Conclusions—Patients with symptomatic intracranial vertebral artery or basilar stenosis are at high risk of stroke, MI, or sudden death. Further studies are needed to clarify optimal therapy for these patients. (Stroke. 1998;29:1389-1392.)

Key Words: aspirin ■ atherosclerosis ■ cerebrovascular disorders ■ stroke ■ warfarin

Atherosclerotic stenosis of the major intracranial arteries is an important cause of ischemic stroke.1-3 In the United States, intracranial arterial stenosis causes approximately 10% of ischemic strokes,1,6,3-10 ie, approximately 40,000 ischemic strokes annually. Several retrospective studies have shown that the annual risk of stroke in patients with carotid siphon or MCA stenosis is 4% to 12% per year.1,6,8-10 The Extracranial-Intracranial (EC-IC) Bypass Study17,18 provides prospective data on the risk of stroke in patients with symptomatic carotid siphon or MCA stenosis. In that trial, patients with carotid siphon or MCA stenosis who were treated medically (ie, management of risk factors and 1300 mg/d aspirin) had an annual stroke rate of 8% to 10%.17,18

While there are numerous studies on the risk of stroke in patients with carotid siphon or MCA stenosis, there are limited data on the prognosis of patients with angiographically proved stenosis of the intracranial vertebral arteries, basilar artery, or PCAs. Three studies19-21 of small series of patients suggest that the risk of stroke associated with intracranial vertebral artery, basilar artery, or PCA stenosis is 2.5% to 5.5% per year, which is substantially lower than the risk associated with carotid siphon or MCA stenosis. In view of the limited data on the prognosis of patients with symptomatic intracranial posterior circulation stenosis, we undertook this study to assess the risk of ischemic stroke, MI, and sudden death in these patients. A secondary aim of this pilot study was to compare the efficacy of warfarin versus aspirin for preventing ischemic stroke, MI, or sudden death in patients with symptomatic intracranial vertebral artery, basilar artery, or PCA stenosis.

Subjects and Methods

Study Design and Patient Identification

Patients enrolled in the WASID study22 were candidates for the current study. WASID was a retrospective, multicenter, nonrandomized study that compared the efficacy of warfarin versus aspirin for preventing stroke, MI, or sudden death in patients with symptomatic stenosis (50% to 99%) of a major intracranial artery (carotid siphon; anterior, middle, or posterior cerebral artery; vertebral artery; basilar artery; or posterior inferior cerebellar artery).22

Potential candidates for WASID were identified by reviewing the reports of consecutive angiograms performed at 7 participating centers between 1985 and 1991. An attempt was made to retrieve the angiograms of all patients whose reports indicated a “moderate,” “severe,” or “≥50%” intracranial stenosis. The exact degree of stenosis was measured by the local investigator through comparison...
of the diameter of the vessel at the site of stenosis (D stenosis) with the normal diameter of the vessel just distal to the stenosis (D distal) using the following formula: % stenosis = (1−[D stenosis/D distal])×100%.23 Patients whose angiogram reports indicated a severe or ≥50% intracranial stenosis but whose angiograms were not available for review (only 6% of patients) were still considered potential candidates for the study. The medical records of patients with a measured intracranial stenosis of ≥50% or an angiogram report indicating a severe or ≥50% stenosis were subsequently reviewed.

Inclusion and Exclusion Criteria
Inclusion criteria for the current study were (1) 50% to 99% stenosis of one of the following arteries in the posterior circulation: intracranial vertebral artery, basilar artery, PCA, or PICA; (2) a transient ischemic attack or stroke in the distribution of the stenotic artery; and (3) therapy with aspirin or warfarin.

Exclusion criteria were occlusion of an intracranial artery; nonatherosclerotic intracranial vasculopathies, such as dissection, moyamoya disease, or vasculitis; asymptomatic stenosis of a major intracranial artery; distal branch stenosis of an intracranial artery; coexistent cardioembolic source (ie, atrial fibrillation, mitral stenosis, prosthetic valve, MI within 6 weeks, intracardiac clot, ventricular aneurysm, or bacterial endocarditis); a severe neurological deficit from the qualifying stroke or from a stroke occurring during cerebral angiography; stroke prevention treatment other than aspirin or warfarin (eg, angioplasty, warfarin and aspirin concurrently, ticlopidine, or dipyridamole alone); and absence of follow-up data (ie, no notes on the chart after angiography and no patient contact).

Treatment, Follow-up, and End Points
Treatment with aspirin or warfarin was based on local physician preference. The most common dose of aspirin prescribed for stroke prophylaxis was 325 mg/d, and warfarin therapy was typically adjusted to maintain prothrombin times in the range of 1.2 to 1.6 times control. None of the centers were using the prothrombin time international normalized ratio for measuring levels of anticoagulation during the period 1985 to 1991.

Follow-up of patients was by chart review and telephone or personal interview. Patients were followed until occurrence of an end point, death from a nonvascular cause, change in antithrombotic therapy, or date of last contact. End points were stroke in any vascular territory, MI, or sudden death. Sudden death was defined as death of sudden onset that could not be explained by a known nonvascular process. Stroke in the territory of the stenotic artery was defined as a new infarct on CT or MRI, in a region of the brain supplied by the symptomatic stenotic artery or (in the absence of an infarct on brain imaging) as the development of a new neurological deficit during the period 1985 to 1991.

Outcome of Patients With Posterior Circulation Intracranial Stenosis
During a median follow-up of 13.8 months, 15 patients (22%) had an ischemic stroke (4 were fatal; 10 were in the same territory as the symptomatic stenotic artery), 3 patients (4.5%) had a fatal MI or sudden death, and 6 patients (9%) had a nonfatal MI. The rates of primary end points (per 100 patient-years of follow-up) were 13.1 for ischemic stroke in any vascular territory (8.7 in the same territory as the stenotic artery, 4.4 in a different territory), 2.6 for fatal MI or sudden death, and 5.2 for nonfatal MI. The artery-specific stroke rates for the basilar artery, vertebral artery, and PCA/PICA stenoses are shown in Table 1.

Warfarin Versus Aspirin: Risk Factors, Location, and Severity of Stenoses
Risk factor profiles and angiographic findings of patients in the 2 treatment groups are shown in Table 2. There were no significant differences between the 2 groups in the rates of traditional vascular risk factors, previous stroke, or type of qualifying event (ie, transient ischemic attack or stroke). Additionally, the mean age of patients and mean percent
TABLE 2. Risk Factor Profiles: Warfarin Group Versus Aspirin Group

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Warfarin Group (n=42)</th>
<th>Aspirin Group (n=26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65.4</td>
<td>66.0</td>
<td>0.82</td>
</tr>
<tr>
<td>Male</td>
<td>30 (71%)</td>
<td>23 (88%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>34 (81%)</td>
<td>21 (81%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Black</td>
<td>5 (12%)</td>
<td>3 (11%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3 (7%)</td>
<td>2 (8%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>29 (69%)</td>
<td>20 (80%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Ever smoker</td>
<td>22 (54%)</td>
<td>18 (75%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Current smoker</td>
<td>8 (20%)</td>
<td>4 (17%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20 (48%)</td>
<td>11 (44%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Cholesterol &gt;200 mg/dL</td>
<td>18/32 (56%)</td>
<td>11/22 (50%)</td>
<td>0.77</td>
</tr>
<tr>
<td>History of CAD</td>
<td>16 (38%)</td>
<td>10 (38%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>11 (28%)</td>
<td>6 (23%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Qualifying event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>16 (38%)</td>
<td>12 (46%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Stroke</td>
<td>26 (62%)</td>
<td>14 (54%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Mean % stenosis of intracranial artery</td>
<td>76%</td>
<td>77%</td>
<td>0.68</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease (angina, myocardial infarction, or coronary bypass surgery).

Stenosis of the symptomatic intracranial artery in both treatment groups were similar (Table 2). The percentage of patients who had a measured intracranial stenosis of 80% to 99% or an angiogram report indicating a severe intracranial stenosis was 55% (23 of 42) in the warfarin group and 50% (13 of 26) in the aspirin group. Of 33 patients with bivertebral or basilar artery stenoses, 24 (73%) were treated with warfarin and 9 (27%) were treated with aspirin (P=0.09).

End Points and Hemorrhagic Complications: Warfarin Group Versus Aspirin Group

Patients treated with aspirin had a significantly higher rate of ischemic stroke in any vascular territory compared with patients treated with warfarin (stroke rates per 100 patient-years of follow-up were 21.5 on aspirin versus 6.3 on warfarin; P=0.02). There were no significant differences, however, between the 2 groups in the rates of ischemic stroke, MI, and sudden death combined (27.4/100 patient-years on aspirin versus 15.7/100 patient-years on warfarin; P=0.18) or in the rates of MI and sudden death combined (5.9/100 patient-years on aspirin versus 9.4/100 patient-years on warfarin; P=0.49).

Hemorrhagic complications occurred in 7 patients on warfarin (5 minor, 2 major: 1 fatal intracerebral hemorrhage and 1 fatal gastrointestinal hemorrhage). The rates of both minor and major hemorrhagic complications were 11 per 100 patient-years of follow-up in the warfarin group compared with 0 per 100 patient-years of follow-up in the aspirin group (P<0.01). The rate of major hemorrhagic complications in the warfarin group was 3.2 per 100 patient-years of follow-up.

Stroke in Same Territory as Stenotic Artery: Warfarin Versus Aspirin

Of 26 patients treated with aspirin for a median follow-up of 19.7 months, 6 (23%) had a stroke in the same territory as the stenotic intracranial artery (2 of 13 patients [15%] with unilateral vertebral artery stenosis, 3 of 9 patients [33%] with stenosis involving the basilar artery, and 1 of 4 [25%] with PCA or PICA stenosis). The rate of stroke in the same territory as the stenotic artery in patients on aspirin (per 100 patient-years) was 11.7 (9.6 in patients with 50% to 79% stenosis versus 15.1 in patients with 80% to 99% stenosis).

Of 42 patients treated with warfarin for a median follow-up of 11 months, 4 (10%) had a stroke in the same territory as the stenotic intracranial artery (2 of 19 [11%] with stenosis involving the basilar artery, 2 of 5 [40%] with bivertebral stenoses, 0 of 13 [0%] with unilateral vertebral artery stenosis, and 0 of 5 [0%] with PCA or PICA stenosis). The rate of stroke in the same territory as the stenotic artery in patients on warfarin (per 100 patient-years) was 6.3 (3.7 in patients with 50% to 79% stenosis versus 8.2% in patients with 80% to 99% stenosis).

Discussion

Previous studies19–21 suggest that the risk of stroke associated with intracranial vertebral artery, basilar artery, or PCA stenosis is approximately 2.5% to 5.5% per year. Moufarrij et al19 studied 44 patients (mean age, 57 years) with angiographically proved stenosis of ≥50% of the intracranial vertebral artery or basilar artery. Both asymptomatic and symptomatic patients were included. Treatment consisted of aspirin or dipyridamole in 18 (41%), warfarin in 14 (32%), no antithrombotic therapy in 7 (16%), and undetermined treatment in 5 (11%). During a mean follow-up of 6.1 years, 8 patients (18%) had a stroke (3 fatal; 5 of the 8 strokes were in the territory of the stenotic artery) and 5 patients (11%) died from causes unrelated to stroke (2 cardiac). Six of 8 strokes occurred in patients on a regimen of aspirin or dipyridamole, and 1 occurred in a patient on no antithrombotic therapy; treatment was not determined in the other patient who had a stroke. None of the patients taking warfarin had a stroke.

Pessin et al20 followed 9 patients with symptomatic stenosis (40% to 90%) of the middle or distal segments of the basilar artery for 1 month to 13 years (8 of 9 patients were followed for ≥2 years). The mean age was 62 years; 5 were treated with warfarin and 2 with aspirin or dipyridamole, and 2 were on no antithrombotic therapy. During follow-up, 1 patient (11%) taking warfarin had a fatal brain stem stroke and 2 patients died (1 of the original stroke and 1 of alcohol abuse). In a study of 6 patients with PCA stenosis who were treated with warfarin, 1 patient had a stroke (MCA territory) and 2 patients died (1 of traumatic brain hemorrhage and 1 of sudden death) during follow-up of 4 months to 4 years.21

In the current study of 68 patients with ≥50% stenosis of the intracranial vertebral artery, basilar artery, PCA or PICA, the rates of stroke were substantially higher (Table 1) than in previous studies of patients with posterior circulation stenosis. Possible explanations for the difference in stroke rates between these studies are the higher frequency of vascular risk factors and severe stenoses in the current study and inclusion of asymptomatic patients and lower mean age of patients in previous studies. Patients with basilar artery or

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vertebral artery stenoses (particularly bilateral vertebral artery stenosis) had the highest rate of stroke in this study (Table 1). Moreover, the stroke rates in patients with basilar artery or vertebral artery stenosis were higher than the rates of stroke reported in patients with symptomatic stenosis of the carotid siphon or MCA.\textsuperscript{11-18} and approached the stroke rates of patients with symptomatic extracranial carotid stenosis of \( \geq 70\% \).\textsuperscript{23}

Despite the higher frequency of basilar artery or bilateral vertebral artery stenoses in the warfarin group (57\% of patients) compared with the aspirin group (35\% of patients), patients treated with warfarin had a significantly lower rate of ischemic stroke than patients treated with aspirin. However, patients on warfarin had a significantly higher rate of hemorrhagic complications, which partly offset the overall benefit of warfarin. Although the warfarin group had a lower rate of major ischemic events (stroke, MI, and sudden death combined) than the aspirin group, this difference was not statistically significant. This may have been due to the low power of the study.

Patients with severe stenosis (80\% to 99\%) had a substantially higher rate of stroke in the same territory of the stenotic artery than patients with moderate stenosis (50\% to 79\%) in both treatment groups. This finding suggests that symptomatic verteobasilar stenosis behaves similarly to symptomatic extracranial carotid artery stenosis, which is associated with a higher risk of ipsilateral stroke for each decile increase in percent stenosis above 70\%.\textsuperscript{23} The high rate of stroke in the territory of a severely stenotic vertebral or basilar artery with either antithrombotic agent suggests that adjunctive stroke-preventive therapies (eg, intracranial angioplasty\textsuperscript{24-26} may be needed for patients with symptomatic high-grade vertebral or basilar artery stenosis.

The results of this retrospective, nonrandomized pilot study suggest that patients with symptomatic basilar artery or intracranial vertebral artery stenosis are at high risk of stroke and that warfarin may be more effective than aspirin for preventing stroke in these patients. However, this retrospective study has several limitations, including a nonrandomized study design; the possibility that patients in this study may constitute a high-risk subgroup of patients with posterior circulation stenosis who were selected to undergo angiography; and the lack of standardized therapy, such as a uniform dose of aspirin and international normalized ratio target range. As such, a recommendation regarding the use of warfarin for posterior circulation stenosis must await the results of a prospective randomized study.

Acknowledgments

This article is dedicated to the memory of Michael S. Pessin MD, one of the original WASID investigators, an inspirational teacher, and a close colleague of the Study Group.

References


Appendix

Prognosis of Patients With Symptomatic Vertebral or Basilar Artery Stenosis
The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Study Group

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