

**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.)**

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

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On average, women benefit less from carotid endarterectomy for symptomatic stenosis than men, partly because of a marginally higher operative risk of stroke and/or death and a lower risk of stroke with medical treatment alone. However, women do still benefit from endarterectomy for 70% to 99% stenosis and may actually benefit more than men if surgery is performed soon after the presenting event. However, although the incidence of ischemic stroke and transient ischemic attack (TIA) is only slightly higher in men than in women, data from clinical trials and routine practice consistently show that substantially fewer carotid endarterectomies for symptomatic stenoses are performed in women than in men. Although there is some evidence of underinvestigation of women with stroke and with coronary events, 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 men and lower rates of symptomatic occlusion, 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.4,16,17 In brief, 
multiple overlapping methods of “hot” pursuit were used to achieve 
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,4,7 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 vascu-
tician using an ATL Ultramark HDI 5000 scanner. A few 
patients underwent contrast-enhanced magnetic resonance angiogra-
phy (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% 
Ito 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 under-
went 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 to-
gramy 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 prospec-
tively 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 
National Institutes of Health Stroke Scale score ≤5 (nondisabling stroke) 
at the time of first assessment to identify cases in whom 
investigation and intervention would definitely be indicated and to 
facilitate high rates of face-to-face follow-up. In both study 
populations, patients who did not attend an imaging appointment 
were excluded from the analysis, but reasons for nonimaging 
were recorded.

In contrast to the OXVASC population, analysis of age-
and sex-specific rates of carotid imaging was not possible in the NOPCT 
population because we did not have reliable data on the total 

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<tr>
<th>Sex Difference in Symptomatic Carotid Stenosis</th>
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<tr>
<td><strong>Table. Age and Sex Structures of the OXVASC and NOPCT Populations</strong></td>
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<td>Age Group, y</td>
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numbers of patients presenting with TIA and stroke. However, in 
both the OXVASC and NOPCT populations, we determined the age-
and sex-specific incidences of 50% to 69% and 70% to 99% 
symptomatic carotid stenosis and occlusion based on the midstudy 
age and sex population structures, and we determined rates of 
subsequent intervention. Intervention for restenosis was not included 
unless patients were recently symptomatic. Intervention for 
contralateral asymptomatic carotid stenosis in patients with a sympto-
matich occlusion was also excluded. Sex-dependant relative rates were 
calculated with Poisson statistics, and analyses are presented for both 
populations separately and pooled.

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 
males, 327 females) 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
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, 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). 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), perhaps because of the greater disinclination of women than men to agree to be randomized in clinical trials 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. 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%, \( P=0.038 \)). 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. 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. 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...
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 NOPCT\textsuperscript{27} 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.\textsuperscript{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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