Stroke

Relationship Between Blood Pressure and Stroke Recurrence in Patients With Intracranial Arterial Stenosis

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Background—Many clinicians allow blood pressure to run high in patients with intracranial stenosis to protect against hypoperfusion. We sought to determine whether higher blood pressure decreases the risk of stroke in these patients.

Methods and Results—Data on 567 patients in the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial were analyzed. Time to ischemic stroke and stroke in the same territory of the stenotic vessel was compared in patients grouped by mean systolic blood pressure (SBP) and mean diastolic blood pressure (DBP) during the study. Additional analyses were based on severity and location of stenosis. Ischemic stroke risk increased with increasing mean SBP and DBP on univariate analysis (P<0.0001, P<0.0001) and after adjustment for risk factors (P=0.0008, P<0.0001). Elevated mean SBP and DBP also resulted in increased risk of stroke in the territory in univariate (P=0.0065, P<0.0001) and adjusted (P=0.0002, P=0.0005) analyses. The increased risk of stroke with increasing SBP was driven largely by patients in the highest SBP group. Patients with moderate (<70%) stenosis had increased risk of stroke (P<0.0001, P=0.003) and stroke in the territory (P=0.0002, P=0.010) with increased SBP and DBP. Patients with severe (≥70%) stenosis had increased risk of stroke and stroke in the territory with elevated DBP (P=0.004, P=0.004).

Conclusions—In patients with intracranial stenosis, higher blood pressure is associated with increased (not decreased) risk of ischemic stroke and stroke in the territory of the stenotic vessel. These findings argue strongly against the common clinical practice of maintaining high blood pressure in patients with intracranial stenosis. (Circulation. 2007;115:2969-2975.)

Key Words: blood pressure • cerebral infarction • cerebrovascular circulation • hypertension • intracranial arteriosclerosis • prevention • stenosis

The optimal target blood pressure level in patients with symptomatic stenosis of a major intracranial artery (middle cerebral artery, internal carotid artery, vertebral artery, or basilar artery) is unknown. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) does not provide target blood pressure levels for stroke patients specifically but recommends a blood pressure <140/90 mm Hg in general to decrease stroke and cardiovascular risk.1 Clinical trials and epidemiological studies of stroke patients have demonstrated that lowering blood pressure reduces the risk of stroke.2-6 However, it is common practice to allow blood pressures ≥140/90 mm Hg in patients with intracranial stenosis in the United States. This practice is based on expert opinion7-9 and studies that suggest that lowering blood pressure may increase the risk of stroke in some patients with severe carotid stenosis.10

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The recently completed Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial, which compared aspirin and warfarin in patients with symptomatic 50% to 99% stenosis of a major intracranial artery, provided a unique opportunity to evaluate the relationship between blood pressure level and risk of stroke in these patients.

Methods

Study Design
Patients enrolled in the WASID trial were included in this post hoc analysis. The WASID trial was an investigator-initiated, randomized, double-blind, multicenter clinical trial conducted at 59 sites in North America to compare aspirin with warfarin in patients with symptomatic intracranial stenosis.11 Two of the 569 patients enrolled in WASID had no blood pressure information and therefore were excluded. Details of the study design have
been published previously. All patients had a transient ischemic attack or nondisabling stroke within 90 days that was attributable to angiographically verified 50% to 99% stenosis of a major intracranial artery (carotid, middle cerebral, vertebral, or basilar). Patients with tandem extracranial carotid stenosis, cardiac source of embolism, or uncontrolled severe hypertension (systolic blood pressure [SBP] >180 mm Hg or diastolic blood pressure [DBP] >115 mm Hg) were excluded.

During follow-up, patients were contacted monthly by phone and seen in person every 4 months to determine whether any strokes had occurred. All patients had blood pressure measured at baseline and every 4-month visit. Blood pressure was measured from the right arm with the patient sitting at rest with the arm supported at the level of the heart. At each visit, if the initial blood pressure reading was >140/90 mm Hg, a second reading was taken at the end of the visit, and the lower of the 2 readings was used.

Elevated blood pressure was managed by the study neurologist and the patient’s primary care physician, who were initially requested to follow the guidelines established in the National High Blood Pressure Education Program (1993) consensus document and subsequently the JNC7 guidelines when they were released in 2003.

Patients were followed up to the time of a stroke, death, or a common termination date (Final follow-up visits for patients who were alive without a stroke were done during August 2003). Ischemic stroke was defined as a new focal neurological deficit of sudden onset lasting ≥24 hours and not caused by hemorrhage. Ischemic stroke was considered “possibly in the same territory of the symptomatic stenotic intracranial artery when the neurological signs correlated with a new infarct on computed tomography or magnetic resonance imaging in an area of the brain supplied by the symptomatic stenotic artery. Ischemic stroke was considered “probably in the territory of the symptomatic stenotic artery when the neurological signs localized to an area of the brain supplied by the symptomatic stenotic artery but without new infarct on brain imaging. In this analysis, ischemic strokes that were definitely or probably in the territory of the stenotic artery were considered in the territory. The territory of ischemic stroke was determined by the local investigator and independently by a central investigator. In cases when disagreement existed as to whether the stroke was in or out of the territory, a second central investigator independently adjudicated the location, and the classification made by 2 of the 3 investigators was used.

Statistical Analyses
Because no difference was found between the 2 treatment arms with respect to ischemic stroke prevention, patients assigned to warfarin or aspirin were combined in this analysis. Summary statistics for continuous variables are reported as mean±SD. All analyses were done with SAS/STAT (9.1.3) software (SAS Institute, Cary, NC).

Primary Analysis
Blood pressure was averaged over the course of the entire study period for each patient. For the primary analysis, the risk of ischemic stroke in any vascular territory and the risk of stroke within the territory of the stenotic vessel were compared in groups of patients stratified by mean SBP (<119, 120 to 139, 140 to 159, ≥160 mm Hg) and mean DBP (<79, 80 to 89, ≥90 mm Hg). These blood pressure categories were chosen on the basis of the JNC7 classification of normal blood pressure, prehypertension, stage 1 hypertension, and stage 2 hypertension. The DBP categories of JNC7 stage 1 (90 to 99 mm Hg) and 2 (≥100 mm Hg) hypertension were combined because of the small number of patients with stage 2 hypertension (n=3).

The cumulative probability of an ischemic event was estimated with the product-limit method. A log-rank test was used to test whether an increasing category of mean SBP or DBP was associated with increased risk of any ischemic stroke or ischemic stroke in the territory of the stenotic artery. Cox proportional-hazards regression was used to estimate hazard ratios for increasing category of mean SBP or DBP, with the lowest category as the reference, both unadjusted and adjusted for other risk factors potentially related to stroke.

The assumption of proportional hazards was tested by fitting a model that included terms for the blood pressure categories and the interaction of these categories with the logarithm of follow-up time. The statistical significance of the interaction terms was assessed with a simultaneous test; a nonsignificant test result (P>0.05) indicated that the proportional-hazards assumption was met. The assumption was met for SBP and DBP for any ischemic stroke and for SBP for stroke in the territory. The assumption was not met for DBP for stroke in the territory (P=0.0018). However, a graph of the hazard functions for the blood pressure categories suggested that the functions were parallel until later follow-up times when relatively few events occurred (ie, the majority [83%] of the events occurred during the first year, and the interactions were not significant when times to event or last follow-up after 1 year were censored at that time [P=0.089]). Therefore, we proceeded as if the assumption were met.

Subgroup Analyses
The analyses comparing categories of mean blood pressure described above were done for subgroups of patients with moderate (<70%) and severe (≥70%) intracranial stenosis and by arterial location of intracranial stenosis (ie, anterior circulation [carotid or middle cerebral] and posterior circulation [vertebral or basilar]). These analyses were done separately within each subgroup. In addition, in an effort to determine the effect of blood pressure on stroke risk early in the follow-up period, an analysis was done in which events and last follow-up visits occurring after 4 months were censored at 4 months.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
Patient Characteristics
At baseline, the mean age of the 567 patients was 63.6±11.4 years; 38% were female, 30% were black, 38% were diabetic, 71% had a lipid disorder, and 84% were hypertensive. The average blood pressure throughout the follow-up period of all patients was 140±13/77±8 mm Hg. Two hundred sixty-seven patients (47%) had a mean SBP during follow-up that was greater than the JNC7-recommended target SBP of <140 mm Hg (stage 1 and 2 hypertension), and 34 (6%) had mean DBP that exceeded the JNC7 target DBP of <90 mm Hg (stage 1 and 2 hypertension). The mean follow-up time was 1.8±1.3 years. The average number of blood pressure readings during that time was 5.8±3.6. With regard to antihypertensive therapy, 18% of patients were taking 1, 25% were taking 2, 22% were taking 3, and 24% of patients were taking ≥4 antihypertensive medications. The percentage of patients taking no antihypertensive medications was 11%. Table 1 shows the percentage of patients taking antihypertensive medications from various drug classes throughout the course of the study.

Relationship of Blood Pressure and Stroke Risk
When the data were analyzed using the JNC7 categories for blood pressure, the risk of any ischemic stroke was found to increase with increasing mean SBP and DBP (P<0.0001 and P<0.0001, respectively) using a log-rank trend test (Figure, A). Increasing mean SBP and DBP were associated with increased risk of ischemic stroke in...
the territory of the stenotic artery ($P=0.0065$ and $P<0.0001$, respectively) (Figure, B). Hazard ratios and 95% CIs are presented in Table 2.

The increase in stroke risk with increasing SBP appears to be driven largely by events in the highest blood pressure group. When analyzed without the highest group (SBP $\geq 160$ mm Hg), no significant difference existed in stroke rates among the blood pressure groups. This may be due to the small sample size in some groups.

### Relationship of Blood Pressure and Stroke Adjusted for Risk Factors

Elevated mean SBP ($P=0.0008$) and DBP ($P<0.0001$) were associated with increased risk of stroke after adjustment for age, type of qualifying event (transient ischemic attack versus stroke), gender, body mass index, time from qualifying event, history of diabetes mellitus, history of hypertension, race, percentage of intracranial artery stenosis at study entry, and hyperlipidemia (Table 2). Similarly, stroke in the territory also was increased in patients with elevated mean SBP ($P=0.0002$) and DBP ($P=0.0005$) after adjustment for the factors listed above.

### Blood Pressure Versus Stroke Risk Within Patient Subgroups

**Moderate and Severe Stenosis**

There were 353 patients with moderate ($<70\%$) stenosis, 206 patients with severe ($\geq 70\%$) stenosis, and 8 patients missing a central reading of percent stenosis. Among the patients with moderate stenosis, increasing mean SBP and DBP were associated with a greater risk of any ischemic stroke ($P<0.0001$ and $P=0.003$) (Table 3) and stroke in the territory ($P=0.0002$ and 0.010), similar to the group at large.

In the patients with severe stenosis, only increasing mean DBP was significantly associated with increased risk of any ischemic stroke ($P=0.004$) or ischemic stroke within the territory ($P=0.004$). Although increasing mean SBP was not associated with an increased risk of stroke ($P=0.32$) or stroke in the territory ($P=0.43$) in patients

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**TABLE 1. Percentage of Patients Taking Hypertensive Agents From Each Class at Any Point Throughout the Follow-Up Period**

<table>
<thead>
<tr>
<th>Antihypertensive Class</th>
<th>Patients on Medication in Class at Any Point, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
<td>61</td>
</tr>
<tr>
<td>$\beta$-Blocker</td>
<td>48</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>45</td>
</tr>
<tr>
<td>Diuretic</td>
<td>45</td>
</tr>
<tr>
<td>Vasodilator</td>
<td>17</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>16</td>
</tr>
<tr>
<td>$\alpha$-Agonist</td>
<td>11</td>
</tr>
</tbody>
</table>
with severe stenosis, no evidence existed for a reduction in stroke risk with higher blood pressures (Table 4).

**Anterior and Posterior Circulation**

In analyses of data from the subgroup of patients with stenotic posterior circulation arteries (vertebral and basilar, \( n = 243 \)), the risk of ischemic stroke was significantly increased with increasing mean SBP and DBP (\( P = 0.0012 \) and \( P = 0.0009 \)). Ischemic stroke within the territory of the stenotic artery also was significantly increased in patients with posterior circulation stenosis with increasing mean SBP and DBP (\( P = 0.0093 \) and \( P = 0.008 \)). In patients with anterior circulation stenosis (carotid and middle cerebral, \( n = 306 \)), the risk of ischemic stroke also was significantly increased with increasing mean SBP and DBP (\( P = 0.0092 \) and \( P = 0.0023 \)). Ischemic stroke within the territory of the stenotic artery was not significantly increased in patients with anterior circulation stenosis with increasing mean SBP (\( P = 0.24 \)) but was associated with increasing mean DBP (\( P = 0.0075 \)).

**TABLE 2. Hazard Ratios and 95% CIs According to Average SBP and DBP for Any Ischemic Stroke and Stroke in Territory**

<table>
<thead>
<tr>
<th>Blood Pressure, mm Hg</th>
<th>Sample Size, n</th>
<th>Events, n (%)</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>Events, n (%)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SBP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \leq 119 )</td>
<td>32</td>
<td>3 (9)</td>
<td>...</td>
<td>...</td>
<td>3 (9)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>120–139</td>
<td>268</td>
<td>42 (16)</td>
<td>1.6 (0.5–5.3)</td>
<td>0.046</td>
<td>35 (13)</td>
<td>1.4 (0.4–4.5)</td>
<td>0.590</td>
</tr>
<tr>
<td>140–159</td>
<td>218</td>
<td>40 (18)</td>
<td>2.0 (0.6–6.4)</td>
<td>0.252</td>
<td>22 (10)</td>
<td>1.1 (0.3–3.7)</td>
<td>0.881</td>
</tr>
<tr>
<td>( \geq 160 )</td>
<td>49</td>
<td>21 (43)</td>
<td>5.8 (1.7–19.6)</td>
<td>0.004</td>
<td>17 (35)</td>
<td>4.7 (1.4–16.0)</td>
<td>0.014</td>
</tr>
<tr>
<td><strong>DBP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \leq 79 )</td>
<td>348</td>
<td>46 (13)</td>
<td>...</td>
<td>...</td>
<td>32 (9)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>80–89</td>
<td>185</td>
<td>49 (26)</td>
<td>2.1 (1.4–3.2)</td>
<td>0.0003</td>
<td>36 (19)</td>
<td>2.2 (1.4–3.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>( \geq 90 )</td>
<td>34</td>
<td>11 (32)</td>
<td>3.0 (1.6–5.8)</td>
<td>0.001</td>
<td>9 (26)</td>
<td>3.5 (1.7–7.3)</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

*The hazard ratios (HRs) and probability values are for comparisons between the lowest blood pressure category and each of the higher blood pressure categories.

**History of Hypertension**

There were 475 patients with a history of hypertension at study entry. These patients demonstrated an increased risk of ischemic stroke (\( P = 0.0003 \) and \( P < 0.0001 \)) and an increased risk of ischemic stroke in the territory (\( P = 0.015 \) and \( P < 0.0001 \)) with increasing mean SBP and DBP, similar to the group at large.

**Early Events**

Fifty-five patients had an ischemic stroke within the first 4 months of the follow-up period. In analyses of only these early strokes, increasing mean SBP and DBP did not have a significant reduction on the risk of stroke overall or stroke in the territory.

**Discussion**

The practice of maintaining higher blood pressure in patients with symptomatic stenosis of a major intracranial artery to protect against hypoperfusion and stroke is not...
supported by the results of this study. In fact, higher SBPs and DBPs were associated with increased risk of ischemic stroke overall and an increase in stroke in the territory of the stenotic vessel. Although the high risk of stroke with increased SBP was driven largely by the SBP ≥ 160 mm Hg group, no evidence existed that maintaining SBP in a moderately hypertensive range (ie, 140 to 159 mm Hg), as is commonly done in clinical practice, was protective against stroke. Previous studies have demonstrated that patients with heterogeneous and often undefined causes of stroke have a lower risk of stroke recurrence with lowering of blood pressure, but this study is the first to demonstrate this finding among patients with symptomatic intracranial stenosis.

The increased risk of stroke in the same territory in patients with higher blood pressures may have been due to the effects of elevated blood pressure on the progression of atherosclerosis. The severity of intracranial atherosclerosis, which is the most important predictor of the risk of stroke in these patients, has been shown to be related to blood pressure in a multivariate analysis. This suggests that the association between higher blood pressure and increased risk of stroke in the same territory may be explained by progressive stenosis in patients with poorly controlled blood pressure. Ischemic stroke in territories other than that of the symptomatic intracranial artery in patients with higher blood pressures may have been related to penetrating artery disease or progression of previously asymptomatic large artery disease.

Another possible explanation for the lower rates of stroke among patients with lower blood pressures is that specific antihypertensive agents (eg, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and diuretics) may confer other benefits (so called “pleiotropic effects”) for stroke prevention besides blood pressure lowering. One of these benefits may be that angiotensin-converting enzyme inhibitors have a unique ability to maintain cerebral perfusion in patients with large-vessel atherosclerosis. Given that most patients in this study were taking multiple antihypertensive medications, we did not have sufficient power to evaluate the possible pleiotropic effects of the different classes of antihypertensives.

Our findings do not support previous recommendations that have advised against lowering blood pressure in patients with chronic hypertension and large-artery occlusive disease because of concern over stroke from hypoperfusion. Chronic hypertension is believed to shift the autoregulatory plateau of the cerebral pressure-flow relationship toward a higher pressure to maintain normal cerebral blood flow and thereby protect the brain against high intravascular pressure. This shift in autoregulation theoretically makes the brain more susceptible to ischemia at normal blood pressures, resulting in increased stroke risk at low normal blood pressures or a J-shaped curve for blood pressure and stroke risk. However, in our study, 475 patients (84%) with chronic hypertension did not have a decreased risk of ischemic stroke in the territory of the stenotic vessel when their blood pressure was elevated but did in fact demonstrate an increased risk of stroke in the territory. These findings are consistent with research demonstrating that chronically hypertensive patients readapt their cerebral blood flow autoregulation toward normal when their blood pressure is effectively treated. Our findings suggest that patients with intracranial atherosclerosis and chronic hypertension do not demonstrate a J-curve effect and argue strongly against the common clinical practice of maintaining high blood pressure in patients with intracranial stenosis.

We also sought to determine whether certain subgroups of patients with intracranial stenosis might require higher blood pressures to prevent stroke. One of these subgroups was patients with severe (≥ 70%) stenosis. On the basis of the hypoperfusion hypothesis, one might expect that patients with severe intracranial stenosis would be more susceptible to hypoperfusion with lower blood pressure. Although the subgroup of patients in our study with severe stenosis did not demonstrate a decreased stroke risk with
lower SBP (as seen in the patients with moderate stenosis), no evidence existed of an increased risk of stroke with lower SBP in patients with severe stenosis. This finding suggests that although patients with severe intracranial stenosis might not benefit as much from lowering blood pressure for preventing a stroke in the territory of a stenotic intracranial artery (possibly because their disease is already so severe), it is still advisable to lower their blood pressure to reduce the risk of stroke in other territories and to reduce other medical complications from hypertension. Of note, our inability to demonstrate an increased stroke risk with elevated SBP in patients with severe stenosis might also have been due to a lack of power given the small number of patients in this group.

Another subgroup of patients commonly thought to benefit from higher blood pressures is patients with stenosis of the posterior circulation arteries. Our analysis, however, showed that patients with posterior circulation stenosis, when analyzed separately, demonstrated the same increased risk of ischemic stroke and ischemic stroke in the territory with increasing blood pressure seen in the group at large. This finding suggests that allowing patients with posterior circulation stenosis to have chronically elevated blood pressures does not appear to be beneficial.

Although it appears that lowering blood pressure in patients with symptomatic intracranial stenosis decreases the risk of the stroke, the optimal timing of blood pressure reduction remains an issue. This study did not examine the effect of lowering blood pressure in acute, unstable patients with intracranial stenosis; thus, the findings are not applicable in that setting. However, our analysis of the temporal relationship between blood pressure levels and stroke risk indicates that lowering blood pressure soon after enrollment was not associated with an increased risk of stroke by 4 months and that the benefit of lower blood pressure may be achieved within 1 year and continues to grow for several years.

The main limitations of this study are that it is a post hoc analysis and was based on blood pressure measures that were averaged throughout the follow-up period. Therefore, we cannot provide a direct correlation between each ischemic stroke and the blood pressure levels at the time of the stroke. For example, a patient with initially severely elevated blood pressure who was brought under good control later in the follow-up period could have had a stroke while normotensive. Another limitation was the small number of patients in some blood pressure groups, which may have resulted in our inability to demonstrate a significant difference between each of the blood pressure groups. As can be seen in the Figure and Table 2, the largest differences are between the ≥160 mm Hg category and the lower blood pressure categories. Finally, although some standardization existed for blood pressure measurement technique during follow-up, no standardization existed in the type of equipment used to measure each blood pressure. This variability may have limited the accuracy of the readings used in these analyses.

Despite these limitations, the data from this study show a strong association between elevated blood pressure and increased risk of ischemic stroke in patients with intracranial stenosis. These results argue against the common practice of allowing higher blood pressures in patients with intracranial stenosis to protect against hypoperfusion.

Sources of Funding

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Disclosures

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References

Allowing blood pressures of $\geq 140/90$ mm Hg (permissive hypertension) in patients with intracranial stenosis is common practice in the United States and is based on the theory that lowering blood pressure in these patients decreases perfusion through the stenotic artery, thereby causing ischemia in the territory of the stenotic artery. Few or no clinical data are available to support or refute this widely accepted theory. This study of patients with symptomatic intracranial stenosis finally provides some evidence to address this theory. The results of this study show that allowing chronically elevated blood pressures in patients with symptomatic intracranial atherosclerosis does not decrease the risk of stroke in the territory of the stenotic artery. In fact, permissive hypertension in patients with intracranial stenosis actually increases the risk of stroke in the territory of the stenotic vessel and stroke overall. Even patients with severe (>70%) stenosis or posterior circulation stenosis, patients thought to particularly benefit from elevated blood pressures, did not show any benefit with higher blood pressures. Therefore, the results of this study argue strongly against the common clinical practice of maintaining high blood pressure in patients with intracranial stenosis.

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