Relationship Between Blood Pressure and Stroke Risk in Patients With Symptomatic Carotid Occlusive Disease

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Background and Purpose—Blood pressure lowering in patients with a previous transient ischemic attack (TIA) or stroke reduces the risk of recurrent stroke and coronary vascular events. However, there is uncertainty about the risks and benefits in patients with severe carotid occlusive disease, particularly those with a carotid occlusion or bilateral ≥70% carotid stenosis in whom cerebral perfusion is often impaired and may depend directly on systemic blood pressure. Therefore, we studied the effect of carotid artery disease on the relationship between blood pressure and stroke risk in patients with recent TIA or stroke.

Methods—We compared the relationship between blood pressure (systolic and diastolic blood pressures, pulse pressure) and stroke risk in TIA and stroke patients with documented stenosis of at least 1 carotid artery [European Carotid Surgery Trial (ECST) and North American Symptomatic Carotid Endarterectomy Trial (NASCET)] with that in TIA and stroke patients with a low prevalence of carotid disease [United Kingdom Transient Ischaemic Attack (UK-TIA) Aspirin Trial]. In ECST and NASCET, we also determined the relationship between blood pressure and stroke risk in patients with unilateral carotid occlusion and patients with bilateral ≥70% carotid stenosis.

Results—Stroke risk on medical treatment increased with blood pressure in ECST and NASCET, but the relationships were less steep than in the UK-TIA trial. The relationship between blood pressure and stroke risk was not affected by the presence of a unilateral carotid occlusion but was significantly affected by the presence of bilateral carotid stenosis ≥70% (interaction: systolic blood pressure, P=0.002; diastolic blood pressure, P=0.03; pulse pressure, P=0.003). In this group, the relationship was inverted because of the high stroke risks at lower blood pressures. This interaction was not present after carotid endarterectomy and was not present for the risk of myocardial infarction.

Conclusions—The risk of stroke increases with blood pressure in the great majority of patients with symptomatic carotid artery disease, but the relationship is less steep than in other patients with TIA or stroke. The relationship is unaffected by unilateral carotid occlusion alone but is inverted in patients with bilateral ≥70% carotid stenosis, suggesting that aggressive blood pressure lowering may not be advisable in this group. These patients represent only a few percent of all patients with TIA or stroke but have a high risk of recurrent stroke. (Stroke. 2003;34:2583-2592.)

Key Words: blood pressure ■ carotid endarterectomy ■ carotid stenosis ■ hypertension

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Population-based studies have shown steep and continuous linear relationships between both systolic (SBP) and diastolic (DBP) blood pressures and risk of stroke,\(^1,2\) and treatment of hypertension is highly effective in the primary prevention of stroke.\(^3,4\) In contrast, until recently, there was only limited evidence in favor of blood pressure lowering in secondary prevention of stroke.\(^5,6\) and physicians tended to be less aggressive in this group of patients.\(^7,8\) However, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) has now shown that blood pressure lowering does reduce the risk of stroke and other major vascular events in patients who have had a previous transient ischemic attack (TIA) or stroke,\(^9,10\) even in those with blood pressures

<140/85 mm Hg; it is now recommended that blood pressure be reduced routinely.\(^10\)

About 20% of patients with TIA or stroke have significant stenosis or occlusion of at least 1 carotid artery.\(^11,12\) This is frequently associated with stenosis of the vertebral arteries, carotid siphon, and cerebral arteries.\(^13,14\) Although this group of patients has a high prevalence of hypertension\(^15\) and a particularly high risk of recurrent stroke,\(^16,17\) physicians have been concerned that blood pressure lowering may reduce cerebral perfusion. Loss of the normal autoregulatory capacity of the cerebral circulation, so that cerebral blood flow is directly dependent on perfusion pressure, is common in 2

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groups of patients: those with a carotid occlusion and those with bilateral ≥70% carotid stenosis. However, there is no mention of these groups in hypertension guidelines, and no data on the presence or severity of carotid disease were recorded in the trials of blood pressure lowering after stroke or TIA.

It has been argued that the results of PROGRESS cannot be extrapolated to patients with severe carotid disease. In the absence of trial data, observational data on the relationship between blood pressure and stroke risk have previously been a useful guide to the effects of blood pressure reduction in subsequent trials. However, although the presence of early carotid plaque is associated with increased arterial stiffness and a particular pattern of hypertension, there are no published observational data in patients with more advanced occlusive carotid disease. We therefore performed 2 analyses of the relationship between blood pressure and stroke risk in cohorts of patients with a recent TIA or minor ischemic stroke. First, we compared a cohort of patients with a low prevalence of carotid disease [United Kingdom Transient Ischemic Attack (UK-TIA) Aspirin Trial] with 2 cohorts with well-documented advanced carotid disease [European Carotid Surgery Trial (ECST) and North American Symptomatic Carotid Endarterectomy Trial (NASCET)]. Second, in ECST and NASCET, we determined the relationship between blood pressure and stroke risk in patients with unilateral carotid occlusion and patients with bilateral ≥70% carotid stenosis.

Methods

UK-TIA Trial

The UK-TIA Aspirin Trial was a randomized, double-blind, placebo-controlled, parallel-group trial of aspirin (1200 or 300 mg) versus placebo in 33 centers in the United Kingdom. Patients were eligible if they had had a TIA or ischemic stroke within the previous 6 months. Carotid imaging had been performed in 508 patients (21%) in whom large-artery disease was suspected. The proportions of patients with ≥50% and ≥70% symptomatic carotid stenosis were 6% (31 of 508) and 1% (5 of 508), respectively. A detailed clinical assessment, including recording of blood pressure (single measurement in clinic) and vascular risk factors, was performed before randomization. In total, 2435 patients were included in the final analysis. Patients were followed up by a neurologist every 4 months until death or the end of the trial. All strokes, myocardial infarctions, and deaths were recorded. Definitions and detailed methods are reported elsewhere.

ECST and NASCET

The designs of ECST and NASCET were very similar. ECST recruited from 100 centers in 14 European countries; NASCET, from 106 centers mainly in North America. Briefly, in each trial, patients were recruited if they had a recent carotid distribution TIA, minor ischemic stroke, nondisabling major ischemic stroke, or a retinal infarction and had a stenosis of the ipsilateral (symptomatic) carotid artery. Patients were seen by a neurologist or a stroke physician before randomization to confirm eligibility and had angiography (ideally by selective catheterization) of the symptomatic carotid artery and contralateral carotid artery. Clinical assessment included recording of blood pressure (single measurement in clinic) and vascular risk factors. Patients were randomized [50:50 in NASCET; 60:40 (surgery:no surgery) in ECST] to immediate carotid endarterectomy plus best medical treatment versus best medical treatment alone. Follow-up was performed by a neurologist or a stroke physician at 1, 3, 6, 9, and 12 months and every 4 months thereafter in NASCET and at 4 and 12 months and annually thereafter in ECST.

Data from ECST and NASCET have been pooled as part of an individual patient data meta-analysis of trials of endarterectomy for symptomatic carotid stenosis. This required reassessment of the carotid bifurcation angiograms from the 3018 ECST patients to ensure comparability of the measurements of degree of stenosis between ECST and NASCET. The definition of stroke used for the purpose of analysis of outcomes in the original ECST reports was also changed to be consistent with NASCET. All the necessary data had been recorded in ECST. For both studies, stroke was now defined as any cerebral or retinal event with symptoms lasting >24 hours.

Analysis

The relationship between blood pressure and stroke risk was determined in each of the 3 trials. All patients who were included in the original trial analyses were studied. Continuous measurements of blood pressure (mm Hg) at randomization were categorized in the same way as in the previous UK-TIA Aspirin Trial analysis8: diastolic (<80, 80 to 89, 90 to 99, ≥100 mm Hg) and systolic (<130, 130 to 149, 140 to 169, ≥170 mm Hg). Pulse pressure was categorized as ≤50, 51 to 60, 61 to 70, >70 mm Hg. Cox proportional-hazards analysis was used to determine the hazard ratio (HR) of stroke for each category, and confidence intervals were calculated by the method of floating absolute risk. The HR for the second category (SBP, 130 to 149 mm Hg; DBP, 80 to 89 mm Hg; pulse pressure, 51 to 60 mm Hg) was fixed at 1. The study outcome was time to first stroke (hemorrhage, infarct, or unknown type) in any territory, censoring for nonstroke death. All analyses were adjusted for age, sex, and previous coronary heart disease. The same analyses were performed for the relationship between blood pressure and myocardial infarction (fatal and nonfatal) in each of the 3 trials. Analysis of the relationship between blood pressure and risk is complicated by regression dilution bias, i.e., the reduction in the strength of the relationship that results from imprecise measurements of blood pressure. To correct for this bias, estimates of the regression dilution ratio over the appropriate period of follow-up were used to calculate the median “usual” blood pressure values in each category. This was done by multiplying the range between the median baseline values in the lower and upper categories by the relevant regression dilution coefficient, assuming symmetrical convergence about the midpoint of the second and third categories. HRs were then plotted against these median usual values, rather than the median baseline values, to show the relationship between usual blood pressure and risk. A nonparametric method was used to calculate regression dilution coefficients from follow-up blood pressure measurements. For SBP, DBP, and pulse pressure, the mean values in each of the 4 groups defined by baseline measurements were calculated at baseline and at each time of follow-up. The regression dilution coefficient at any time point is then given by the difference between the means of the upper and lower groups at that time point divided by the corresponding difference at baseline. Coefficients were calculated through repeated measurements at the median period of follow-up for each trial. Graphs of the regression coefficients at each time point on follow-up are available from the authors.

To obtain a corrected continuous variable analysis, the baseline measurements were transformed by allocating the median usual measurement for each category to every individual in that category. HRs per 20–mm Hg increase in SBP and 10–mm Hg increase in DBP and pulse pressure were then calculated by including this variable in the Cox model. The estimated coefficients and standard errors were used to test for significant differences in the relationships between blood pressure and risk between the different trial populations and the between groups defined according to severity of stenosis.

Analysis of the Effect of Unilateral Carotid Occlusion or Bilateral ≥70% Carotid Stenosis

The relationship between blood pressure and stroke risk was determined in patients with unilateral carotid occlusion versus patients...
without carotid occlusion and in patients with versus patients without bilateral ≥70% carotid stenosis. Patients with carotid occlusion and bilateral ≥70% carotid stenosis were studied because cerebral perfusion studies have shown that impaired perfusion is particularly common in these groups18–21 and because 70% linear stenosis (~90% area stenosis) is the point above which flow models show a clear reduction in volume flow across a stenosis.35,36

Analyses were confined to ECST and NASCET patients who had adequate angiographic views of both carotid arteries. In view of the relatively small number of patients with either carotid occlusion or bilateral carotid stenoses ≥70%, blood pressure was initially categorized as above or below the median value rather than into quartiles. The HRs for stroke risk in patients with blood pressures above versus below the median were derived from a Cox model adjusted for age, sex, and previous ischemic heart disease and stratified by study. The statistical significance of any differences in the relationship between blood pressure and stroke risk across the stenosis groups was determined by inclusion of an interaction term in the Cox model. Analyses were performed separately in patients who were randomized to medical treatment and in patients randomized to surgery. Analyses were also performed in the medical and surgical groups combined to study the relationship between blood pressure and risk of myocardial infarction. All analyses were performed with SPSS for Windows, version 10.0.5.

Results

Individual patient data were available for all patients in the original trials (2435 in UK-TIA, 3018 in ECST, 2885 in NASCET). Mean±SD follow-up was 80±28 months in the UK-TIA trial, 73±35 months in ECST, and 60±31 months in NASCET. The proportions of patients with ≥50% and ≥70% symptomatic carotid stenosis were 40% (n=1189) and 18% (n=507), respectively, in ECST and 53% (n=1517) and 23% (n=659) in NASCET. Other clinical characteristics are shown in Table 1. The UK-TIA population was younger than in ECST or NASCET, had fewer strokes, had more recent events, and included fewer diabetics. ECST patients tended to be younger than in NASCET, and their events had occurred less recently. Mean SBP and DBP at baseline were lowest in NASCET, but pulse pressure was lowest in the UK-TIA trial. A higher proportion of patients in NASCET were on blood pressure–lowering drugs at baseline. In ECST and NASCET, blood pressure was stable between baseline and follow-up at 1 year, whereas there were small declines in pressure in the UK-TIA trial.

In the UK-TIA trial, there were strong positive linear relationships (Figure 1) between usual SBP and stroke risk [HR per 20 mm Hg, 2.05; 95% confidence interval (CI), 1.56 to 2.70; \(P<0.001\)] and usual DBP and stroke risk [HR per 10 mm Hg, 2.44; 95% CI, 1.65 to 3.60; \(P<0.001\)] and a weaker relationship between pulse pressure and stroke risk (HR per 10 mm Hg, 1.46; 95% CI, 1.16 to 1.85; \(P=0.002\)). There was no heterogeneity in these relationships between the 3 treatment groups (SBP, \(P=0.79\); DBP, \(P=0.94\); pulse pressure, \(P=0.74\)). In the ECST and NASCET medical treatment groups, the relationships were weaker than in the UK-TIA trial and of only borderline statistical significance (Figure 1). Both trials showed a positive linear relationship between usual DBP and stroke risk (HR per 10 mm Hg: ECST, 1.37; 95% CI, 0.97 to 1.96; \(P=0.09\); NASCET, 1.51 95% CI, 1.06 to 2.02; \(P=0.01\)), but they were statistically significantly less steep than in the UK-TIA trial (both \(P<0.05\)). For usual SBP and pulse pressure, there was a positive linear relationship across the lower 3 quartiles but no further increase in risk in the top quartile. There were no differences between the trials in the relationship between blood pressure and risk of myocardial infarction.

Effect of Severe Carotid Disease

In both ECST and NASCET, an angiographic view of the symptomatic carotid artery was available in all patients, but an acceptable angiographic view of the contralateral carotid artery was available in only 2834 patients (94%) in ECST and 2648 patients (92%) in NASCET. These 5482 patients were included in the analysis of the effect of unilateral carotid occlusion and bilateral ≥70% carotid stenosis on the relationship between blood pressure and stroke risk. Unilateral carotid occlusion (contralateral to the symptomatic stenosis in all cases) was present in 252 patients. No patient had bilateral carotid occlusion. The HRs for stroke risk on medical treatment in patients with blood pressures above versus below

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**Table 1. Baseline Clinical Characteristics of the 3 Trial Populations**

<table>
<thead>
<tr>
<th>Trial</th>
<th>ECST</th>
<th>NASCET</th>
<th>UK-TIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>General, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>3018</td>
<td>2885</td>
<td>2435</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2168 (71.8)</td>
<td>2012 (69.7)</td>
<td>1787 (73.4)</td>
</tr>
<tr>
<td>Female</td>
<td>850 (28.2)</td>
<td>873 (30.3)</td>
<td>648 (26.6)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>1744 (57.8)</td>
<td>1161 (40.2)</td>
<td>1629 (66.9)</td>
</tr>
<tr>
<td>65–74</td>
<td>1098 (36.4)</td>
<td>1315 (45.6)</td>
<td>671 (27.6)</td>
</tr>
<tr>
<td>≥75</td>
<td>176 (5.8)</td>
<td>409 (14.2)</td>
<td>135 (5.5)</td>
</tr>
<tr>
<td>Presenting event, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1313 (43.5)</td>
<td>1306 (45.3)</td>
<td>506 (20.8)</td>
</tr>
<tr>
<td>Cerebral TIA</td>
<td>1083 (35.9)</td>
<td>1033 (35.8)</td>
<td>1585 (65.1)</td>
</tr>
<tr>
<td>Ocular event only</td>
<td>622 (20.6)</td>
<td>546 (18.9)</td>
<td>344 (14.1)</td>
</tr>
<tr>
<td>Time since last event, d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7</td>
<td>169 (5.6)</td>
<td>357 (12.4)</td>
<td>434 (17.9)</td>
</tr>
<tr>
<td>7–30</td>
<td>918 (30.4)</td>
<td>927 (32.1)</td>
<td>955 (39.4)</td>
</tr>
<tr>
<td>31–90</td>
<td>1160 (38.4)</td>
<td>1047 (36.3)</td>
<td>891 (36.8)</td>
</tr>
<tr>
<td>&gt;90</td>
<td>771 (25.6)</td>
<td>554 (19.2)</td>
<td>141 (5.8)</td>
</tr>
<tr>
<td>Medication, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure–lowering drug</td>
<td>1168 (38.7)</td>
<td>1577 (54.7)</td>
<td>660 (27.1)</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>362 (12.0)</td>
<td>571 (19.8)</td>
<td>243 (10.0)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>46 (1.5)</td>
<td>71 (2.5)</td>
<td>31 (1.3)</td>
</tr>
<tr>
<td>Treated diabetes</td>
<td>354 (11.7)</td>
<td>622 (21.6)</td>
<td>90 (3.7)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1400 (46.4)</td>
<td>1218 (42.2)</td>
<td>1292 (53.1)</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD SBP</td>
<td>150.7 (21.9)</td>
<td>146.2 (20.1)</td>
<td>150.8 (25.1)</td>
</tr>
<tr>
<td>Mean±SD DBP</td>
<td>86.2 (11.2)</td>
<td>81.4 (10.1)</td>
<td>87.9 (11.8)</td>
</tr>
<tr>
<td>Mean±SD pulse pressure</td>
<td>64.5 (17.2)</td>
<td>64.8 (16.7)</td>
<td>62.9 (17.7)</td>
</tr>
<tr>
<td>At 1-y follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD SBP</td>
<td>153.3 (22.4)</td>
<td>146.5 (20.9)</td>
<td>146.8 (23.2)</td>
</tr>
<tr>
<td>Mean±SD DBP</td>
<td>87.0 (10.8)</td>
<td>81.6 (10.3)</td>
<td>86.4 (11.5)</td>
</tr>
<tr>
<td>Mean±SD pulse pressure</td>
<td>66.3 (18.0)</td>
<td>64.9 (16.9)</td>
<td>60.4 (18.5)</td>
</tr>
</tbody>
</table>

*Data unavailable on 14 patients in the UK-TIA trial.*
The median are shown in Table 2. There were no definite differences between the patients with and without carotid occlusion. There was a trend toward a lower risk of stroke in patients with higher DBP in the carotid occlusion group, but this was not statistically significantly different from the positive relationship between DBP and stroke risk in the no-occlusion group.

Of the 1216 patients with ≥70% symptomatic carotid stenosis, 150 (12.3%) had bilateral ≥70% carotid stenosis. In this group, there were statistically significant negative relationships between SBP and stroke risk on medical treatment (HR, 0.41; 95% CI, 0.19 to 0.90; \(P=0.02\)) and pulse pressure and stroke risk (HR, 0.43; 95% CI, 0.20 to 0.91; \(P=0.02\)) (Table 2) and a negative trend for DBP (HR, 0.58; 95% CI, 0.25 to 1.33; \(P=0.19\)). The difference from the positive relationships in patients without bilateral ≥70% carotid stenosis was highly statistically significant for SBP (\(P=0.002\)) and pulse pressure (\(P=0.003\)) and of borderline significance for DBP (\(P=0.06\)). These interactions were not present in patients who had carotid endarterectomy in the surgery group (SBP, \(P=0.87\); DBP, \(P=0.12\); pulse pressure, \(P=0.71\)) or for the risk of myocardial infarction on follow-up (SBP, \(P=0.52\); DBP, \(P=0.86\); pulse pressure, \(P=0.38\)).

To further explore the effect of ≥70% carotid stenosis on the relationship between blood pressure and stroke risk, we divided patients into 3 mutually exclusive carotid stenosis groups: both stenoses <70%, unilateral ≥70% stenosis, and bilateral ≥70% stenosis. Figure 2 shows the relationship between stroke risk and the predefined SBP categories in the 3 stenosis groups after adjustment for age, sex, and previous ischemic heart disease. Figure 1. Relationships between usual SBP, usual DBP, usual pulse pressure, and stroke risk in the UK-TIA trial, NASCET, and ECST. HRs are derived from a Cox model after adjustment for age, sex, and previous ischemic heart disease.
TABLE 2. HRs (95% CI) for Risk of Stroke in Patients With Blood Pressures Above Versus Below the Median Value and Categorized According to Severity of Carotid Disease

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio (95% CI) [P]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBP*</td>
</tr>
<tr>
<td>Contralateral carotid occlusion</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.29 (1.09–1.52) [0.003]</td>
</tr>
<tr>
<td>Yes</td>
<td>1.38 (0.69–2.77) [0.35]</td>
</tr>
<tr>
<td>Interaction</td>
<td>[0.56]</td>
</tr>
<tr>
<td>Both stenoses &gt;70%</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.37 (1.16–1.61) [0.0002]</td>
</tr>
<tr>
<td>Yes</td>
<td>0.41 (0.19–0.90) [0.02]</td>
</tr>
<tr>
<td>Interaction</td>
<td>[0.002]</td>
</tr>
</tbody>
</table>

HRs are derived from a Cox proportional-hazards-model-stratified by trial and adjusted for age, sex, and previous coronary heart disease. Statistical significance of the interaction between the severity of carotid disease and relationship between blood pressure and stroke risk was derived from an interaction term in the Cox model.

*Median blood pressures (mm Hg) were as follows: contralateral carotid occlusions: SBP, 146 mm Hg; DBP, 82 mm Hg; pulse pressure, 68 mm Hg; both stenoses >70%: SBP, 146 mm Hg, DBP, 82 mm Hg; pulse pressure, 70 mm Hg.

with unilateral ≥70% stenosis. However, there was a statistically significant negative linear relationship in patients with bilateral ≥70% stenosis (P=0.04) that was significantly different from the relationships in patients with unilateral ≥70% stenosis (P=0.005) and patients with both stenoses <70% (P=0.007). This heterogeneity in the SBP–stroke risk relationship remained significant when assessed across the 3 stenosis groups (P=0.01). However, there was no similar heterogeneity when the analysis was performed in patients who had undergone endarterectomy in the surgery group (P=0.67).

Table 3 shows an analysis of the risk of stroke within each of the prespecified blood pressure categories stratified according to the stenosis groups described above. The effect of stenosis group on stroke risk is confined to the 2 lower blood pressure groups. Compared with patients with both stenoses <70%, the relative hazard of stroke in patients with bilateral ≥70% stenosis was 2.54 (95% CI, 1.47 to 4.39; P=0.001) at SBP of 130 to 149 mm Hg and 5.97 (95% CI, 2.43 to 14.68; P<0.001) at SBP of <130 mm Hg. The 5-year absolute risk of stroke on medical treatment in this stenosis group was 64.3% (95% CI, 44.5 to 84.6) in patients with SBP below the median value compared with 24.2% (95% CI, 10.0 to 38.2; P=0.002) in patients with SBP above the median. This negative relationship between SBP and stroke risk was present in both ECST (50% versus 20%, P=0.19) and NASCET (68% versus 22%, P=0.006) but was reversed after endarterectomy: 13.4% (95% CI, 2.0 to 24.9) versus 18.3% (95% CI, 6.3 to 3.05) (P=0.6).

Discussion

Because the presence and severity of carotid plaque have been shown to be positively associated with increased aortic stiffness and increased SBP and pulse pressure,26–28 our first aim was to compare the relationship between blood pressure and stroke risk in ECST and NASCET, in which all patients had carotid stenosis, with that in the UK-TIA, in which few patients had carotid stenosis. The low prevalence of carotid stenosis in those UK-TIA patients who had angiography is likely to be an overestimate of the overall prevalence because angiography was more likely to be done if there was a suspicion of carotid stenosis (eg, a carotid bruit or large-vessel disease in another territory). There were no differences between the cohorts in SBP and pulse pressure at baseline, but a higher proportion of patients were on blood pressure–lowering medication in ECST and NASCET than in the UK-TIA trial. However, there were significant differences between the UK-TIA trial and ECST and NASCET in the relationships between blood pressure and stroke risk. Overall, the relationships were less steep and less clearly linear in ECST and NASCET. Given that there were no differences between cohorts in the relationship between blood pressure and risk of myocardial infarction, the differences in the relationships between blood pressure and stroke risk are most likely to reflect differences in the predominant cerebrovascular pathology.

The explanation for the leveling off of the relationships between SBP and pulse pressure and stroke risk in the top quartile of blood pressures in ECST and NASCET but not in the UK-TIA trial is unclear. The same trend was present in both trials, suggesting that it was not due to chance. It is possible that it was due to more active treatment of hypertension on follow-up in patients in the top quartile of baseline SBP, but no similar leveling off of stroke risk was seen for DBP, and there was no similar effect in the UK-TIA trial. Another possibility is that in the UK-TIA trial a greater proportion of strokes may have been lacunar infarctions caused by small-vessel disease, whereas in the other 2 trials, most strokes were probably atheroembolic. Overall, therefore, our first conclusion is that the relationships between blood pressure and stroke risk are less steep in populations with a high prevalence of carotid disease than in more general populations of patients with previous TIA and stroke. However, the overall relationships remain positive.

Our second aim was to determine the relationship between blood pressure and stroke risk in patients with a high likelihood...
of impaired cerebral perfusion resulting from severe carotid disease. About 40% to 50% of patients with symptomatic carotid occlusion have impaired perfusion of the ipsilateral cerebral hemisphere.\textsuperscript{18–21} The remainder having sufficient blood flow via collateral vessels to maintain perfusion. We did not find any difference in the relationship between blood pressure and stroke risk on medical treatment between patients with and without unilateral carotid occlusion. These findings support the extrapolation of the results of blood pressure–lowering trials to this group but should be interpreted with caution because we had no physiological data on which patients had reduced perfusion and because the prevalence of impaired perfusion is likely to have been lower distal to these predominantly asymptomatic carotid occlusions (contralateral to the recently symptomatic stenosis) than in previous reports in patients with symptomatic occlusion.\textsuperscript{18–21}

We did find evidence of an altered relationship between blood pressure and stroke risk in patients with bilateral \(\geq 70\%\) stenosis. Impaired cerebral perfusion is present in the majority of such patients and is often severe.\textsuperscript{18–21} The risk of stroke on medical treatment was very high in patients with blood pressures in the lower half of the distribution in both ECST and NASCET, and the interaction between the presence of bilateral \(\geq 70\%\) stenosis and the blood pressure–stroke risk relationship was highly statistically significant. The absence of similar interactions for the risk of myocardial infarction and for the risk of stroke in patients who had been randomized to endarterectomy suggests that this was causal. These findings suggest that aggressive blood pressure lowering may not be safe in patients with bilateral severe carotid disease and that the results of trials of blood pressure lowering after TIA or stroke should not be generalized to this group. Only 2 studies have looked at the physiological effects of blood pressure lowering in patients with carotid disease,\textsuperscript{37,38} but they were small, and most patients had only unilateral moderate or severe carotid stenosis. The prevalence of impaired cerebral perfusion in patients with unilateral \(\geq 70\%\) carotid stenosis is only \(\sim 5\%).\textsuperscript{39} The absence of an effect of unilateral \(\geq 70\%\) carotid stenosis on the relationship between blood pressure and stroke risk in our study is consistent with this finding.

Our results also suggest that severe bilateral stenosis is an additional indication for revascularization to allow reduction in blood pressure to levels that will not be harmful to the heart, kidneys, and other organs. However, our data do not necessarily increase the justification for surgery in patients with asymptomatic carotid stenosis with contralateral \(\geq 70\%\) stenosis or occlusion. Although endarterectomy does improve cerebral hemodynamics in patients with contralateral carotid occlusion,\textsuperscript{40} contralateral occlusion was not associated with increased benefit from surgery in the ACAS trial,\textsuperscript{41} and our results refer only to patients with recently symptomatic carotid stenosis. It is important to note that bilateral \(\geq 70\%\) carotid stenosis is uncommon. Very few population-based studies have reported the prevalence of bilateral severe stenosis specifically, but since only about 5% of the elderly population are found to have one severe carotid stenosis (unilateral or bilateral),\textsuperscript{42–44} the prevalence of bilateral severe stenosis is probably only 1% to 2%. A prevalence of 1.5% was reported in one study of patients aged 36 to 84 years in Moscow.\textsuperscript{45} However, patients with bilateral carotid disease are encountered more frequently in neurology and vascular clinics and consequently in randomized trials of treatments for carotid disease. For example, in the Asymptomatic Carotid Atherosclerosis Study (ACAS) in which all patients had \(\geq 60\%\) “ipsilateral” carotid stenosis, \(\sim 30\%\) of patients had \(\geq 60\%\) contralateral carotid stenosis and \(\sim 12\%\) had \(\geq 80\%\) contralateral stenosis.\textsuperscript{46} Similarly, in ECST and NASCET, 12.3% of patients (150 of 1216) with recently symptomatic \(\geq 70\%\) carotid stenosis had a contralateral \(\geq 70\%\) carotid stenosis or occlusion. Some impression of the prevalence of bilateral...
severe carotid disease in more routine clinical practice can be gained from the prevalence of contralateral carotid occlusion in patients undergoing endarterectomy. A systematic review of surgical case series found that the reported prevalence ranged from 7% to 15% with an overall frequency of 12.5% (887 of 7116). Thus, bilateral severe carotid disease is not uncommon in specialist clinical practice and in randomized trials of treatments for carotid disease. However, it is rare in both the general population and the broader population of patients presenting with TIA or ischemic stroke. For example, because only 20% of patients with stroke or TIA but that it remains positive overall. It is however, have a high risk of recurrent strokes.

Our study has some potential shortcomings. First, analysis of the relationships between blood pressure and stroke risk in patients with bilateral >70% carotid stenosis was based on only 29 strokes in 150 patients. Nevertheless, the differences between this group and those patients with less severe carotid disease were highly statistically significant. Second, our results may have been affected by treatment of hypertension during follow-up. We did not adjust our analyses for additional medication prescribed on follow-up because there was little change in the mean blood pressures on follow-up in any of the trials and because we wanted to study the relationship between stroke risk and the blood pressure at the time when a decision about blood pressure lowering would usually be made.

Conclusions
We have shown that the relationship between blood pressure and stroke risk is less steep in patients with symptomatic carotid stenosis than in more general populations of patients with stroke or TIA but that it remains positive overall. It is thus safe to treat hypertension in the vast majority of patients with stroke or TIA. However, there was a negative relationship between blood pressure and stroke risk in the small proportion of patients who have bilateral >70% carotid stenosis, suggesting that aggressive blood pressure lowering may not be advisable in this group or that they may require revascularization to render the treatment of their hypertension safe. More data are required on the effects of blood pressure lowering on cerebral perfusion in patients with bilateral >70% carotid stenosis, and guidelines on treatment of hypertension should highlight the need for special consideration.

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References
For the secondary prevention of stroke, recent guidelines\(^1,2\) recommend the prescription of blood-pressure–lowering drugs to normotensive and hypertensive patients with previous cerebrovascular complications. Two large placebo-controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet*. 2003;361:107–116.


randomized to indapamide 2.5 mg/d or matching placebo. Follow-up averaged 2 years. Indapamide decreased systolic/ diastolic blood pressure by 5/2 mm Hg and stroke recurrence by 29% ($P<0.001$). The Perindopril Protection Against Recurrent Stroke Study (PROGRESS)$^4$ included 3753 whites and 2352 Asians. Patients randomized to active treatment received perindopril 4 mg/d either alone or in combination with indapamide 2.5 mg/d. Over 4 years of follow-up, active treatment reduced blood pressure by 9/4 mm Hg and the incidence of recurrent stroke by 28% ($P<0.001$). In both trials, hypertensive and nonhypertensive patients benefited from treatment. The blood pressure thresholds delineating hypertension were 140/90 mm Hg in PATS and 160/ 90 mm Hg in PROGRESS. In the nonhypertensive subgroups, the relative risk reductions in stroke recurrence amounted to 49% (n = 913) and 27% (n = 3189), respectively. Neither PATS$^3$ nor PROGRESS$^4$ indicated the level to which blood pressure should be lowered, although goals of <130 mm Hg systolic and 85 mm Hg diastolic, corresponding to current definitions of normotension,$^2$ seem reasonable when such targets can be safely reached without side effects.

For various reasons, the PATS$^3$ and PROGRESS$^4$ findings cannot be extrapolated to patients with occlusive or stenotic disease of the main arteries, which sustain blood flow to the brain. About 20% of patients with transient ischemic attack or stroke have atherosclerotic lesions of the carotid arteries.$^5$ In the presence of carotid lesions, blood pressure falls distal to the stenosis when it narrows the lumen by $\geq 70\%$ or when the residual lumen diameter drops to $\leq 2$ mm.$^6$ In the absence of sufficient collateral circulation, low cerebral perfusion pressure can cause ischemia in the watershed areas between the cerebral vessels.$^6$ Furthermore, the collateral circulation to the brain may be impaired because of an incomplete or hypofunctional circle of Willis$^7$ or stenosis or occlusion of either the contralateral carotid artery or the basilar artery.$^6$ In cases of severe carotid atherosclerosis, cerebral ischemia is more likely to arise when blood pressure proximal to the stenosis is within the nonhypertensive range and when it would be indiscriminately lowered. Finally, regardless of treatment status, patients with high blood pressure have a diminished capacity to autoregulate cerebral blood flow,$^8$ so that they are more vulnerable to the potentially harmful effects of an excessive or too rapid drop in the perfusion pressure.

With regard to the generalizability of the PATS$^3$ and PROGRESS$^4$ findings, the report of Rothwell et al$^9$ raises an important clinical issue. In a quantitative overview of individual patient data,$^9$ these researchers studied the relation between stroke risk and blood pressure in patients with a history of transient ischemic attack or minor stroke who were randomized in the European Carotid Surgery Trial (ECST),$^10$ the North American Symptomatic Carotid Endarterectomy Trial (NASCET),$^{11}$ or the United Kingdom Transient Ischemic Attack Aspirin Trial (UK-TIA).$^{12}$ Of the ECST and NASCET patients, 64.6% and 38.5% had ipsilateral carotid stenosis of $\geq 50\%$, whereas among the UK-TIA patients, this proportion was estimated to be only 6.1%. In the UK-TIA trial, the risk of stroke doubled for each 20–mm Hg increment in systolic blood pressure, whereas in the medically treated ECST and NASCET patients, the corresponding relative risks only approximated 50% and were not significant or were just borderline significant. Furthermore, among the ECST and NASCET patients with unilateral carotid lesions, the relation between stroke and blood pressure was positive, whereas among those with bilateral lesions of $\geq 70\%$, lower blood pressure was even associated with a greater risk of stroke. This interaction between the degree of carotid artery stenosis and blood pressure was specific because it was not present after carotid endarterectomy and because it was not observed in relation to myocardial infarction.$^9$

The meta-analysis of Rothwell et al$^9$ should be interpreted within the context of its limitations. Only 508 UK-TIA patients (20.8%) underwent carotid imaging. At baseline, the UK-TIA population was younger than the ECST or NASCET participants, had fewer and more recent qualifying strokes, and included fewer patients with diabetes mellitus. To what extent these differences between trials may have affected the pooled results$^9$ is difficult to ascertain. Furthermore, to correct for the imprecision in blood pressure measurements at baseline, Rothwell et al corrected their analysis for regression dilution bias. This procedure increases the slope of the relation between the risk of stroke and blood pressure.$^{13}$ From an epidemiological point of view, it provides more accurate estimates of the true impact of blood pressure on cardiovascular outcomes. However, doctors rarely have the opportunity to repeat blood pressure measurements over several years to determine a patient’s usual blood pressure. Within the much shorter time span required for therapeutic decisions, clinicians can rely on 24-hour blood pressure monitoring to approximate a patient’s usual blood pressure.$^{13}$

In the PROGRESS trial,$^4$ treatment with perindopril alone lowered blood pressure by 5/3 mm Hg but did not affect stroke recurrence (95% confidence interval, −19 to 23), whereas in the PATS trial,$^3$ for a similar decrease in blood pressure (5/ 2 mm Hg), monotherapy with indapamide reduced the incidence of stroke by 29% (95% confidence interval, 22 to 43). Despite these findings, experts$^8,14$ recommended that for patients with a history of cerebrovascular disease, long-term treatment with perindopril should be routinely considered, wherever possible in combination with indapamide, regardless of blood pressure level, type of qualifying cerebrovascular event, or geographic region. Beyond the inconsistency between these recommendations for medical treatment and the evidence, the report by Rothwell et al$^9$ highlights that, in terms of priority, immediate blood pressure lowering might not be advisable for the group of stroke patients who have bilateral carotid lesions with a lumen narrowing of $\geq 70\%$. This group may first require revascularization to render safe the treatment of hypertension.$^{15}$ Moreover, in the presence of significant carotid atherosclerosis, risk factor modification, including lipid-lowering treatment, should help to halt or stabilize plaque formation.$^{15}$ Antiplatelet therapy with low-dose aspirin or thienopyridines in most patients and antithrombotic therapy in selected patients with atrial fibrillation are also indicated.$^{15}$ In conclusion, although progressive blood pressure lowering is key to the secondary prevention of stroke,$^{3,4}$ this strategy should be part of a more holistic therapeutic approach, which also accounts for anomalies in the cerebral circulation and risk factors other than just blood pressure.
References
Relationship Between Blood Pressure and Stroke Risk in Patients With Symptomatic Carotid Occlusive Disease

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