Outcome of Symptomatic Intracranial Atherosclerotic Disease

Edgar A. Samaniego, MD; Scott Hetzel, MS; Supriya Thirunarayanan, MD; Beverly Aagaard-Kienitz, MD; Aquilla S. Turk, DO; Ross Levine, MD

Background and Purpose—Patients with intracranial atherosclerotic disease have a 3.6% to 22% annual risk of stroke. In this study, we sought to evaluate the natural history and prognosis of patients with symptomatic intracranial atherosclerotic disease who received medical therapy versus percutaneous transluminal angioplasty and stenting (PTAS) at our institution.

Methods—Charts of all patients with symptomatic intracranial atherosclerotic disease from July 2004 to September 2007 were reviewed and assessed for history of transient ischemic attack or stroke. Patients were either treated with “best medical therapy” (Medical Therapy Group) or PTAS plus antiplatelet agents (PTAS Group) and followed prospectively. A favorable outcome was defined as the absence of transient ischemic attacks, strokes, or vascular death; modified Rankin Scale of ≤3; and no endovascular reintervention of symptomatic in-stent restenosis.

Results—One hundred eleven patients fulfilled entry criteria, with 58 (52.3%) and 53 patients (47.7%) enrolled in the Medical Therapy and PTAS Groups, respectively. Thirty-eight patients of the Medical Therapy Group (65.5%) had a favorable outcome compared with 37 patients of the PTAS Group (69.8%). Combined ischemic end point data for the occurrence of transient ischemic attack, stroke, and vascular death was similar with 14 (24%) events in the Medical Therapy Group versus 15 (28.3%) events in the PTAS Group.

Conclusion—Overall, the combined ischemic end point was the same in the Medical Therapy and PTAS Groups. (Stroke. 2009;40:2983-2987.)

Key Words: angioplasty and stenting ■ atherosclerosis ■ interventional neuroradiology ■ intracranial stenosis

Patients with intracranial atherosclerotic disease (ICAD) have a 3.6% to 22% annual risk of stroke. Approximately 10% of ischemic strokes have been related to ICAD. Based on the Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) trial, ischemic stroke rates in the territory of a moderate to severe symptomatic intracranial stenosis were 11% and 12% at 1 year for warfarin and aspirin, respectively.

Among patients with symptomatic ICAD who “failed” antithrombotic therapy, the subsequent rates of stroke or vascular death were as high as 45% per year. There is no consistent evidence of “best medical therapy” to treat symptomatic ICAD. In most cases, therapeutic decisions are based on anecdotal evidence or personal experience. New treatments for ICAD such as intracranial percutaneous transluminal angioplasty and stenting (PTAS) have emerged as alternative approaches to medical therapy. However, there are limited data available regarding the success and durability of this modality. We report our retrospective, single-center, nonrandomized experience in the management of symptomatic ICAD to determine if patients receiving PTAS experienced better clinical outcomes than those receiving more traditional medical therapy.

Methods

Patient Selection

We retrospectively reviewed the University of Wisconsin Comprehensive Stroke Center medical records of all patients with symptomatic ICAD who presented between July 2004 and September 2007. The study was approved by the University of Wisconsin Institutional Review Board.

Demographic characteristics, vascular risk factors, and history of transient ischemic attacks (TIAs) or stroke were determined by medical records review. The extent and location of ICAD was documented by MR angiography, CT angiography, or intra-arterial digital subtraction angiography. Other possible stroke etiologies such as cardioembolism, paroxysmal embolism with patent foramen ovale, or cervical thromboembolism were ruled out by echocardiography and further imaging. Patients with coagulopathies and nonatherosclerotic causes of intracranial stenosis were excluded from this study.

Treatment Modalities

Patients were treated with “best medical therapy” (Medical Therapy Group) or PTAS plus antiplatelet agents (PTAS Group) after a multidisciplinary committee comprised by a vascular neurologist, a neuroendovascular specialist and, frequently, a vascular neurosurgeon reviewed each case. Antithrombotic selection was based on various published guidelines. This study did not intend to look at antithrombotic agent-specific outcome data.

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Lesions felt amenable for revascularization included those with angiographically verified ≥50% stenosis of a major intracranial artery and TIA or stroke in the vascular territory of the target lesion. PTAS was performed in 31 lesions by using the Wingspan system (Boston Scientific, Fremont, Calif). Twelve lesions were treated using Neuroform stent systems (Boston Scientific) and 14 using various balloon-expandable stent systems.

Patients were followed prospectively on a monthly basis. In some cases, structured telephone interviews were conducted in patients who did not have recent assessments. Favorable outcome was defined as symptom resolution, no new events, and a modified Rankin Scale score of ≤3. Events were defined as TIA, stroke, vascular death, performance of an extracranial–intracranial (EC-IC) bypass in the originally treated vascular territory due to TIA or stroke symptoms, and performance of another PTAS or additional placement of a stent in a symptomatic in-stent restenosis (ISR). ISR was defined as a lesion demonstrating stenosis >50% adjacent to the stent and absolute luminal loss >20% on follow-up imaging as described previously. ISR was considered symptomatic if it was accompanied by TIA symptoms or stroke. To facilitate data analysis, stent occlusion and EC-IC bypass surgery were recorded by their accompanying ischemic event, TIA or stroke. Events and favorable outcomes were registered at each clinic visit or interview session. As part of a post hoc analysis, a combined ischemic end point of TIA, stroke, and vascular death was compiled.

### Statistical Analysis

Demographic comparisons were made between the Medical Therapy and PTAS Groups using either a Pearson χ² test, Fisher exact test, Student t test, or Wilcoxon rank sum test. The time from start-of-observation to time of either loss-to-follow-up or first ischemic event was used to generate Kaplan–Meier curves. Second and third ischemic events (TIA or stroke) were also recorded under the Kaplan–Meier curves. Lost-to-follow-up was considered censored data. A log rank test was used to compare the 2 Kaplan–Meier curves. The start of observation defined in this article was either the initial clinical assessment by our stroke team or, in the PTAS Group, the day the stent was placed.

Subgroup analysis of favorable outcome was performed in the PTAS Group. Comparisons by stent type, deployment of single or multiple stents, and stent location were made using Pearson χ² tests. Number of favorable outcomes using these variables were examined and statistically compared with Pearson χ² test.

### Results

One hundred eleven patients fulfilled entry criteria with 58 patients (52.3%) and 53 patients (47.7%) enrolled in the Medical Therapy and PTAS Groups, respectively (Table 1). The mean age among both groups was 65 years. Patients were predominantly white with 48 (82.7%) in the Medical Therapy Group and 52 (98.1%) in the PTAS Group. Hypertension, hyperlipidemia, coronary artery disease, and previous stroke were the most common vascular risk factors among both groups. History of TIA was documented in 18.9% and 54.7% of the Medical Therapy and PTAS Groups, respectively (P<0.001). Location of atherosclerotic stenoses also varied significantly between groups (P<0.001). Patients in the Medical Therapy Group had more diffuse stenoses and less isolated anterior or posterior circulation lesions, 67.2%, 22.4%, and 10.3%, respectively. Patients in the PTAS group had less diffuse stenoses and more isolated anterior or posterior circulation atherosclerotic lesions, 28.3%, 28.3%, and 43.4%, respectively.

The referral for the first encounter with the stroke team was significantly different between groups (P<0.001). Forty of the 58 (69%) patients in the Medical Therapy Group were either admitted through our emergency department or were transferred from another facility. Nearly 50% of the PTAS Group was initially seen in our stroke clinics.

At the time of presentation, 43 patients (74.4%) of the Medical Therapy Group had an ischemic stroke. These patients had more stroke-related disability with a significantly higher National Institutes of Health Stroke Scale score (average of 5.44, P=0.016), a wider National Institutes of Health Stroke Scale score range (from 0 to 23), and higher modified Rankin Scale values (average of 2.98, P<0.001).

In follow-up, 38 (65.5%) in the Medical Therapy Group did not have an event compared with 37 patients (69.8%) in the PTAS group (Figure 1). The Medical Therapy Group experienced 5 TIAS (8.6%), 5 deaths (8.6%), 3 strokes (5.1%), and one EC-IC bypass surgery (1.7%) due to recurrent TIAs. The PTAS Group experienced 8 neuroendovascular reinterventions (15%), 4 for asymptomatic and 4 for symptomatic ISR; 5 TIAS (9.4%); 2 treatment-related vascular deaths (3.7%); 2 periprocedural strokes (3.7%); and 2

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### Table 1. General Data of the 111 Patients

<table>
<thead>
<tr>
<th></th>
<th>Medical Therapy (n=58)</th>
<th>PTAS (n=53)</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range)</td>
<td>65.17 (39–87)</td>
<td>65.42 (40–88)</td>
<td></td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>25 (43.1)</td>
<td>16 (30.1)</td>
<td></td>
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<tr>
<td>White, n (%)</td>
<td>48 (82.7)</td>
<td>52 (98.1)</td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>46 (79.3)</td>
<td>47 (86.6)</td>
<td></td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>29 (50.0)</td>
<td>25 (47.1)</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>37 (63.7)</td>
<td>33 (62.2)</td>
<td></td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>19 (32.7)</td>
<td>10 (18.8)</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>22 (37.9)</td>
<td>20 (37.3)</td>
<td></td>
</tr>
<tr>
<td>Previous TIA, n (%)</td>
<td>11 (18.9)</td>
<td>29 (54.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous stroke, n (%)</td>
<td>22 (37.9)</td>
<td>20 (37.3)</td>
<td></td>
</tr>
<tr>
<td>Location of stenosis, n (%)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior circulation</td>
<td>13 (22.4)</td>
<td>15 (28.3)</td>
<td></td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>6 (10.3)</td>
<td>23 (43.4)</td>
<td></td>
</tr>
<tr>
<td>Diffuse</td>
<td>39 (67.2)</td>
<td>15 (28.3)</td>
<td></td>
</tr>
<tr>
<td>Patient referral, n (%)</td>
<td>11 (18.9)</td>
<td>25 (47.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinic</td>
<td>7 (12.0)</td>
<td>…</td>
<td></td>
</tr>
<tr>
<td>Emergency department</td>
<td>31 (53.4)</td>
<td>15 (28.3)</td>
<td></td>
</tr>
<tr>
<td>Transferred from OSH</td>
<td>9 (15.5)</td>
<td>13 (24.5)</td>
<td></td>
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<tr>
<td>Presenting condition, n (%)</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>43 (74.1)</td>
<td>30 (56.6)</td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>15 (25.6)</td>
<td>23 (43.4)</td>
<td></td>
</tr>
<tr>
<td>Stroke at presentation, mean (range)</td>
<td>5.44 (0–23)</td>
<td>3.47 (0–16)</td>
<td>0.016</td>
</tr>
<tr>
<td>NIHSS</td>
<td>2.98 (1–5)</td>
<td>1.83 (1–5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>mRS</td>
<td>1.53 (0–13)</td>
<td>0.7 (0–7)</td>
<td></td>
</tr>
<tr>
<td>TIA at presentation, mean (range)</td>
<td>1.33 (0–5)</td>
<td>1.57 (0–5)</td>
<td></td>
</tr>
<tr>
<td>NIHSS</td>
<td>38 (65.5)</td>
<td>37 (69.8)</td>
<td></td>
</tr>
<tr>
<td>mRS</td>
<td>37 (65.5)</td>
<td>37 (69.8)</td>
<td></td>
</tr>
</tbody>
</table>

OSH indicates outside hospital; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; NS, nonsignificant.
EC-IC bypass surgeries (3.7%) due to recurrent TIA.s. One of the vascular deaths in the PTAS Group was related to an acute middle cerebral artery in-stent occlusion with the development of a fatal ischemic stroke. This occurred during discontinuation of all antithrombotic medications because of a gastrointestinal hemorrhage. The other death in the PTAS Group occurred during an attempted basilar artery angioplasty and stenting, which was complicated with dissection and vessel rupture. Combined ischemic end point data for the occurrence of TIA, stroke, and vascular death showed no difference in incidence of ischemic events. Table 2 summarizes ischemic end points; 14 of 58 (24%) patients in the Medical Therapy Group experienced an ischemic event (6 TIs, 3 strokes, and 5 vascular deaths), whereas 15 of 53 (28.3%) patients in the PTAS Group had an ischemic event (11 TIs, 2 strokes, and 2 stroke-related vascular deaths).

**Periprocedural Event Rate**

Two ischemic strokes and one death occurred within 24 hours of PTAS for a periprocedural complication rate of 5.6%. One patient had a cerebral infarct on MRI with neurological signs lasting <24 hours and another patient had a TIA (Table 3).

The 2 stent occlusions reported in this study occurred with balloon-expandable systems; the first stent occlusion happened 2 days after PTAS and the patient underwent EC-IC bypass surgery because of recurrent TIA.s. The second stent occlusion occurred 9 days after PTAS, while the patient was off antiplatelet medications because of a gastrointestinal hemorrhage. Combined ischemic signs, occurring after TIA, stroke, and vascular death showed no difference in incidence of ischemic events. Table 2 summarizes ischemic end points; 14 of 58 (24%) patients in the Medical Therapy Group experienced an ischemic event (6 TIs, 3 strokes, and 5 vascular deaths), whereas 15 of 53 (28.3%) patients in the PTAS Group had an ischemic event (11 TIs, 2 strokes, and 2 stroke-related vascular deaths).

**Table 2. Event Distribution**

<table>
<thead>
<tr>
<th>Event</th>
<th>Event</th>
<th>TIA</th>
<th>Stroke</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Therapy, n (%)</td>
<td>14 (24.1)</td>
<td>6 (10.3)</td>
<td>3 (5.1)</td>
<td>5 (8.6)</td>
</tr>
<tr>
<td>PTAS, n (%)</td>
<td>15 (28.3)</td>
<td>11 (20.7)*</td>
<td>2 (3.7)†</td>
<td>2 (3.7)‡</td>
</tr>
</tbody>
</table>

*Four TIs occurred with symptomatic ISR and one as a periprocedural complication.
†Strokes occurred within 24 hours of PTAS.
‡One death occurred after stent occlusion and the other one as a procedural complication.

**Table 3. PTAS Complications**

<table>
<thead>
<tr>
<th>Event</th>
<th>No.</th>
<th>System</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent occlusion</td>
<td>2</td>
<td>Balloon-expandable stents</td>
<td>EC-IC bypass surgery</td>
</tr>
<tr>
<td>2 days after PTAS</td>
<td></td>
<td></td>
<td>MCA stroke and death</td>
</tr>
<tr>
<td>9 days after PTAS</td>
<td></td>
<td></td>
<td>Ischemic strokes within 24 hours</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Balloon-expandable stents</td>
<td>Symptoms persisted in both cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Deaths within 24 hours 1 Self-expandable stent</td>
</tr>
</tbody>
</table>

MCA indicates middle cerebral artery.

Kaplan–Meier analysis showed that patients in the Medical Therapy and PTAS Groups tend to achieve event-free survival by 12 months of enrollment. Kaplan–Meier curves are practically identical over the first 3 months. Patients in the PTAS Group tended to have a higher incidence of first ischemic events between 3 and 12 months, achieving the exact Kaplan–Meier estimate by 18 months (Figure 2). Average follow-up was 14 months for both groups.

**PTAS Group Subanalysis**

Subgroup analysis of the PTAS Group did not show a significant difference in outcome based on the type of stent used. Favorable outcomes were seen at a similar rate for patients who were treated with a single stent (n=30 [68.2%]) and for those with multiple stents (n=7 [77.8%]; P=0.706). There tended to be more favorable outcomes in patients who had a stent placed only in a posterior circulation lesion (n=22 [73.3%]) compared with anterior circulation (n=14 [63.6%]), but this difference was not statistically different (P=0.827).

**Discussion**

In our series, patients who did not undergo PTAS typically presented to the emergency department or were transferred from another facility. More often they presented with ischemic stroke, higher National Institutes of Health Stroke Scale score and modified Rankin Scale score, and diffuse ICAD. Patients in the PTAS Group typically were first seen at the stroke clinic and more often presented with at least one TIA, and lower National Institutes of Health Stroke Scale score and modified Rankin Scale score when their clinical presentation was stroke and had isolated anterior or posterior ICAD.

The American Stroke Association advocates the use of medical therapies such as antithrombotic agents, statins, and risk factor control for patients with symptomatic ICAD. Endovascular therapies such as PTAS, although appear to be promising, continue to be considered investigational and are used with a humanitarian device exemption. However, endovascular treatment also incorporates medical strategies used in secondary stroke prevention. “Best medical therapy” has been widely used for the treatment ICAD, but combined ischemic end points of TIA, stroke, and vascular death remain high. Furthermore, WASID showed that neither high-dose aspirin nor warfarin was effective in preventing ipsilateral strokes referable to diseased intracranial vascular territories. For all these reasons, the outcome of randomized trials such as

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Figure 1. Patient outcome by study group.
the ongoing Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial will hopefully clarify this complex issue.

Although the long-term outcome of these interventions is unknown, multiple centers have reported technically successful endovascular therapies for the treatment of symptomatic intracranial atherosclerotic lesions. The Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral and Intracranial Arteries (SSYLVIA) trial reported moderate to severe in-stent restenosis within 6 months of intervention in 32.4% of treated intracranial lesions. Even with newer self-expandable stents, the frequency of moderate to severe ISR appears to be as high as 35%. Reinterventions are required in approximately 19% of cases, exposing patients to periprocedural risks. The periprocedural 24-hour complication rate (stroke or death) in this study (5.6%) was similar to the reported in the literature. Although low, the 2 strokes and one procedural related-death represent 20% of the combined ischemic endpoint in the PTAS Group. The 2 strokes occurred with balloon-expandable systems and the vascular death with a Neuroform stent system. Better technology and technical approaches may lower even further periprocedural complications and improve outcome.

Patient selection for endovascular therapy is often based on imaging findings, failure of “best medical therapy,” timing of the ischemic event, and clinical significance of the stenosis. In this study, the qualifying criteria for endovascular treatment in the PTAS Group was more likely a TIA, despite medical therapy, suggesting that the decision to intervene was based on symptom recurrence in healthier patients often electively referred from an outpatient setting. As has been described in the literature, even in symptomatic patients with ICAD referred emergently for endovascular treatment, the decision to intervene was typically made at least after 24 hours of admission. Urgent endovascular treatments have shown a periprocedural complication rate as high as 50%. Therefore, most procedures are performed preventively in patients with repeated TIAs or small strokes. Additionally, several smaller series of acute intervention in ischemic strokes with intracranial self-expandable stents have reported periprocedural hemorrhage and mortality rates of 11% and 33%, respectively. On the other hand, ICAD natural history data reveals a median time of recurrent TIA, stroke, or death of 36 days, and 50% of patients would fail “best medical therapy.”

A Kaplan–Meier analysis used to adjust for variable follow-up between the Medical Therapy and PTAS Groups showed that after 18 months, stabilized clinical trends were maintained (Figure 2). Zaidat et al did not show a trend favorable to PTAS beyond 90 days. Most of the PTAS Group ischemic events occurred within the first 3 months of follow-up, and although the majority of procedures were technically successful, periprocedural complications accounted for 20% of first ischemic events. Another major drawback of angioplasty and stenting is the development of ISR. In an attempt to maintain clinical equipoise and stent patency, patients are often subjected to additional imaging and endovascular procedures during follow-up. This approach unfortunately increases healthcare costs as well as the risk of periprocedural complications. Nevertheless, ISR is only worrisome if it becomes symptomatic; in our series, 50% of ISR were symptomatic.

We acknowledge the limitations of this single-center retrospective study. Because treatment allocation between the
Medical Therapy and PTAS Groups was not randomized, it is conceivable that the different clinical and angiographic characteristics among the 2 groups accounts for different outcomes. The treatment choices made between “best medical therapy” and PTAS were based primarily on clinical presentation, lesion location, lesion accessibility, and the overall suitability for an endovascular procedure. These inherent differences might have affected the rates of clinical end points, mainly because of referral bias. The heterogeneity of endovascular therapies used in this study reflects an evolving technology that has achieved high technical success. Nevertheless, the variability of endovascular systems used undermines the homogeneity required for a suitable comparison with other treatment modalities.

Further subgroup analysis of the PTAS Group showed that stent location was possibly related to a better outcome. When all outcome measures were considered, posterior circulation endovascular interventions trended toward better outcomes than anterior circulation lesions, 73.3% and 63.6%, respectively. Levy et al reported a higher incidence of ISR within the anterior circulation as well.9

Most neurointerventional studies compare their results with the WASID trial.17,21 This a valid alternative given the lack of control groups in the medical arm; nevertheless, this comparison might be deceiving because in WASID there was a time selection bias and some patients deemed to be at high risk of stroke were not enrolled early to allow for a period of observation.9 This single-center study describes the outcome of 2 treatment modalities in a relatively homogeneous population with similar demographics and risk factors. The trend observed of a similar pattern of events for both groups should be verified with a larger trial comparing medical therapy with intracranial stenting;22 this is a crucial issue because the validity of self-expandable stents has been recently questioned.23,24

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Disclosures

None.

References


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