Outcome in Patients Previously on Antithrombotic Therapy in the SAMMPRIS Trial

Helmi L. Lutsep, MD; Stanley L. Barnwell, MD, PhD; Darren T. Larsen, RN; Michael J. Lynn, MS; Mindy Hong, MSPH; Tanya N. Turan, MD; Colin P. Derdeyn, MD; David Fiorella, MD, PhD; L. Scott Janis, PhD; Marc I. Chimowitz, MB, ChB; for the SAMMPRIS Investigators

Background and Purpose—Stenting has been used as a rescue therapy in patients with intracranial arterial stenosis and a transient ischemic attack or stroke when on antithrombotic therapy (AT). We determined whether the stenting versus aggressive medical therapy for intracranial arterial stenosis (SAMMPRIS) trial supported this approach by comparing the treatments within subgroups of patients whose qualifying event (QE) occurred on versus off of AT.

Methods—The primary outcome, 30-day stroke and death and later strokes in the territory of the qualifying artery, was compared between (1) percutaneous transluminal angioplasty and stenting plus aggressive medical therapy (PTAS) versus aggressive medical management therapy alone (AMM) for patients whose QE occurred on versus off AT and between (2) patients whose QE occurred on versus off AT separately for the treatment groups.

Results—Among the 284/451 (63%) patients who had their QE on AT, the 2-year primary end point rates were 15.6% for those randomized to AMM (n=140) and 21.6% for PTAS (n=144; \( P=0.043 \), log-rank test). In the 167 patients not on AT, the 2-year primary end point rates were 11.6% for AMM (n=87) and 18.8% for PTAS (n=80; \( P=0.31 \), log-rank test). Within both treatment groups, there was no difference in the time to the primary end point between patients who were on or off AT (AMM, \( P=0.96 \); PTAS, \( P=0.52 \); log-rank test).

Conclusions—SAMMPRIS results indicate that the benefit of AMM over PTAS is similar in patients on versus off AT at the QE and that failure of AT is not a predictor of increased risk of a primary end point.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00576693.
(Stroke. 2015;46:775-779. DOI: 10.1161/STROKEAHA.114.007752.)

Key Words: antiplatelet agents ■ intracranial arteriosclerosis ■ stroke

Before the publication of the results of the stenting versus aggressive medical therapy for intracranial arterial stenosis (SAMMPRIS) trial, the Wingspan stent was being used in clinical practice as a rescue treatment to prevent recurrent stroke in patients with 50% to 99% intracranial arterial stenosis who had a transient ischemic attack or stroke when on antithrombotic therapy (AT). The rationale for this approach was uncertain because the preceding warfarin aspirin symptomatic intracranial disease (WASID) trial had shown similar rates of recurrent stroke on medical treatment alone in patients whose qualifying event (QE) for that trial occurred on versus off AT.1

SAMMPRIS showed that patients with a transient ischemic attack or stroke within 30 days before enrollment that was attributed to a high grade, 70% to 99%, stenosis of a major intracranial artery had greater benefit from aggressive medical management alone (AMM) than with percutaneous transluminal angioplasty and stenting with the Wingspan stent plus aggressive medical management (PTAS).2,3 SAMMPRIS did not require patients to be refractory to AT to be enrolled in the trial, which provided us with the opportunity to determine whether stenting is a rescue therapy for patients with a transient ischemic attack or stroke when on AT (so-called antithrombotic failures) and to compare the outcomes between patients whose QE for SAMMPRIS occurred on versus off AT. We report the results of these prespecified analyses in this article.
Methods

The study design for the SAMMPRIS trial has been published previously. AMM included antplatelet therapy with clopidogrel 75 mg per day for 90 days and aspirin 325 mg per day indefinitely, careful risk factor management that primarily targeted a systolic blood pressure <140 mmHg (<130 mmHg in diabetics) and an low-density lipoprotein <70 mg/dL, and a lifestyle modification program. Stenting was performed using the Wingspan stent system, and the patients treated with PTAS also received the same AMM, including treatment with the antiplatelet agent regimen, careful risk factor control, and the lifestyle modification program. All patients gave written informed consent to participate, and institutional review boards at all 50 participating sites in the United States approved the study protocol.

The patients in the present study represent all of those enrolled in SAMMPRIS, divided into those who had their QE on AT and those that did not. Patients were included in the AT group whether they were on single or multiple antiplatelet agents or anticoagulants at the time of the QE and irrespective of the duration of treatment. The primary end point consisted of stroke and death within 30 days after enrollment or within 30 days after a revascularization procedure during follow-up and ischemic stroke in the territory of the qualifying artery beyond 30 days after enrollment.

Baseline characteristics were compared between patients taking and not taking an antithrombotic at the time of the QEs using Fisher exact test (for percentages), independent groups t-test (for means), or Wilcoxon rank-sum test (for medians). The same methods were used to compare baseline characteristics between treatment groups. Time to event curves for the primary end point were compared between treatment groups using the log-rank test separately for patients taking and not taking an antithrombotic at the time of the QE. Analyses comparing treatment groups adjusting for baseline characteristics that were different between the treatment groups and that were related to the primary end point were done using proportional hazards regression. The same methods were used to assess the association between the use of an antithrombotic at the time of the QE and time to a primary end point separately for each of the treatment groups.

Results

Baseline Characteristics in Patients On Versus Off AT at Qualifying Event

A total of 451 patients were enrolled in SAMMPRIS and randomized to either AMM (n=227) or PTAS (n=224). The majority, 284/451 (63%), of patients had their QE on AT, whereas 167/451 (37%) patients were not on AT. Of the patients on AT, the majority were on ≥1 antiplatelet agents at the time of the QE (272/284, 95.8%) with 64 (22.5%) on both clopidogrel and aspirin. Fewer patients were on an anticoagulant (12/284, 4.2%). Of the patients on antiplatelet therapy, 182/272 (66.9%) were on a single antiplatelet agent at the time of their QE with the vast majority on aspirin alone (153/182, 84.1%). Other antiplatelet agents used in various combinations included clopidogrel, aspirin/dipyridamole, prasugrel (1 patient), and cilostazol (1 on single therapy and 2 in combination with aspirin or clopidogrel).

Many characteristics differed at baseline between the groups with a QE on versus off AT (Table 1). Patients with their QE on AT were significantly older and had a significantly higher frequency of lipid disorders, coronary artery disease, stroke before the QE, presence of old infarct on baseline brain imaging, and vertebral or basilar stenosis. Patients off AT had a significantly higher frequency of stroke as the QE for SAMMPRIS and middle cerebral artery stenosis.

PTAS Versus AMM in Patients On Versus Off AT at Qualifying Event

Table 2 provides a comparison of treatment groups, AMM and PTAS, for the primary end point within patient groups defined by antithrombotic status at the time of the QE. Of the 284 patients on AT at the time of the QE, 140 patients were randomized to AMM and 144 to PTAS. The Kaplan–Meier curves were significantly different in these 2 groups (P=0.043) and yielded 2-year rates of the primary end point of 15.6% in the AMM group and 21.6% in the PTAS group (Figure 1). Only 64 patients were on clopidogrel plus aspirin at the time of their QE, with 37 of these patients randomized to AMM and 27 to PTAS. The 2-year rates of the primary end point were 18.5% (95% confidence interval, 8.2%–38.9%) in the PTAS group and 23.2% (95% confidence interval, 12.3%–41.1%) in the AMM group, and the Kaplan–Meier curves were not significantly different (P=0.78; Figure 2). Of the 167 patients not on AT at the time of the QE, 87 patients were randomized to AMM and 80 to PTAS. The 2-year rates of the primary end point were 11.6% in the AMM group and 18.8% in the PTAS group, but the Kaplan–Meier curves were not significantly different (P=0.31; Figure 3).

The baseline characteristics listed in Table 1 were compared between the treatments separately for patients on AT, patients on aspirin and clopidogrel, and patients off AT at the time of the QE. The only statistically significant differences between treatments were the following: For patients taking aspirin and clopidogrel at the time of the QE, a higher percentage of patients in the AMM group had a history of coronary artery disease (57% versus 26%; P=0.021);2 For patients not on AT at the time of the QE, the patients in the AMM group were younger on average (56.3±11.9 years versus 60.7±10.9 years; P=0.014). Among patients not on an antithrombotic at the time of the QE, an analysis adjusting for age using proportional hazards regression found that similarly to the unadjusted analysis, treatment was not significantly related to the primary end point (P=0.59).

Outcome in Patients On Versus Off AT at Qualifying Event

For patients randomized to AMM, antithrombotic use at the time of the QE was not significantly related to the primary end point (P=0.96; Table 2). Antithrombotic use was also not statistically significant (P=0.51) when adjusting for baseline factors found to be related to the primary end point among AMM patients (stroke as the QE and the presence of old infarcts in the territory of the stenotic artery). Twenty of 21 (95%) ischemic strokes in the AMM group on antithrombotics were in the territory of the stenotic vessel. In the AMM group not on antithrombotics, 11 of 12 (92%) occurred in the territory of the stenotic vessel.

A similar result was found for patients randomized to PTAS. Antithrombotic use at the time of the QE was not significantly related to the primary end point (P=0.52; Table 2) and was also not statistically significant (P=0.77) when adjusting for baseline factors found to be related to the primary end point among PTAS patients (age, diabetes mellitus, and qualifying stenosis in the basilar artery). All of the ischemic strokes in the PTAS treatment population occurred in the territory of the
stenotic vessel (28/28 in the antithrombotic group and 13/13 in the PTAS group not on antithrombotics).

**Discussion**

The results of this prespecified analysis of the SAMMPRIS data set do not support the practice of using PTAS with the Wingspan stent system as a rescue treatment in intracranial arterial stenosis patients who have a transient ischemic attack or stroke on AT. In fact, the SAMMPRIS data indicate that patients whose QE occurred on AT, which was in most cases antiplatelet treatment with aspirin, had a significantly lower rate of the primary end point in the AMM group compared with the PTAS group. Patients who had been on AT at the time of the QE had a significantly higher frequency of important risk factors than patients who had not been on AT. The presence of these risk factors likely resulted in more medical

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Taking Antithrombotic (n=284)</th>
<th>Not Taking Antithrombotic (n=167)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61.3±11.0</td>
<td>58.4±11.6</td>
<td>0.008</td>
</tr>
<tr>
<td>Male sex</td>
<td>177 (62%)</td>
<td>95 (57%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>62 (22%)</td>
<td>42 (25%)</td>
<td>0.49</td>
</tr>
<tr>
<td>White</td>
<td>208 (73%)</td>
<td>114 (68%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>14 (5%)</td>
<td>11 (7%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>260 (92%)</td>
<td>143 (86%)</td>
<td>0.058</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>137 (48%)</td>
<td>71 (43%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Lipid disorder</td>
<td>263 (93%)</td>
<td>134 (80%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of coronary artery disease</td>
<td>92 (32%)</td>
<td>14 (8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of stroke (not qualifying event)</td>
<td>100 (35%)</td>
<td>18 (11%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>146±21 (n=282)</td>
<td>145±22 (n=165)</td>
<td>0.69</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>153±44 (n=280)</td>
<td>158±43 (n=166)</td>
<td>0.22</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>95±38 (n=280)</td>
<td>100±37 (n=166)</td>
<td>0.13</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>38±10 (n=280)</td>
<td>39±11 (n=166)</td>
<td>0.45</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>31±6</td>
<td>30±6</td>
<td>0.37</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>108 (38%)</td>
<td>60/166 (36%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Previously</td>
<td>106 (37%)</td>
<td>53/166 (32%)</td>
<td></td>
</tr>
<tr>
<td>Currently</td>
<td>70 (25%)</td>
<td>53/166 (32%)</td>
<td></td>
</tr>
<tr>
<td>Physical activity in target†</td>
<td>96/283 (34%)</td>
<td>46/166 (28%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Presence of old infarcts</td>
<td>110/276 (40%)</td>
<td>34/161 (21%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Qualifying event was stroke</td>
<td>165 (58%)</td>
<td>129 (77%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time from qualifying event to randomization, days</td>
<td>8 (4,18)</td>
<td>7 (4,18)</td>
<td>0.58</td>
</tr>
<tr>
<td>Symptomatic artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td>59 (21%)</td>
<td>35 (21%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>108 (38%)</td>
<td>89 (53%)</td>
<td></td>
</tr>
<tr>
<td>Vertebral artery</td>
<td>45 (16%)</td>
<td>15 (9%)</td>
<td></td>
</tr>
<tr>
<td>Basilar artery</td>
<td>72 (25%)</td>
<td>28 (17%)</td>
<td></td>
</tr>
<tr>
<td>Percent stenosis of symptomatic artery‡</td>
<td>80±6</td>
<td>81±7 (n=166)</td>
<td>0.48</td>
</tr>
<tr>
<td>Categories of percent stenosis of the symptomatic artery‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70% to 79%</td>
<td>134 (47%)</td>
<td>75/166 (45%)</td>
<td>0.83</td>
</tr>
<tr>
<td>80% to 89%</td>
<td>119 (42%)</td>
<td>70/166 (42%)</td>
<td></td>
</tr>
<tr>
<td>90% to 99%</td>
<td>31 (11%)</td>
<td>21/166 (13%)</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±standard deviation or number (%) except for time from qualifying event to randomization for which the values are median (25th percentile and 75th percentile). HDL indicates high-density lipoprotein; and LDL, low-density lipoprotein.

*P value comparing groups for Fisher exact test (for percentages), independent groups t test (for means), or Wilcoxon rank-sum test (for median of time from qualifying event to randomization).

†The target range for physical activity was 30 min or more of moderate exercise ≥3 times per week.

‡According to a reading of the angiogram by the site interventionist.
care and the use of AT in these patients before enrollment in SAMMPRIS. It is possible that certain of the risk factors contributed to the risk of intervention with PTAS.6 The fact that these patients had more benefit from AMM than PTAS provides compelling support for the use of aggressive medical management in these patients.

In patients who had their QE on a combination of clopidogrel and aspirin, the primary outcome was slightly lower in the PTAS group than in the AMM group, but this was not statistically significant (P=0.78). The lack of randomization in patients who had their QE on dual antiplatelet therapy coupled with the small number of patients in this subgroup limits any definitive conclusions regarding the comparative efficacy of PTAS versus AMM for this subgroup. Further studies are needed to determine whether patients with intracranial arterial stenosis who have a stroke on dual antiplatelet therapy are at higher risk of recurrent stroke and, if so, whether this risk can be mitigated by intensive management of vascular risk factors or other treatments, such as ischemic conditioning,7 or another endovascular approach, such as angioplasty.8

Of note, following the SAMMPRIS trial, the Food and Drug Administration changed the Humanitarian Device Exemption outlining the use of the Wingspan stent to stipulate that the device could only be used in patients with 70% to 99% stenosis who have had ≥2 strokes, despite aggressive medical management which includes strict blood pressure and low-density lipoprotein control not just the use of antiplatelet therapy.9

The findings in the present study that patients on an antiplatelet agent at the time of the QE are at no greater risk of a primary end point than patients not on an antiplatelet agent support those of the earlier WASID trial that compared warfarin to aspirin in patients with symptomatic intracranial stenosis. A post hoc analysis of the WASID trial found no difference in outcomes, either a combined end point of stroke or vascular death or stroke in the territory of the stenotic vessel, in patients who were on an antiplatelet at the time of their QE versus those who were not on an antiplatelet.1

Although recurrent stroke rates were lower in SAMMPRIS than in WASID, the rates in patients both on and off of AT are still undesirably high and better therapies are needed.

This study has some important limitations. Although the analyses were prespecified, the study was not powered specifically to compare outcomes in patients on versus off AT at the time of the QE. In particular, there was limited power to

---

Table 2. Results for the Primary End Point According to Treatment and the Use of Antithrombotic Use at the Time of the Qualifying Event

<table>
<thead>
<tr>
<th>Antithrombotic Status</th>
<th>Medical Group</th>
<th>PTAS Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Patients</td>
<td>No. Patients</td>
</tr>
<tr>
<td>On antithrombotic</td>
<td>140</td>
<td>116</td>
</tr>
<tr>
<td>Not on antithrombotic</td>
<td>87</td>
<td>80</td>
</tr>
</tbody>
</table>

P value† 0.96 0.52

CI indicates confidence interval; and PTAS, percutaneous transluminal angioplasty and stenting plus aggressive medical therapy.

*P value for the logrank test comparing the time to event curves of the 2 treatment groups separately for patients who were and were not taking an antithrombotic medication at the time of the qualifying event.

†P value for the logrank test comparing the time-to-event curves of patients who were and were not taking an antithrombotic medication at the time of the qualifying event separately for each of the treatment groups.

---

![Figure 1](http://stroke.ahajournals.org/)

**Figure 1.** Kaplan–Meier curves for the primary end point in the 2 treatment groups for patients taking an antithrombotic at the time of the qualifying event. PTAS indicates percutaneous transluminal angioplasty and stenting with the Wingspan stent plus aggressive medical management.

![Figure 2](http://stroke.ahajournals.org/)

**Figure 2.** Kaplan–Meier curves for the primary end point in the 2 treatment groups for patients taking aspirin and clopidogrel at the time of the qualifying event. PTAS indicates percutaneous transluminal angioplasty and stenting with the Wingspan stent plus aggressive medical management.
investigate outcomes in patients on various antithrombotic therapies, including those on dual antiplatelet treatment. Additionally, other features of the patients, such as use of statins and blood pressure control at the time of the QE, which may have affected subsequent risk of a primary end point, were not collected.

The present study has shown that antithrombotic failure is not a predictor of increased risk of a primary end point in either treatment arm. In the group that failed AT, PTAS did not serve as a rescue therapy. Aggressive medical management is the treatment of choice in patients with symptomatic intracranial stenosis, and management should not be influenced by whether or not the patient was already on AT.

Sources of Funding

The stenting and aggressive medical management for preventing recurrent stroke in intracranial stenosis (SAMMPRIS) trial is funded by the National Institute of Neurological Disorders and Stroke (grant number: U01 NS058728).

Disclosures

M.J. Lynn received salary support from the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) grant. He receives grant support from the National Eye Institute. He is the principal investigator of the Coordinating Center for Infant Aphakia Treatment Study (EY013287) and a coinvestigator on the Core Grant for Vision Research (EY006360). Dr Turan has received salary support from the SAMMPRIS grant and served on the Executive Committee and as Director of Risk Factor Management. She is the current recipient of a National Institute of Health (NIH)-funded grant. She serves on Clinical Events Committees for trials funded by Gore & Associates, Boehringer Ingelheim, and the NIH. Dr Derdeyn has received salary support from the SAMMPRIS grant. He serves on the angio core laboratory for a trial (Microvention) and on 2 Data and Safety Monitoring Boards (SILK Road and Penumbra). Dr Fiorella has received salary support from the SAMMPRIS grant. He has received institutional research support from Siemens Medical Imaging and Microvention, consulting fees from Codman/Johnson and Johnson, NFocus, W.L. Gore and Associates, and EV3/Covidien, and royalties from Codman/Johnson and Johnson. He has received honoraria from Scintia and has ownership interest in CVSL and Vascular Simulations. Dr Janis is a program director at the National Institute of Neurological Disorders and Stroke. Dr Chimowitz is the grant recipient (U01 NS058728) for the National Institute of Neurological Disorders and Stroke (NINDS)-funded SAMMPRIS trial discussed in this article. He has received salary support from the SAMMPRIS grant. Stryker Neurovascular donated stents for the SAMMPRIS trial and paid for some third party monitoring in the trial. AstraZeneca donated the statin medication for the SAMMPRIS trial. He has served as an expert witness in legal cases. The other authors report no conflicts.

References

Outcome in Patients Previously on Antithrombotic Therapy in the SAMMPRIS Trial: Subgroup Analysis
Helmi L. Lutsep, Stanley L. Barnwell, Darren T. Larsen, Michael J. Lynn, Mindy Hong, Tanya N. Turan, Colin P. Derdeyn, David Fiorella, L. Scott Janis and Marc I. Chimowitz for the SAMMPRIS Investigators

Stroke. 2015;46:775-779; originally published online January 15, 2015;
doi: 10.1161/STROKEAHA.114.007752
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
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:
http://stroke.ahajournals.org/content/46/3/775

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/