIA or ischemic stroke in the NOPCT population and hence, on the proportion of patients imaged. However, we did have these data in the OXVASC population, and there was no sex
difference in imaging rates. The fact that the measured incidence of 50% to 99% symptomatic carotid stenosis in patients age <75 years was the same in OXVASC and NOPCT27 and that we found the same sex difference in both studies suggest that any major investigation bias in NOPCT was unlikely. Fourth, we did not perform statistical power calculation before the study started. However, to compensate for relatively small numbers of endarterectomies in certain age groups, we performed age-group and population-adjusted pooled analyses. We therefore believe that our results are reliable and without any substantial bias due to small numbers. Finally, it is theoretically possible that there is a sex difference in the quantification of severity of stenosis by carotid ultrasound, with some systematic underestimation of severity in women. The absolute size of the carotid arteries is smaller in women, and there are also sex differences in the relative sizes of the internal and external carotid arteries at the bifurcation.28,29 However, we think that any such quantification bias is unlikely to account for the nearly 2-fold excess of 70% to 99% stenosis in men and that the validity of this sex difference is supported by the 3-fold excess of symptomatic carotid occlusion in men.

In conclusion, the widespread finding of lower rates of intervention for 50% to 99% symptomatic carotid stenosis in women in routine clinical practice can be explained by sex differences in incidence. We found no evidence of any investigation or intervention bias.

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Disclosures

None.

References

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