Failure of Antithrombotic Therapy and Risk of Stroke in Patients With Symptomatic Intracranial Stenosis

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Background and Purpose—We sought to determine if patients with intracranial stenosis who have a transient ischemic attack or stroke on antithrombotic therapy are at particularly high risk for recurrent stroke.

Methods—We compared baseline features and the rates of stroke or vascular death and stroke in the territory of the symptomatic artery between patients ON (n=299) versus OFF (n=269) antithrombics at the time of their qualifying event for the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial.

Results—In univariate analyses, there was no difference in the rates of stroke or vascular death (21% versus 23%; hazard ratio [ON/OFF], 0.91; 95% CI, 0.64 to 1.29; P=0.59) or stroke in territory (13% versus 14%; hazard ratio [ON/OFF], 0.90; 95% CI, 0.57 to 1.39; P=0.61) between patients ON versus OFF antithrombics at the time of their qualifying event. A multivariable analysis adjusted for the difference in risk factors between patients ON and OFF antithrombotic therapy also showed no significant differences in the combined end point of stroke or vascular death (hazard ratio [ON/OFF], 0.86; 95% CI, 0.55 to 1.34; P=0.51) or stroke in territory (hazard ratio [ON/OFF], 1.01; 95% CI, 0.58 to 1.77; P=0.97) between patients ON versus OFF antithrombotic therapy at the time of the qualifying event.

Conclusions—Patients with intracranial stenosis who fail antithrombotic therapy are not at higher risk of stroke than those who do not fail antithrombotic therapy. Given our finding that patients ON and OFF antithrombotic therapy are both at high risk for stroke in the territory, intracranial stenting trials should not be limited to just those who fail antithrombotic therapy. (Stroke. 2009;40:505-509.)

Key Words: anticoagulation ■ antiplatelet ■ cerebral arteries ■ cerebrovascular disease ■ intracranial stenosis

Intracranial arterial stenosis accounts for approximately 8% to 10% of ischemic strokes that occur annually in the United States,1 and patients with intracranial stenosis may have a risk of recurrent stroke as high as 20% in the first 2 years despite medical therapy.2 A previous retrospective study has suggested that patients with intracranial stenosis who have stroke symptoms while on antithrombotic therapy (antiplatelet agents or anticoagulants), so-called “antithrombotic failures,” may be at particularly high risk of recurrent stroke.3

As a result of their presumed high-risk status, patients with intracranial stenosis who fail antithrombotic therapy are frequently recommended different treatments for secondary stroke prevention despite a lack of evidence for this approach. For example, patients who were on antiplatelet agents at the time of their stroke symptoms may be prescribed antiagulation or considered for interventional procedures such as intracranial angioplasty or stenting, which have yet to be studied in a large, controlled clinical trial. In this study, we sought to determine if patients with intracranial stenosis who present with transient ischemic attack (TIA) or stroke while on antithrombotic medications are indeed at higher risk of recurrent ischemic stroke than patients who are not on antithrombotic medications at the time of their initial symptoms. Additionally, as an exploratory aim, we sought to determine if patients with intracranial stenosis who present with TIA or stroke while on antiplatelet therapy are at lower risk of recurrent stroke if treated with warfarin.

Methods

Patient Entrance Criteria

Data on the 569 patients enrolled in the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial were used for this post hoc analysis. Details of the WASID study design have been published previously.4 In brief, WASID was a randomized, double-blinded, multicenter clinical trial designed to compare the efficacy of dose-adjusted warfarin (target international normalized ratio, 2 to 3) versus 1300 mg aspirin for the prevention of recurrent stroke in patients with symptomatic intracranial stenosis. Inclusion criteria included TIA or stroke that occurred within 90 days before randomization (considered the qualifying event), which was attributable to angiographically proven 50% to 99% stenosis of a major intracranial artery (internal carotid, middle cerebral, vertebral, or...
Definitions of ON Versus OFF Antithrombotic Therapy

For the purpose of these analyses, patients were considered to be ON antithrombotic therapy if they reported taking an antplatelet agent or warfarin at the time of their qualifying event for WASID. Patients were OFF antithrombotic therapy if they reported taking no antiplatelet agent or warfarin at the time of their qualifying event for WASID. The reason for antithrombotic use at the time of the qualifying event for WASID was not recorded.

End Points

The outcome variables used in these analyses were the same as those in the primary paper: the combined end point of stroke or vascular death (primary end point), stroke in the territory of the stenotic artery (secondary end point), and major hemorrhage (safety end point).

Statistical Methods

In an effort to determine if patients deemed “antithrombotic failures” had worse outcomes in WASID, baseline features and vascular end points (rates of stroke or vascular death, ischemic stroke in the territory of the stenotic artery, and major hemorrhage) were compared between patients ON versus OFF antithrombotic therapies at the time of the qualifying event in univariate and multivariable analyses. Baseline features of the 2 groups were compared using either an independent groups t test (for means) or χ² test (for percentages). The cumulative probability of an event versus time was estimated using the product limit method and was compared between the treatment groups using the log rank test. Cox proportional hazards regression was used to calculate both unadjusted and adjusted hazard ratios (ON/OFF). The Supremum tests confirmed the proportional hazards assumptions. Hazard ratios were adjusted for baseline factors, which were found to differ between the groups, as listed in Table 1, except for low-density lipoprotein, which was not included because of missing data. With the sample size in WASID, there was 80% power to detect a hazard ratio of 1.65 for stroke or vascular death and 1.89 for stroke in territory for patients ON versus OFF antithrombotic therapy at the time of the qualifying event.

As an additional exploratory analysis, we compared the outcomes of patients on an antiplatelet agent at the time of the qualifying event who were subsequently randomized to aspirin or warfarin in an effort to determine if warfarin is an effective “rescue therapy.” Similar time to event methods were used for these analyses. Hazard ratios for these analyses are presented as aspirin/warfarin ratios. There was 80% power to detect a hazard ratio of 2.16 for stroke or vascular death and 2.65 for stroke in territory for patients on aspirin versus warfarin. An interaction term was added to the Cox proportional hazards regression models to test the interaction between the use of antithrombotic therapy at the qualifying event (ON versus OFF) and treatment assignment (warfarin versus aspirin).

Results

Baseline Features

At the time of their qualifying event for WASID, 299 patients were ON antithrombotic therapy (260 on antiplatelet and 39 on anticoagulation) and 269 were OFF antithrombotic therapy.

The baseline characteristics of patients ON versus OFF antithrombotic medication at the time of the qualifying event are listed in Table 1. Compared with patients OFF antithrombotic therapy at the time of their qualifying event, patients ON antithrombotic therapy (antiplatelets or anticoagulants) were significantly more likely to be older, white, or have a history of a prior stroke, hypertension, lipid disorder, coronary artery disease, and tobacco use. Patients ON antithrombotic therapy were also significantly more likely to be on a statin and had a lower low-density lipoprotein level at the time of the qualifying event. Patients OFF antithrombotic therapies at the time of their qualifying event were more likely to be black, have stroke as their qualifying event, and have a higher frequency of middle cerebral artery stenosis.

End Points in Patients ON Versus OFF Antithrombotic Therapy

Comparison of outcomes between patients ON versus OFF antithrombotic therapy revealed no significant differences in the percentage of patients with the combined end point of stroke or vascular death (21% versus 23%; hazard ratio [ON/OFF], 0.91; 95% CI, 0.64 to 1.29; \( P = 0.59 \)) or stroke in territory (13% versus 14%; hazard ratio [ON/OFF], 0.90; 95% CI, 0.57 to 1.39; \( P = 0.61 \)) in the univariate analyses, as shown in Table 2. A multivariable analysis adjusted for the difference in risk factors between patients ON and OFF antithrombotic therapy also showed no significant differences in the combined end point of stroke or vascular death (hazard ratio [ON/OFF], 0.86; 95% CI, 0.55 to 1.34; \( P = 0.51 \)) or stroke in territory (hazard ratio [ON/OFF], 1.10; 95% CI, 0.58 to 1.77; \( P = 0.97 \)) between patients ON versus OFF antithrombotic therapy at the time of qualifying event. Patients ON versus OFF antithrombotic therapy did not significantly differ with respect to the percentage of major hemorrhage during follow-up (6.7% versus 4.8%; hazard ratio [ON/OFF], 1.32; 95% CI, 0.66 to 2.65; \( P = 0.44 \)).

Patients OFF Antithrombotic Therapy

Among patients who were OFF antithrombotic therapy at the time of their qualifying event, there was no difference between those randomized to aspirin or warfarin for the end points of stroke or vascular death or stroke in territory, as shown in Table 3.

Patients ON Antithrombotic Therapy

Forty-six percent of patients in WASID were on an antiplatelet agent at the time of their qualifying event. Among these patients, 126 were randomized to aspirin and 134 were randomized to warfarin. There was no significant difference in the rate of stroke or vascular death in the patients randomized to aspirin versus warfarin, as shown in Table 3. However, there was a trend toward a lower rate of stroke in the territory in warfarin arm (9%) than the aspirin arm (17%; \( P = 0.07 \)).

Although not statistically significant, the direction of the difference between aspirin and warfarin was in favor of aspirin for patients OFF antithrombotic therapy at the time of the qualifying event and in favor of warfarin for patients ON antithrombotic therapy. The interaction between use of antithrombotic therapy at the qualifying event and treatment assignment was not statistically significant for either stroke or vascular death (\( P = 0.13 \)) or stroke in territory (\( P = 0.10 \)).

Among patients who were ON antithrombotic therapy at the time of their qualifying event, there was no significant difference between those randomized to aspirin or warfarin for the end point of major hemorrhage during follow-up (5.6% versus 7.7%; hazard ratio [aspirin/warfarin], 0.81; 95% CI, 0.33 to 1.98; \( P = 0.64 \)).
The results of this post hoc analysis of the WASID data set do not support the commonly held belief that patients with intracranial stenosis who present with TIA or stroke while on antithrombotic therapy are at particularly high risk of recurrent ischemic stroke. In patients enrolled in WASID who were on an antithrombotic agent at the time of their qualifying event, we could not detect an increased risk of either the combined end point (stroke or vascular death) or stroke in the territory compared with those who were not previously on antithrombotic agents. In contrast, the Warfarin-Aspirin Recurrent Stroke Study (WARSS) trial, a multicenter secondary prevention stroke trial with over 2000 patients, found that the rates of recurrent stroke and death in patients who were on antithrombotic therapy at the time of the qualifying event were increased compared with patients who were not.
antithrombotic therapy at the time of the qualifying event were higher during the study than those who were “naïve” to antithrombotics at the start of the trial.\textsuperscript{3} WARSS differed from WASID in that WARSS included patients with heterogeneous causes of stroke, whereas WASID was limited to patients with intracranial stenosis. Their finding that patients with stroke who “fail medical therapy” are at higher risk than those who are not “medical failures” raises the possibility that intracranial stenosis may be such a high-risk condition that antithrombotic therapy has relatively little impact on recurrent events.

We found the 1-year rate of stroke or vascular death to be 15% (2-year rate 21%) in patients who were on antithrombotic therapy at the time of their qualifying event. A previous retrospective single center study\textsuperscript{3} of 52 patients with symptomatic intracranial stenosis reported a substantially higher risk of recurrent events in patients on antithrombotic therapy compared with our study. However, the high recurrent event rate in their report was due in part to the inclusion of TIA as an end point. In addition, patients with intracranial stenosis referred for evaluation at this major tertiary referral center may be a particularly high-risk cohort. On the other hand, referral bias might have also affected the WASID cohort, because some patients perceived to be particularly high risk (ie, those who had failed antithrombotic therapy, particularly warfarin) might not have been referred for enrollment into WASID and therefore the risk of recurrent events in patients “ON” antithrombotics in our study might be an underestimate. Nevertheless, the WASID database used for this analysis is the largest multicenter cohort of patients with symptomatic intracranial stenosis and therefore may provide a better estimate of the true event rates in this population.

We did find significant differences in baseline features between patients ON versus OFF antithrombotic therapies at the time of enrollment in WASID. Many of these differences in baseline features are explained by the fact that older patients with multiple risk factors and a history of coronary artery disease or stroke would be expected to be put on an antiplatelet agent and statin. In addition, patients on antithrombotic therapy were more likely to have a TIA rather than a stroke as their qualifying event. The lower rate of stroke as a qualifying event in patients on antithrombotic therapy may be due to the ability of antithrombotic agents (both antiplatelets and anticoagulants) to prevent the progression from TIA to stroke in some patients. Despite the differences in baseline features between patients ON versus OFF antithrombotic therapy at baseline, there was no difference in outcome between these groups in multivariable analyses, which took the differences in baseline features between the 2 groups into account.

In our exploratory analysis, we did not find strong evidence to support the theory that warfarin might be an effective “rescue therapy” in patients with intracranial stenosis who have stroke symptoms while on antiplatelet agents. When analyzing the subset of WASID patients on antiplatelet agents at the time of their qualifying event, we found no difference in the rate of stroke or vascular death (the primary end point in WASID) between patients randomized to warfarin versus aspirin. There was a trend toward lower rates of stroke in the territory for patients previously on antiplatelet therapy who were randomized to warfarin compared with aspirin. However, we did not find an interaction between prior treatment with antiplatelets and treatment assignment in WASID, although there was limited power to detect such an interaction. Our findings are consistent with data from WARSS, which also demonstrated that in patients on antithrombotic agents at the time of their qualifying event, warfarin was no better than aspirin for prevention of recurrent stroke during the trial.\textsuperscript{7}

### Table 2. Unadjusted Comparison of End Points Between Patients ON Versus OFF Antithrombotic Therapy at the Time of the Qualifying Event

<table>
<thead>
<tr>
<th>End Point</th>
<th>ON Antithrombotic (n=239)</th>
<th>OFF Antithrombotic (n=269)</th>
<th>Hazard Ratio On/Off (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or vascular death, no. of patients (%)</td>
<td>64 (21%)</td>
<td>61 (23%)</td>
<td>0.91 (0.64–1.29)</td>
<td>0.59</td>
</tr>
<tr>
<td>1-year event rate, %</td>
<td>15</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-year event rate, %</td>
<td>21</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke in territory, no. of patients (%)</td>
<td>39 (13%)</td>
<td>38 (14%)</td>
<td>0.90 (0.57–1.39)</td>
<td>0.61</td>
</tr>
<tr>
<td>1-year event rate, %</td>
<td>10</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-year event rate, %</td>
<td>14</td>
<td>15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 3. Unadjusted Comparison of End Points Between Patients Randomized to Aspirin versus Warfarin

<table>
<thead>
<tr>
<th>End Point</th>
<th>Aspirin (n=126)</th>
<th>Warfarin (n=134)</th>
<th>Hazard Ratio (aspirin/warfarin; 95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients ON antithrombotic at the time of qualifying event</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke or vascular death, no. of patients (%)</td>
<td>29 (23%)</td>
<td>24 (18%)</td>
<td>1.32 (0.77–2.28)</td>
<td>0.31</td>
</tr>
<tr>
<td>Ischemic stroke in territory, no. of patients (%)</td>
<td>21 (17%)</td>
<td>12 (9%)</td>
<td>1.92 (0.95–3.91)</td>
<td>0.07</td>
</tr>
<tr>
<td>Patients OFF antithrombotic at time of qualifying event</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke or vascular death, no. of patients (%)</td>
<td>27 (20%)</td>
<td>34 (26%)</td>
<td>0.75 (0.45–1.25)</td>
<td>0.27</td>
</tr>
<tr>
<td>Ischemic stroke in territory, no. of patients (%)</td>
<td>18 (13%)</td>
<td>20 (15%)</td>
<td>0.85 (0.45–1.61)</td>
<td>0.62</td>
</tr>
</tbody>
</table>
Although the limited power of this WASID analysis prevents a definitive conclusion regarding the efficacy of warfarin as a “rescue therapy,” the higher rates of major hemorrhage associated with warfarin use in WASID combined with our finding that patients previously on antithrombotic agents had a slightly higher (not significant) increase in major hemorrhage during follow-up when on warfarin likely outweighs any potential benefit of warfarin in this population.

Our findings that “medical failures” are not at higher risk of stroke has several implications for current and future treatment of patients with intracranial stenosis. Because stroke rates on aspirin are high and warfarin is not established as a safe and effective “rescue treatment,” other methods of stroke prevention such as intracranial stenting need to be evaluated in clinical trials. Currently, endovascular treatment with the Wingspan intracranial stent is available under a US Food and Drug Administration humanitarian device exemption for patients with 50% to 99% stenosis who have failed medical therapy. Given our finding that “medical failures” are not at higher risk for stroke in the territory than other patients, intracranial stenting trials should not be limited to those who fail medical therapy. Instead, future studies comparing intracranial stenting with medical therapy should focus on other high-risk features for stroke in territory such as severe stenosis and recent symptoms.

Sources of Funding
WASID was supported by a grant (R01 NS36643 to M.I.C.) from the National Institute of Neurological Disorders and Stroke, National Institutes of Health (NIH). In addition, the following General Clinical Research Centers, funded by the NIH, provided local support for the evaluation of patients in the trial: Emory University (M01 RR 00039), Case Western University, MetroHealth Medical Center (5M01 RR00080), San Francisco General Hospital (M01 RR00083-42), Johns Hopkins University School of Medicine (M01 RR00052), Indiana University School of Medicine (5M01 RR000750-32), Cedars-Sinai Hospital (M01 RR00425), and the University of Maryland (M01 RR165001).

Disclosures
T.N.T. is the recipient of funding from the American Academy of Neurology (AAN) Foundation Clinical Research Training Fellowship and received fees from Bristol-Myers Squibb/Sanoﬁ Pharmaceuticals Partnership for participation in a Speakers’ Bureau. G.C. received funding from a research grant (1 R01 NS36643) from the US Public Health Service, National Institute of Neurological Disorders and Stroke (NINDS) for this trial. M.J.L. received funding from a research grant (1 R01 NS36643) from the US Public Health Service, NINDS for this trial. S.R.L. received funding from a research grant (K24NS43992) from the US Public Health Service, NINDS. M.I.C. received a research grant (1 R01 NS36643) from the US Public Health Service, NINDS to fund this trial. He is also supported by grants 1 K24 NS050307 and 1 R01 NS051688-01 from the National Institutes of Health/NINDS. He reports being paid fees by the Bristol-Myers Squibb/Sanoﬁ Pharmaceuticals Partnership, Astra-Zeneca, and the Sankyo Lilly Partnership for consulting on antithrombotic agents that were not evaluated in this trial and from Guidant Corporation for consulting on a medical device (an intracranial stent) that was not evaluated in this trial.

References
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for the WASID Investigators

Stroke. 2009;40:505-509; originally published online December 18, 2008;
doi: 10.1161/STROKEAHA.108.528281
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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