Low Risk of Ipsilateral Stroke in Patients With Asymptomatic Carotid Stenosis on Best Medical Treatment
A Prospective, Population-Based Study

Lars Marquardt, MD; Olivia C. Geraghty, MRCP; Ziyah Mehta, PhD; Peter M. Rothwell, PhD

Background and Purpose—The annual risk of ischemic stroke distal to ≥50% asymptomatic carotid stenoses was ≈2% to 3% in early cohort studies and subsequent randomized trials of endarterectomy. This risk might have fallen in recent years owing to improvements in medical treatment, but there are no published prognostic data from studies initiated within the last 10 years.

Methods—In a population-based study of all patients with transient ischemic attack (TIA) or stroke in the Oxford Vascular Study, we studied the risk of TIA and stroke in patients with ≥50% contralateral asymptomatic carotid stenoses recruited consecutively from 2002 to 2009 and given intensive contemporary medical treatment.

Results—Of 1153 consecutively imaged patients presenting with stroke or TIA, 101 (8.8%) had ≥50% asymptomatic carotid stenoses (mean age, 75 years; 39% women; 40% age ≥80 years). During 301 patient-years of follow-up (mean, 3 years), there were 6 ischemic events in the territory of an asymptomatic stenosis, 1 minor stroke (initially 50% to 69% stenosis), and 5 TIs (2 initially 50% to 69% stenosis; 3 to 70% to 99% stenosis), 3 of which led to subsequent endarterectomy. The average annual event rates on medical treatment were 0.34% (95% CI, 0.01 to 1.87) for any ipsilateral ischemic stroke, 0% (95% CI, 0.00 to 0.99) for disabling ipsilateral stroke, and 1.78% (95% CI, 0.58 to 4.16) for ipsilateral TIA.

Conclusions—In the first study of the prognosis of ≥50% asymptomatic carotid stenosis to be initiated in the last 10 years, the risk of stroke on intensive contemporary medical treatment was low. Larger studies are required to determine whether this apparent improvement in prognosis is generalizable. (Stroke. 2010;41:e11-e17.)

Key Words: carotid stenosis ■ stroke ■ TIA ■ statins

The prevalence of stenosis of the proximal carotid arteries increases from the fifth decade of life onward and affects ≈7% of women and >12% of men older than 70 years. Participants with asymptomatic carotid stenoses are at increased risk of ipsilateral carotid territory ischemic stroke and of acute coronary events and vascular death. In previously published randomized trials, carotid endarterectomy (CEA) reduced the risk of ipsilateral carotid territory ischemic stroke during the next few years by ≈50%, although the absolute risk reduction was low (~1% per year), and there was uncertainty about benefit in women. Benefit from surgery depends on achieving a low operative risk, and there is some evidence that the operative risk in routine clinical practice is higher than that in large, randomized, controlled trials. It has also been suggested that the risk of stroke associated with best medical treatment might now be lower than in the 3 large randomized trials, which recruited subjects between 1983 and 2003. In a recently published systematic review, Abbott was able to show that the risk of ipsilateral and any-territory stroke in patients with asymptomatic carotid stenoses with medical intervention alone has fallen since the mid-1980s. Taken together with evidence that there has been no similar reduction in the operative risk of CAE in recent years, it is possible that the absolute benefit from CAE for asymptomatic stenosis will now be even smaller than in the previous randomized trials. However, there are very few studies of the risk of stroke distal to asymptomatic stenoses managed by what would now be regarded as best medical treatment. The 2 most recent published studies were both initiated in 1996, but the benefit of statin treatment in older patients, for example, was only demonstrated convincingly with the publication of the results of the Heart Protection Study in 2004. In the absence of any published prognostic data on asymptomatic stenosis from studies initiated within the last 10 years, we performed a prospective, population-based, cohort study of the risk of ipsilateral stroke in patients with ≥50% asymptomatic carotid artery stenosis identified after investigation for transient ischemic attack (TIA) or minor ischemic stroke in another territory and who were therefore on intensive contemporary medical treatment.

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From the Stroke Prevention Research Unit, Department of Clinical Neurology, University of Oxford, Oxford, UK.
Correspondence to Prof Peter M. Rothwell, Stroke Prevention Research Unit, University Department of Clinical Neurology, Level 6, West Wing, John Radcliffe Hospital, Oxford, OX3 9DU, UK. E-mail peter.rothwell@clneuro.ox.ac.uk
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Subjects and Methods

The study was nested within the Oxford Vascular Study (OXVASC), a population-based study of all acute vascular events in a population of ~90 000 individuals registered with 63 primary care physicians in 9 general practices in and around Oxford, UK. Methods of OXVASC have been reported previously14,15 and were approved by the local research ethics committee. In brief, multiple overlapping methods of “hot” pursuit were used to achieve near-complete ascertainment of all individuals with TIA or stroke. These included an urgent neurovascular clinic to which participating general practitioners and the local accident and emergency department send all individuals with suspected TIA or stroke whom they would not normally admit to hospital; daily assessment of admissions to the medical, stroke, neurology, and other relevant hospital wards; and daily searches of the local accident and emergency department attendance register. To not miss patients who presented late, were referred to other services, or were not referred to secondary care, 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.

Consecutive patients with TIA or stroke, either admitted to hospital or seen in the OXVASC outpatient clinic between April 1, 2002, and March 31, 2009, were considered for inclusion in this study. Stroke was defined as the sudden onset of a focal neurologic deficit lasting >24 hours without any evidence for other underlying diseases being potentially responsible for the neurologic deficit (eg, brain tumor). TIA was defined as an episode with stroke-like symptoms lasting <24 hours.

All patients gave informed consent and were seen by study physicians as soon as possible after their initial presentation. Event characteristics and risk factors were recorded, and all cases were subsequently reviewed by the study senior neurologist. All patients received intensive contemporary medical intervention, including antplatelet agent(s), usually aspirin and/or clopidogrel, for the first 30 days and then usually aspirin and dipyridamole thereafter. Furthermore, all patients were treated with a statin, most commonly simvastatin 40 mg daily, unless contraindicated. Antihypertensive medication was initiated or increased in all patients whose blood pressure was >130/80 mm Hg at baseline or during follow-up. Blood glucose was measured in all patients, and further investigation or treatment was arranged as appropriate. All patients were given advice on lifestyle, particularly the need to stop smoking if relevant.

Carotid ultrasonography was performed by an experienced vascular technician using an ATL Ultramark HDI 5000 scanner. Some patients underwent contrast-enhanced magnetic resonance angiography instead of carotid ultrasonography (Philips Achieva 1.5-T scanner with a neurovascular coil). Stenosis was classified by the NASCET method of measurement of carotid stenosis.16 Asymptomatic carotid stenosis was defined as a ≥50% diameter reduction of the carotid artery without evidence of any previous stroke or TIA in the territory of the apparently asymptomatic carotid artery.

Analysis was restricted to patients with a TIA or an ischemic stroke with a National Institutes of Health Stroke Scale (NIHSS) score ≤5 at the time of first assessment to facilitate high rates of face-to-face follow-up, of CAE on the recently symptomatic side, and of compliance with intensive contemporary medical intervention. Otherwise, all patients with an asymptomatic carotid bifurcation stenosis of ≥50% were included in the analysis. Carotid occlusions, proximal common carotid stenoses, and distal internal carotid stenoses were excluded. In patients who had presented with a posterior circulation TIA or stroke and had asymptomatic stenoses of both carotid arteries, the artery with the most severe stenosis was included in the analysis.

To ensure that any apparently asymptomatic stenosis was truly asymptomatic, we specifically asked all patients about any previous TIA or stroke and searched hospital records to identify previous events referred to secondary care. Patients also consented to allow us to search their primary care medical records to identify previous events that had not been referred to secondary care in Oxfordshire or that had been investigated elsewhere. 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. Patients were asked about recurrent symptoms, medications, and disability scores. All recurrent strokes that presented to medical attention would also be identified acutely by ongoing daily case ascertainment within OXVASC. All patients with recurrent events were reassessed by a study physician and reviewed by the senior neurologist. Vascular territory was assessed by the study neurologist who first assessed the patient and subsequently by the senior neurologist.

Risk of TIA or stroke distal to the asymptomatic carotid stenosis was determined from the date that the stenosis was identified on vascular imaging, which was usually a few days after their presenting TIA or stroke. Any TIA or stroke that occurred in association with CAE or stenting of the recently symptomatic stenosis was included in the analysis, as were any events associated with any subsequent CAE or stenting for the asymptomatic stenosis.

Results

Of 1256 patients with a TIA or an ischemic stroke with an NIHSS score ≤5 in OXVASC between April 1, 2002, and March 31, 2009, 1153 (92%) underwent carotid imaging. Initial imaging was performed with ultrasound in 1118 and with contrast-enhanced magnetic resonance angiography in 35 patients. The main reasons for nonimaging (n=103) were that patients did not attend the appointment, they were seen at home and were too frail to come to hospital or they refused further investigation, they had another event or died before the investigation, and was uncertain in 5 cases. An additional 124 patients underwent carotid imaging, of whom 103 had an NIHSS score ≥6 and 21 patients had carotid occlusion and were therefore excluded from further analysis as described earlier.

Of the 1153 imaged patients, 177 had ≥50% stenosis of at least 1 carotid bifurcation, of whom 109 had ≥50% symptomatic carotid stenoses and 101 had a ≥50% asymptomatic carotid stenosis. Of these 101 patients, 75 presented with a contralateral carotid territory TIA or stroke (as opposed to a posterior circulation event), of whom 33 also had ≥50% contralateral symptomatic stenosis and 3 had symptomatic carotid occlusion. Clinical characteristics are shown in Table 1. Sixty-nine patients had 50% to 69%...
asymptomatic carotid stenosis and 32 had 70% to 99% asymptomatic stenosis.

Mean follow-up was 3.0 years (range, 1 to 84 months), with a total of 301 patient-years of follow-up before stroke or death. Of the 33 patients who had ≥50% symptomatic and asymptomatic carotid stenoses, 25 underwent CAE for the symptomatic stenosis early during follow-up. Only 1 patient underwent CAE for asymptomatic stenosis during follow-up, and no patients underwent angioplasty/stenting. Two patients underwent coronary artery bypass surgery during the observation time.

Table 2 shows medication use and control of blood pressure at 1, 12, and 24 months of follow-up. Almost all (97%) patients were on antithrombotic treatment at 1 and 12 months of follow-up, and 96% were on antithrombotic treatment at 24 months of follow-up. Eighty-six percent were taking a statin at 1 month; 83%, at 12 months; and 81%, at 24 months. Eighty-eight percent were taking at least 1 blood pressure–lowering agent at 1 month; 85%, at 12 months; and 82%, at 24 months. At the 5-year follow-up, 94% of patients were on antithrombotic treatment, 79% were on a statin, and 84% were on at least 1 blood pressure–lowering agent.

There were 6 ischemic events in the territory of an asymptomatic stenosis during follow-up: 1 minor stroke (initially 50% stenosis) and 5 TIAs (2 initially 50% to 69% stenosis; 3 to 70% to 99% stenosis). The average annual risks were 0.34% (95% CI, 0.01 to 1.87) for any ipsilateral carotid territory ischemic stroke, 0% (95% CI, 0.00 to 0.99) for disabling ipsilateral carotid territory ischemic stroke, and 1.78% (95% CI, 0.58 to 4.16) for ipsilateral carotid territory ischemic TIA (Table 3). Figure 1 shows the Kaplan–Meier hazard curves for risk of ipsilateral carotid territory TIA or stroke. Three patients subsequently underwent CAE for these now-symptomatic stenoses. Reimaging was performed at the time of the ipsilateral event in 4 patients (1 stroke, 3 TIAs), none of whom had an increase in severity of the previously asymptomatic stenosis.

Of the 25 patients who underwent CAE for a symptomatic carotid artery stenosis, 1 had a periprocedural ipsilateral stroke and 3 patients had periprocedural ipsilateral TIAs (no events occurred ipsilateral to the asymptomatic carotid stenosis). Of the 3 patients who had CAE after a stroke or TIA ipsilateral to a previously asymptomatic carotid stenosis, 1

### Table 2. Medication and Control of Blood Pressure Assessed at 1, 12, and 24 Months of Follow-Up in Imaged Patients With ≥50% Asymptomatic Carotid Stenosis

<table>
<thead>
<tr>
<th></th>
<th>1-Month Follow-Up,*</th>
<th>12-Month Follow-Up,*</th>
<th>24-Month Follow-Up,*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=99</td>
<td>n=85</td>
<td>n=79</td>
</tr>
<tr>
<td>Antplatelet agent or oral anticoagulation</td>
<td>96 (97%)</td>
<td>82 (97%)</td>
<td>76 (96%)</td>
</tr>
<tr>
<td>Antplatelet agent</td>
<td>85 (86%)</td>
<td>77 (90%)</td>
<td>72 (91%)</td>
</tr>
<tr>
<td>Oral anticoagulation</td>
<td>10 (10%)</td>
<td>6 (7%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Statin</td>
<td>85 (86%)</td>
<td>71 (83%)</td>
<td>64 (81%)</td>
</tr>
<tr>
<td>Blood pressure–lowering agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One or more drug</td>
<td>87 (88%)</td>
<td>72 (85%)</td>
<td>65 (82%)</td>
</tr>
<tr>
<td>Two or more drugs</td>
<td>65 (66%)</td>
<td>56 (66%)</td>
<td>51 (64%)</td>
</tr>
<tr>
<td>Three or more drugs</td>
<td>20 (20%)</td>
<td>22 (26%)</td>
<td>17 (21%)</td>
</tr>
<tr>
<td>Systolic blood pressure, mean, mm Hg (SD)</td>
<td>142 (22)</td>
<td>140 (26)</td>
<td>139 (24)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean, mm Hg (SD)</td>
<td>91 (11)</td>
<td>85 (12)</td>
<td>84 (10)</td>
</tr>
<tr>
<td>Mean blood pressure ≤160/90 mm Hg</td>
<td>50 (51%)</td>
<td>47 (55%)</td>
<td>48 (61%)</td>
</tr>
<tr>
<td>Mean blood pressure ≤140/90 mm Hg</td>
<td>39 (39%)</td>
<td>35 (41%)</td>
<td>37 (47%)</td>
</tr>
</tbody>
</table>

*Analysis excludes patients who died before relevant follow-up and patients with incomplete data.

### Table 3. Average Annual Risk of Vascular Events and Deaths During Follow-Up

<table>
<thead>
<tr>
<th>Events</th>
<th>Average Annual Risk, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral stroke</td>
<td>0.34 (0.01–1.87)</td>
</tr>
<tr>
<td>Ipsilateral TIA</td>
<td>1.78 (0.58–4.16)</td>
</tr>
<tr>
<td>Other territory stroke</td>
<td>8.32 (5.08–12.85)</td>
</tr>
<tr>
<td>Other territory TIA</td>
<td>5.15 (2.74–8.81)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4.70 (2.50–8.04)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>1.03 (0.21–3.01)</td>
</tr>
<tr>
<td>Vascular death</td>
<td>7.70 (5.79–12.98)</td>
</tr>
<tr>
<td>Nonvascular death</td>
<td>2.01 (0.82–4.76)</td>
</tr>
</tbody>
</table>

Figure 1. Kaplan–Meier hazard curves for risk of ipsilateral carotid territory ischemic TIA or stroke during 6 years distal to the asymptomatic carotid stenosis. The numbers below represent the numbers of patients reaching each follow-up.
patient had a periprocedural ipsilateral stroke. In our cohort of patients with asymptomatic carotid stenoses, the average annual risk rates for vascular events other than ipsilateral stroke or TIA (Table 3) were 8.32% (95% CI, 5.08 to 12.85) for stroke in another vascular territory, 5.15% (95% CI, 2.74 to 8.81) for TIA in another vascular territory, 4.70% (95% CI, 2.50 to 8.04) for myocardial infarction, 1.03% (95% CI, 0.21 to 3.01) for unstable angina, and 9.71% (95% CI, 6.50 to 13.94) for death.

Discussion

Although the sample size of our study was relatively small, we consider the data useful for several reasons. First, it is a first-ever, population-based, prospective study of the prognosis of asymptomatic stenosis in patients with TIA or stroke in another vascular territory. This group of patients is interesting to study because they are very likely to be prescribed the best medical intervention. They are also clinically important, because in the absence of widespread population screening in most countries, they account for a significant proportion of all patients in whom CAE or stenting for asymptomatic carotid stenosis is considered in routine clinical practice. Second, there are no published studies on the prognosis of asymptomatic stenosis initiated within the last 10 years, during which time there have been improvements in best medical intervention. Third, all patients were followed up face to face as well as by review of primary and secondary care medical records, such that we were very unlikely to have missed stroke events and were able to identify TIA during follow-up. Fourth, by nesting the study in a population-based TIA and stroke incidence study with near-complete case ascertainment and with no exclusion by age, we were able to include many elderly and frail patients, which avoided any inclusion bias that might have led to underestimation of the risk of stroke. Finally, given the very low rates of CAE for asymptomatic stenosis in the United Kingdom, we were very nearly able to study prognosis without invasive intervention, with only 1 patient undergoing CAE of an asymptomatic stenosis during follow-up.

The average annual risk of ipsilateral stroke and/or TIA in patients with asymptomatic ≥50% carotid stenosis on intensive contemporary medical intervention was very low, albeit with relatively wide CIs. Larger studies are required, but our results are consistent with those of 2 other studies initiated in the 1990s and published during the last few years.11,12 Figure 2 shows the average annual risk rates of stroke distal to 50% to 99% asymptomatic stenoses from the most relevant published studies that reported information on annual risk rates for stroke in patients with asymptomatic carotid stenosis. However, these studies were heterogeneous in their methodology, differentiation of clinical information provided, and statistical analysis. Most studies did not differentiate between hemorrhagic and ischemic stroke, and some studies did not differentiate between ipsilateral and any stroke. Of note, the only sufficiently large studies that reported an annual risk of stroke <1.5% recruited patients during the last 10 to 15 years.11,12 The lower risk of stroke in more recent studies is perhaps clearer when the exact recruitment and follow-up periods are taken into account (Figures 2b and 2c) rather than just the date of publication (Figure 2a).

The low risk of ipsilateral ischemic stroke in our patients with significant asymptomatic stenosis is very likely to be due to some extent to intensive medical intervention, particularly the use of statins and blood pressure-lowering medication. Carotid disease appears to gain particular benefit from statin treatment. In the Heart Protection Study, patients with a baseline history of stroke or TIA (any vascular territory) or carotid surgery/stenting who were randomized to simvastatin 40 mg were half as likely as those randomized to placebo to have undergone CAE or angioplasty during follow-up.17 Similar results were found in the SPARCL trial, with patients randomized to atorvastatin (rather than placebo) being less likely to undergo a revascularization procedure (coronary, carotid, or peripheral) during follow-up.18 In a SPARCL substudy, it was shown that later carotid revascularization was reduced by 56% in the group randomized to atorvastatin.19 The reduction in coronary event rates and all recurrent stroke was lower in both trials, which is also consistent with the high rate of vascular events in other territories in our study. In contrast to the very high rate of use of statins in our cohort, only 17% of patients recruited in ACST from 1993 to 1996 were on lipid-lowering therapy at study entry. Although this rate increased to 58% in those recruited from 2000 to 2003, many patients were on what would now be regarded as subtherapeutic doses (eg, simvastatin 10 mg daily).20 ASED did not report data about statin use at study entry,11 and only 45% of patients in SMART were on statin treatment at entry.12

The average annual risk of stroke in vascular territories other than that of the asymptomatic stenosis was relatively high in our analysis (8.32%). However, for various reasons, our cohort was different from others in other randomized trials and general stroke incidence studies, which could explain this relatively high risk. First, all of our patients had extensive large-artery disease with carotid and/or vertebrobasilar stenoses ≥50%. Second, we also included the early risk of stroke in our analysis, unlike many previous randomized clinical trials. Third, we used a very rigorous definition for stroke by including all minor and nondisabling events as well as major and disabling ones.

Our study does have a number of shortcomings. First, the number of patients with asymptomatic carotid stenoses (n=101) was not sufficiently large to provide narrow CIs around the estimate of average annual risk of ipsilateral stroke. However, it can be argued that a small but methodologically rigorous study without selection bias provides more reliable data than does a large study with various potential selection biases. As detailed earlier, we are unlikely to have underestimated risk because of our inclusion of "symptomatic" patients, irrespective of age, and our frequent face-to-face follow-up. As was shown in the ACAS trial, many patients with known asymptomatic stenoses do not report TIA or minor strokes to medical attention, such that these events were only identified at the next scheduled face-to-face follow-up, despite the fact that patients were repeatedly requested to report all events immediately.21 It is also interesting to note that the similarly small studies published in the 1980s and 1990s reported risk estimates that
Figure 2. Average annual risk rates of stroke in patients with at least 50% asymptomatic carotid stenosis in OXVASC and in other published studies that reported data. The size of each bubble reflects the relative number of patients in the study. a, Risk of any and/or ipsilateral stroke, displayed by year of publication. b, Risk of any and/or ipsilateral stroke, displayed by recruitment period (horizontal bar; dashed line indicates estimated recruitment period). c, Risk of ipsilateral (to asymptomatic carotid stenosis) stroke displayed by recruitment period (horizontal bar; dashed line indicates estimated recruitment period).
were highly consistent with larger cohort studies and randomized trials that were performed in the same era (Figure 2). Second, the majority of patients had only 50% to 69% stenosis, with about a third of our patients having an asymptomatic carotid stenosis of 70% to 99%. However, in contrast to symptomatic carotid stenosis,22–24 there is little evidence that the risk of stroke increases with degree of stenosis across the 50% to 99% range.20,25 Third, we studied patients with TIA or minor stroke rather than completely asymptomatic patients. However, as mentioned earlier, this is the group in whom asymptomatic carotid stenosis is most commonly found and accounts, in many countries, for the majority of CAEs for asymptomatic stenosis, and some were included in ACAS and in ACST. Moreover, because all included patients had severe large-artery disease, this group should, if anything, have a higher risk of stroke than do truly asymptomatic patients, if one assumes similar intensity of medical treatment. Third, we were unable to include all patients in our study who had a stroke or TIA in a territory other than that of the asymptomatic carotid stenosis because 8% of patients did not undergo vascular imaging, mainly because they were too frail to attend a hospital appointment. However, with 92% we achieved an overall relatively high imaging rate. It is certainly possible that a small selection bias could have resulted from not including patients who did not undergo imaging. However, in any previous study, these 8% of patients who did not undergo investigation would also have not been included because they would not have been identified. We were only able to identify these patients because of the population-based setting of our study. Furthermore, owing to their general condition, these patients would have been unlikely to be eligible for CAE or stenting. Finally, because patients had had a previous TIA or stroke and because they were being followed up, it could be argued that patients who subsequently developed an ipsilateral TIA during follow-up were more likely to be identified and have a CAE for their now-symptomatic carotid stenosis than would be likely in truly asymptomatic patients. However, because only 3 patients with a TIA subsequently underwent CAE during follow-up and 2 of these presented to medical attention independently of the OXVASC study follow-up, substantial bias due to our follow-up is unlikely. Moreover, previous research in our cohort has shown that patients with previous TIA or stroke do not seek medical attention after recurrent TIA any more quickly than do patients with incident TIA.26

If other studies confirm the low risk of stroke due to asymptomatic stenosis after intensive contemporary medical intervention alone, then this improvement in prognosis will have major implications for routine clinical practice. The benefit from CAE for asymptomatic carotid stenosis in the previous large trials was already small20,25 and was very dependent on low operative risk.27 There is already evidence that the operative risk of CAE in routine clinical practice is significantly higher than that seen in the trials.28 For example, a systematic review of operative risks in surgical case series that published operative risks for asymptomatic stenosis shortly after ACAS reported that operative mortality was 8 times higher than in ACAS (1.11% vs 0.14%, P = 0.01) and that the risk of stroke and death was ≈3 times higher among comparable studies in which outcome was assessed by a neurologist (4.3% vs 1.5%, P < 0.001).28 If the risk of stroke after intensive contemporary medical intervention alone is now lower than in large, randomized, controlled trials, it is highly unlikely than any overall benefit from surgery would remain. Some useful data should be available in future from the SPACE II Trial, which will randomize patients with asymptomatic carotid artery stenosis to CAE versus stenting versus medical intervention alone.

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**Disclosure**

None.

**References**


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Low Risk of Ipsilateral Stroke in Patients With Asymptomatic Carotid Stenosis on Best Medical Treatment

A Prospective, Population-Based Study

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背景和目的：一项早期的队列研究以及之后的一些内膜切除术的随机对照临床研究结果提示，远端狭窄≥50%的无症状颈动脉狭窄患者缺血性卒中的年发生率约在2%-3%。近年来这个比率可能因医疗水平的改善而下降，然而近10年内尚无这些研究的预后相关数据的公布。

方法：在基于人群的牛津血管研究(Oxford Vascular Study)中，所有患者患有短暂性脑缺血发作(TIA)或缺血性卒中，连续入组了自2002至2009年以来存在对侧狭窄≥50%的无症状颈动脉狭窄患者，评估他们发生TIA和卒中的风险，并给予强化的现代化医疗干预措施。

结果：在连续入组并且影像学提示存在卒中或TIA的1153例患者中，101例(8.8%)存在≥50%的无症状颈动脉狭窄(平均年龄75岁，39%为女性，40%的患者年龄≥80岁)。随访301患者-年中(平均3年)，无症状狭窄区域的缺血性事件6例，其中1例为轻微卒中(源自50%-69%的狭窄)，5例为TIA(2例源自50%-69%的狭窄，3例源自70%-99%的狭窄)。这一事件发生后进行了对侧内膜切除术。医疗干预情况下同侧任意缺血性卒中事件的年平均发生率为0.34%(95%CI, 0.01-1.87)，同侧致残性卒中的发生率为0%(95%CI, 0.00-0.99)，同侧TIA的发生率为1.78%(95%CI, 0.58-4.16)。

结论：近10年开始的这项关于≥50%的无症状颈动脉狭窄患者的预后的第一个研究结果提示，在接受密集的现代化医疗干预情况下发生同侧卒中的风险较低。需要更大型的研究进一步证明这种预后明显改善的情况。

关键词：颈动脉狭窄，卒中，短暂性脑缺血发作，他汀类药物

(Stroke. 2010;41:e11-e17. 陈盼 译 刘丽萍 校)
缺血性卒中患者，发现≥50%的无症状颈动脉狭窄，并因此进行了强化的现代医学治疗干预后，发生同侧卒中的风险。方

对像和方法

本研究是嵌套在牛津血管研究(Oxford Vascular Study，OXVASC)中，后者为一个基于人群的急性血管性事件研究，由来自英国牛津郡内及周边的9个全科诊所的63位初级保健医师登记入组了约91000例研究对象。OXVASC的方法先前已报道过[14,15]，并通过了当地的研究伦理委员会的审核。简而言之，该研究应用了重叠的“热门”方法，近乎完全明确地判断个体是否有TIA或者卒中。这些方法包括建立紧急血管神经病诊所，参与的全科医师和当地急症室把所有疑似TIA或者卒中的患者送至上述诊所，而不是将这些患者收入院；每日评估内科、卒中单元、神经科及其他相关病房的入院情况。每日搜索当地急诊室的签到薄。为了不漏掉那些延迟就诊的患者，或者被转到其他医疗机构，或者没有转至二级预防保健机构的患者，每个月进行一次对家庭医生诊断编码、医院出院编码以及当地医院做的所有头部和颈动脉影像学结果的电脑辅助搜索。

连续的TIA或者卒中患者，凡是在2002年4月1日至2009年3月31日期间收入院或在OXVASC门诊就诊的均入组本研究。卒中定义为突发的持续时间大于24小时的局部神经功能缺损，并无任何证据证明存在其他潜在的导致该神经功能缺损的疾病(例如脑肿瘤)。TIA定义为卒中样症状的发作，持续时间小于24小时。

所有患者都获得了知情同意，并在初现症状后尽快与研究医生见面。记录事件的临床特点和危险因素，随后所有病例都通过这项研究的上级神经科医师的复核。所有患者都接受了强化的医疗干预，包括抗血小板药物治疗，通常在前30天内使用的是阿司匹林和/或氯吡格雷，之后通常是阿司匹林和潘生丁。此外，除用药禁忌外，所有患者都给予了他汀类药物治疗，最常用的为辛伐他汀40mg。当患者基线或随访期间血压大于130/80mmHg时开始或增加抗高血压药物治疗。所有患者都测定血糖值并给予适当的进一步测定或治疗。所有患者均给予健康生活方式的建议，尤其是吸烟者给予戒烟的劝诫。

颈动脉超声检查由一位工作经验丰富的血管检查技术人员使用一台ATL Ultramark HDI 5000扫描仪完成。一些患者进行了增强磁共振血管成像(Philips Achieva 1.5-T扫描仪，一个神经血管线圈)检查代替了颈动脉超声检查。狭窄的分类参考测量颈动脉狭窄的NASCET方法[16]。无症状性颈动脉狭窄的定义是：颈动脉直径减少≥50%以上，并且在显著的无症状颈动脉狭窄所在区域没有任何先前的卒中或者TIA发作。

我们仅限于分析首次评估时国立卒中研究所卒中量表(NIHSS)评分≤5分的患者，以利于提高之后面对面的随访率，提高近期存在症状侧CEA手术率，以及提高强化的现代化医疗干预的依从性。另外，所有颈动脉分支狭窄≥50%的无症状患者被纳入分析。颈动脉闭塞，近端颈总动脉狭窄及远端颈内动脉狭窄被排除在外。表现为后循环TIA或卒中的患者，并存在双侧颈动脉的无症状性的狭窄，那么最严重的那支狭窄动脉被纳入分析。

为了确保任何明显的狭窄的确是有症状性狭窄，我们特别询问了患者所有以往的任何一次TIA或卒中病史，并核查了医疗记录确认之前的血管事件适用于二级预防。患者也同意让我们搜索他们的初级保健医疗记录，以确定之前的血管事件不适用于牛津二级预防或者在其他地方被调查过。患者在30天，6个月，1年，2年，5年由研究护士或医生进行面对面的随访。询问患者复发症状，用药情况和残疾指数。所有引起医疗重视的复发性卒中将很快被OXVASC研究中一直进行的日常案例鉴定得以确认。所有存在复发事件的患者将被研究医生重新评估，并通过上级神经科医师的审核。首诊患者的就诊医生评估血管区域之后再由资深神经科医师审核。

无症状颈动脉狭窄的远端发生TIA或卒中的风

表1 影像学检查提示狭窄≥50%无症状颈动脉狭窄患者的人口学特征和临床数据

| 年龄，平均，岁(SD) | 75.2 (9.6) |
| 年龄≥80岁 | 40 (40%) |
| 女性 | 39 (39%) |
| 高血压 | 69 (68%) |
| 糖尿病 | 16 (16%) |
| 目前吸烟 | 15 (15%) |
| 之前吸烟 | 61 (60%) |
| 心房颤动(之前或目前存在) | 12 (12%) |
| 表现为卒中事件 | 53 (52%) |
| 表现为TIA事件 | 48 (48%) |
| 先前的周围血管疾病 | 22 (22%) |
| 先前的心肌梗死 | 14 (14%) |
| 既往TIA病史 | 17 (17%) |
| 既往卒中病史 | 26 (26%) |

* 在无症状颈动脉狭窄的不同区域
险自血管成像发现狭窄那天开始，通常在发生 TIA 或卒中后的几天内。任何与近期症状性狭窄支架治疗或 CEA 手术相关的 TIA 或者卒中发作将被列入分析，正如把任何与之后的 CEA 手术或无症状狭窄支架治疗相关的事件列入分析一样。

### 结果

1256 例 NIHSS 评分 ≤5 分且入组时间在 2002 年 4 月 1 日至 2009 年 3 月 31 日之间的缺血性卒中或 TIA 患者中，1153(92%) 例患者进行了颈动脉成像检查。其中 1118 例患者进行了首次超声检查，35 例患者进行了增强磁共振成像。没有进行影像学检查 (n=103) 的主要原因是患者并没有赴约，他们被发现在家或者过于虚弱以致不能到医院，或拒绝接受进一步的检查，他们发生了另一个事件或在调查前死亡了，其中 5 例原因不明。另外 124 例进行颈动脉影像学检查的患者中有 103 例 NIHSS 评分 ≥6 分，21 例患者存在颈动脉闭塞，因此按先前描述的标准被排除在外，不再进行进一步分析。

1153 例经过影像学检查的患者中，177 例至少有一条颈动脉分支存在 ≥50% 的狭窄，其中 109 例存在 ≥50% 的症状性颈动脉狭窄，101 例存在 ≥50% 的无症状性颈动脉狭窄。这 101 例中，75 例表现为对侧颈内动脉 TIA 或卒中（相对于后循环事件而言），其中 33 例同时存在对侧 ≥50% 的症状性狭窄，3 例存在症状性颈动脉闭塞。临床特征见表 1。69 例患者无症状颈动脉狭窄率在 50%-69%，32 例患者无症状颈动脉狭窄率在 70%-99%。

平均随访时间为 3 年（范围自 1 至 84 个月），发生卒中或死亡之前共完成 301 患者 - 年的随访。33 例狭窄 ≥50% 的症状性合并无症状性颈动脉狭窄患者中，25 例患者在随访早期接受了 CEA 手术治疗。仅有 1 例患者在随访期间因无症状颈动脉狭窄接受了 CEA 手术，进行支架成形术的患者数为 0。在观察期间，2 例患者接受了冠状动脉搭桥手术。

表 2 显示了在第 1、12、24 个月随访时患者的药物使用情况和血压控制情况。几乎所有患者 (97%)
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在第 1、12 个月随访时在服用抗血栓药物，第 24 个月随访时服用抗血栓药物治疗。86%的患者在第 1 个月随访时服用他汀类药物，第 12 个月随访时服用比例为 83%，24 个月时为 81%。88%的患者在第 1 个月随访时服用了至少一种降压药物，第 24 个月时为 82%。在 5 年随访点时，94%的患者在接受抗血栓治疗，79%在服用他汀类药物，84%患者在服用至少一种降压药物。

随访期间在无症状狭窄区域发生了 6 例缺血性事件：1 例小卒中（最初为 50%的狭窄），5 例 TIA（2 例最初狭窄为 50%-69%；3 例最初狭窄为 70%–99%）。平均每年发生任一单侧颈动脉区的缺血性卒中风险为 0.34%（95% CI，0.01-1.87），发生任一侧颈动脉区域致残性缺血性卒中的风险为 0%（95% CI，0.00-0.99）。发生同侧颈动脉区域缺血性 TIA 的风险为 1.78%（95% CI，0.58-4.16）（见表 3）。图 1 显示了用 Kaplan-Meier 风险曲线描述的发生同侧颈动脉区域 TIA 或卒中的风险。3 例患者因成为症状性狭窄而接受了之后的 CEA 手术治疗。同侧事件发生后 4 例患者复查了影像学检查（1 例卒中，3 例 TIA），这些之前无症状的狭窄程度均没有增加。

25 例症状性颈动脉狭窄接受 CEA 手术的患者中，1 例在围手术期发生了同侧卒中，3 例在围手术期发生了同侧 TIA（没有脑血管事件发生在无症状颈动脉狭窄的同侧）。3 例因先前无症状颈动脉狭窄发生同侧缺血性卒中或 TIA 而接受 CEA 手术治疗的患者中，1 例患者发生了围手术期的同侧卒中。在我们的队列中，无症状颈动脉狭窄的患者发生血管性事件（除外同侧的卒中及 TIA）的年平均风险见表 3，在其他血管区域发生卒中的年平均风险为 8.32%（95% CI，5.08-12.85），在其他血管区域发生 TIA 的风险为 5.15%（95% CI，2.74-8.81），心肌梗死为 4.70%（95% CI，2.50-8.04），不稳定型心绞痛为 1.03%（95% CI，0.21-3.01），死亡为 9.71%（95% CI，6.50-13.94）。

讨论

虽然我们的研究样本量较少，但是我们认为数据有用的原因有几个。首先，该研究是第一次基于人群的，观察在其他的血管区域发生卒中或 TIA 的无症状颈动脉狭窄患者预后的前瞻性研究。本研究之所以对这组患者感兴趣，是因为他们很可能接受最优化的医疗干预。这些患者也具有重要的临床意义，因为在大多数国家缺乏广泛的人群筛查的情况


下，这些患者在很大比例上代表了常规临床实践中无症状性颈动脉狭窄患者考虑接受 CEA 手术或支架成形术的情况。第二，近 10 年内尚无关于无症状性颈动脉狭窄患者预后的研究结果发表，而最优化的医疗干预措施在这期间也有改善。第三，所有患者通过面对面的随访，并且核对了初级和二级保健医疗记录，因此我们不太可能漏掉卒中事件，并能够在随访期间识别 TIA 的发生。第四，通过把本研究嵌套在一个基于人群的 TIA 和卒中事件研究中，后项研究能得到接近完全的确定案例并且没有年龄的限制，这样我们能纳入很多老年人和体弱的患者，从而避免任何导致对卒中风险评估不足的入组偏倚。

最后，由于在英国无症状颈动脉狭窄患者接受 CEA 手术治疗的比率非常低，在随访中也只有 1 例无症状狭窄患者接受了 CEA 手术治疗，所以我们几乎能够研究在没有侵入性医疗干预情况下患者预后情况。

在强化的现代医疗干预情况下，狭窄≥50%的无症状颈动脉狭窄患者发生同侧卒中和 / 或 TIA 的年平均风险非常低，尽管可信区间范围相对较大。更大规模的研究是必需的，但我们的结果也与 20 世纪 90 年代开始招募并在过去数年发表的 2 项其他研究的结果一致 [11,12]。图 2 显示了从最相关的已发表的研究中得出的狭窄程度为 50%-99%的无症状狭窄患者远端发生卒中的年平均风险率。然而，这些研究在方法学、提供的临床资料和统计分析等处均存在异质性。大多数研究没有区分出血性和缺血性卒中，一些研究没有区分同侧卒中和任何侧卒中。值得注意的是，在过去 10-15 年招募患者的仅有的足够大型的研究 [11,12] 报道的卒中年风险率 <1.5%。当考虑到确切的招募和随访时间，而不是仅仅公布发表日期（图 2a）时，最近的研究得出更低的卒中年风险也显得更为清晰准确（图 2b 和 2c）。在这些存在明显无症状狭窄的患者发生同侧缺血性卒中的机率很低，很可能在一定程度上是由于进行了强化的医疗干预，尤其是他汀类药物和降血压药物的使用。颈动脉疾病似乎从他汀类药物治疗中获得了特殊的益处。在心脏保护研究中，基线时存在卒中或 TIA（任意血管区域）病史或颈动脉外科手术/支架治疗史的患者，被随机分配至 40 mg 辛伐他汀组，后续随访期间可能接受 CEA 手术或血管成形术的比例，相对于被随机分配到安慰剂组的患者来说，近乎一倍 [17]。SPARCL 试验中发现类似的结果，被随机分配至阿托伐他汀（而不是安慰剂）组的患者在后续随访期间似乎较少经历血管重建（冠状动脉，
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图 2 OXVASC 研究中至少存在 50% 狭窄程度的无症状颈动脉狭窄患者年平均卒中风险率和其他研究公布的数据。每个气泡的大小反映了研究中的患者相对数量。a. 按出版年次显示的任何卒中和或同侧卒中的风险。b. 按入组患者的时间段（横向显示的标杆，虚线代表估计的入组时间段）显示的任何卒中和或同侧卒中的风险。c. 按入组时间段（横向显示的标杆，虚线代表估计的入组时间段）显示的同侧（对无症状颈动脉狭窄）卒中的风险。

颈动脉或周围动脉) 手术。一项 SPARCL 亚组研究的结果表明，随机分配至阿托伐他汀组的患者进行择期颈动脉血管重建术的比例减少了 56%。冠脉事件发生率和所有复发性卒中的减少程度在这两项试验中都较低，这同我们的研究中其他区域的血管性事件高发率相一致。与我们的队列研究中非常高比例的他汀类药物使用率相反，ACST 研究纳入的自 1993-1996 年的患者在进入研究时接受降血脂
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治疗的比例仅为17%。尽管这个比例在2000-2003年入组时上升到58%，很多患者接受的治疗剂量现在被视为低于治疗剂量(例如辛伐他汀10mg/天)\(^{20}\)。

ASED研究未报道进入研究时他汀类药物使用的情况\(^{11}\)。SMART研究中患者在入组时接受他汀类药物治疗的比例仅为45%\(^{12}\)。

在我们的分析结果中，血管所在区域而不是无症状狭窄的区域发生卒中的年风险率相对较高（8.32%）。然而，由于种种原因，我们的队列研究与其它随机对照试验和一般的卒中发病率研究有所区别。首先，我们的患者均存在广泛的大血管疾病，表现为颈动脉和/or椎基底动脉狭窄≥50%。第二，和以往的许多随机临床试验不同，在我们的分析中同时纳入了卒中的早期风险。第三，我们使用了一个很严格的卒中定义，除外大卒中和致残性卒中外还囊括了所有小卒中和非致残性卒中。

我们的研究也有一些缺点。首先，无症状颈动脉狭窄的患者数量（n=101）未足以使评估同侧卒中年平均风险的可信区间范围变小。然而，可以说一项小型但方法学严谨、不存在选择偏倚的研究比一项大型但存在各种潜在选择偏倚研究所提供的数据更为可靠。正如先前详细描述的，因为我们研究的"症状性"患者的纳入标准、无年龄限制以及频繁的面对面随访，使我们不太可能低估风险。正如在ACAS试验中提示的，许多已知存在无症状狭窄的患者不对医疗救护者上报TIA或者轻微卒中事件，导致这些事件在下一个安排的面对面访视点才被确认，尽管患者被再要求立即上报所有的事件\(^{21}\)。同样引起我们关注的是，在20世纪80和90年代公布的类似小型研究结果估计与同一时期进行的大型队列研究和随机临床试验的结果高度一致（图2）。第二，大多数患者狭窄程度只有50%-69%，大约三分之一的患者无症状性颈动脉狭窄程度为70%-99%。然而，对于症状性颈动脉狭窄而言\(^{22,23}\)，很少有证据认为，在50%-99%的狭窄范围内，发生卒中的风险随着狭窄程度的增加而增加\(^{22,23}\)。

第三，我们研究的是TIA或轻微卒中患者，而不是完全无症状的患者。然而，正如前面提到的，最常发现无症状性颈动脉狭窄并最具代表性的正是这组人群。在许多国家，这一人群占无症状颈动脉狭窄接受CEA手术治疗的大多数，并且一些患者被纳入ACAS和ACST研究中。此外，因为所有被纳入的患者都存在严重的大血管疾病，假设给予类似的强化医疗干预，存在TIA或小卒中的这组患者应该比真正的无症状患者具更高的卒中风险。第三，在研究中我们无法纳入所有在无症状颈动脉狭窄区域之外发生卒中或TIA的患者，因为8%的患者主要因为太虚弱不能如约来医院进行血管影像学检查。然而，我们的整体影像学检查率相对较高，达92%。当然因为没有进行影像学检查的患者未被入组，可能导致小的选择偏倚。然而，在任何之前的研究中，这些没有经过影像学检查的8%的患者也没有被纳入，因为他们没有办法被识别。我们能识别这些患者因为我们的研究设定的背景是基于人群的。此外，由于他们的一般情况，这些患者本身也不太可能适合接受CEA或支架治疗。最后，由于患者以前有过TIA或卒中并进行继续随访，可以说，这些在随访期间发生同侧TIA的患者比真正的无症状患者更容易被识别，而且更可能为了治疗现有的症状性颈动脉狭窄而接受CEA手术。然而，因为只有3例发生TIA的患者在随访期间接受了CEA手术，其中2例独立于OXVASC研究的随访而寻求了医疗救护，因我们的随访而引起重大偏移的可能性较小。此外，我们之前进行的队列研究显示，先前存在TIA或卒中病史的患者在TIA反复发作后并不比偶发TIA的患者更快寻求医疗救护\(^{20}\)。

如果其他研究证实，卒中的低风险是仅仅因为无症状颈动脉狭窄患者接受了强化的现代化医疗干预，那么这样的预后改善将对常规临床实践产生重大提示。之前的大型试验表明，对于无症状颈动脉狭窄者行CEA治疗获益非常小\(^{20,25}\)，并且非常依赖于低手术风险\(^{27}\)。已经有证据指出，在日常临床实践中CEA的手术风险显著高于试验中得到的\(^{28}\)。例如已发表的一项关于外科案例系列手术风险的系统综述，其报道的关于无症状狭窄的手术风险，紧随ACAS研究的报道之后，手术死亡率为ACAS中报道的8倍（1.11%比0.14%，P=0.01）；其发生卒中和死亡的风险约为其他可比性研究的3倍，可比性研究的临床结局由一位神经病学专家评估（4.3%比1.5%，P=0.001）\(^{29}\)。如果仅仅进行强化的现代化医疗干预后发生卒中的风险低于大型随机对照的临床试验，那么外科手术极有可能不存在任何的整体获益。从今后的SPACE II试验中应该能得到一些有用的数据，这项研究将把无症状颈动脉狭窄患者随机分配至CEA组、支架治疗组和单独内科治疗组。

参考文献(略)