Long-Term Outcome After Angioplasty and Stenting for Symptomatic Vertebral Artery Stenosis Compared With Medical Treatment in the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS)

A Randomized Trial

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Background and Purpose—The long-term outcome of endovascular intervention compared with best medical management of patients with symptomatic vertebral artery stenosis is uncertain. We therefore compared these treatments in a randomized trial with long-term follow-up.

Methods—In the international, multicenter Carotid And Vertebral Artery Transluminal Angioplasty Study, 16 patients with symptomatic vertebral artery stenosis were randomized in equal proportions to receive endovascular therapy (balloon angioplasty or stenting) or best medical treatment alone. An independent neurologist followed up the patients for as long as 8 years.

Results—Endovascular intervention was technically successful in all 8 patients, but 2 patients experienced transient ischemic attack at the time of endovascular treatment. There were no deaths or strokes in any arterial territory within the first 30 days. During a mean follow-up period of 4.7 years, no patient in either treatment group experienced a vertebrobasilar territory stroke, but 3 patients in each treatment arm died of myocardial infarction or carotid territory stroke, and 1 endovascular patient had a nonfatal carotid territory stroke.

Conclusions—Patients with vertebral artery stenosis were more likely to have carotid territory stroke and myocardial infarction during follow-up than have recurrent vertebrobasilar stroke. The trial failed to show a benefit of endovascular treatment of vertebral artery stenosis, but the numbers of patients included was small. Larger randomized trials are required to determine whether vertebral artery stenting is justified in patients at higher risk of vertebrobasilar stroke. Treatment of patients with vertebral artery stenosis should focus on global reduction of vascular risk, including prevention of carotid territory stroke and myocardial infarction. (Stroke. 2007;38:000-000.)

Key Words: angioplasty randomized trial stents stroke prevention vertebral artery stenosis

Compared with symptomatic internal carotid artery stenosis, little is known about the natural history and optimal management of symptomatic vertebral artery stenosis. Atherosclerosis of the vertebral artery is thought to be an etiologic factor in ∼20% of posterior circulation strokes, either alone or in combination with other factors.1 Vertebral artery stenosis occurs most frequently at the vessel origin as it arises from the subclavian artery.2 Because this site may be difficult to visualize with noninvasive imaging, the contribution of vertebral artery stenosis to posterior circulation stroke may have been underestimated. The safety and efficacy of invasive treatment are uncertain, and until recently, most patients with vertebral artery stenosis have been treated with medical treatment alone. However, what constitutes best medical treatment is uncertain, because there have been no randomized, controlled trials of antiplatelet or anticoagulant drugs in patients known to have vertebral artery stenosis.

Reports of surgical treatment of patients with extracranial vertebral artery stenosis suggest that endarterectomy and vessel reconstruction are feasible and may have a favorable outcome.3,4 However, surgery at this site is technically challenging because of the difficulty in accessing the vessel origin, and complications are not infrequent.5 Endovascular treatment (percutaneous transluminal balloon angioplasty [PTA]...
and/or stenting) is an alternative, less-invasive approach to treat atherosclerotic vertebral artery stenosis. Numerous non-randomized case series have reported the outcome after endovascular treatment for extracranial and intracranial vertebral artery stenosis and basilar artery stenosis. Most patients in these series were treated with primary stenting, and most centers reported good technical success rates, with an average 30-day major stroke or death rate of 3.2%. The Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS) incorporated 3 separate randomized trials. We have previously published data from the trial in which patients with carotid stenosis were randomized between endovascular treatment and endarterectomy. The results of the second trial, in which patients with carotid stenosis not suitable for endarterectomy were randomized between endovascular treatment and medical treatment alone, will be the subject of a future report. The third separate trial randomized patients with vertebral artery stenosis to receive either endovascular treatment or best medical management alone. These data are the subject of this report. We did not incorporate a trial comparing endovascular treatment with surgical treatment for vertebral artery stenosis because our centers were not willing to treat patients with vertebral stenosis surgically.

**Patients and Methods**

Requirements for enrollment as a trial center in CAVATAS for treatment of patients with carotid or vertebral artery stenosis have been described previously. Six centers in England, Finland, Italy, Spain, and the United States randomized patients with vertebral stenosis in CAVATAS. Patients with vertebral stenosis were included if the investigator thought that both the patient and the lesion were suitable for either endovascular treatment or best medical management alone and if the investigator was uncertain which treatment option was best for the patient. It was anticipated that patients would have had symptoms in the vascular territory supplied by the stenosed vertebral artery within 6 months of randomization, although patients with more distant symptoms could be randomized if intervention was considered appropriate by the clinician, eg, if they were awaiting coronary artery bypass surgery. Patients were excluded if they were unable to give informed consent or unwilling to undergo intervention or if they had a disabling stroke with no useful recovery of function within the vertebrobasilar territory. All randomized patients underwent digital subtraction angiography with or without Doppler ultrasound imaging to establish the presence and quantify the severity of vertebral artery stenosis. Copies of the catheter angiograms were submitted to the central office for concealed review and measurement of stenosis severity. One investigator (M.M.B.) measured the severity of stenosis of the vertebral arteries with a micrometer. Measurements were performed before treatment, blinded to the allocated treatment arm. The stenosis severity was calculated from the catheter angiogram according to the following formula: percent stenosis = 100(1 − A/V), where A = diameter of the residual lumen at the point of maximal stenosis and V = diameter of disease-free distal vertebral artery at the point where the walls were approximately parallel. This is similar to the method used to measure carotid stenosis in the North American Symptomatic Carotid Endarterectomy Trial.

After obtaining informed consent, patients were randomly allocated in equal proportions to endovascular intervention with best medical treatment or to best medical treatment alone by a telephone call or fax to the Clinical Trial Service Unit in Oxford, England. Randomization began in March 1992 and was stopped in July 1997 at the end of the preplanned 5-year recruitment period. The randomizing physician was responsible for prescribing best medical treatment. Before 1994, patients underwent PTA with balloon catheters. Stents for use in the carotid and vertebral arteries were developed during the course of the trial and could be used in patients assigned to endovascular intervention from 1994 onward. Endovascular treatment was considered technically successful when a balloon catheter was dilated across the stenosis at least once or a stent was deployed.

Patients were followed up at 1 month after treatment and then at 6 months, 12 months, and yearly after randomization by an independent neurologist. All outcome events were reported to the central office. We recorded transient ischemic attacks (TIAs); nondisabling, disabling, and fatal strokes in the vertebrobasilar or carotid territory; myocardial infarction; and death from any cause. Stroke outcome events were classified as “nondisabling” when the patient did not require help, or “disabling” when the patient required help from another person as a result of the stroke to undertake everyday activities for >30 days after symptom onset. Strokes were considered to be fatal when death occurred as a direct result of stroke at any time after the event. The diagnosis of stroke was informed by the results of neuroimaging. TIA was defined as an acute disturbance of focal neurologic function with symptoms lasting <24 hours attributed to cerebrovascular disease.

For the primary outcome analysis, we planned to compare the risk of fatal and nonfatal vertebrobasilar territory strokes during follow-up in the 2 treatment groups. Secondary end points included the risk of vertebrobasilar TIA, fatal and nonfatal carotid territory stroke, and fatal myocardial infarction.

The degree of residual stenosis immediately after endovascular treatment was measured on a posttreatment catheter angiogram. Although further imaging follow-up was not mandatory, it was recommended that Doppler ultrasound with or without catheter angiography be carried out within the first year in patients allocated to endovascular treatment. It was not considered ethical to perform follow-up catheter angiography in the medically treated patients. We calculated the incidence of restenosis of the treated vertebral artery in endovascular patients who had additional catheter angiography during follow-up. Restenosis was defined as the presence of <50% stenosis immediately after treatment, with an increase in stenosis to >50% during follow-up.

**Statistical Methods**

All data were analyzed on an intention-to-treat basis with SPSS, version 11.0 (SPSS). We used the Mann–Whitney U test or t test to compare continuous variables and the Fisher exact test to compare categorical variables between groups. The log-rank test was used to compare the frequency of recurrent cerebrovascular events between groups. P < 0.05 was considered statistically significant.

**Results**

Seventeen patients thought to have vertebral artery stenosis were initially randomized. One patient was included in error after angiography had shown subclavian, not vertebral, artery stenosis. This patient was excluded from the analysis, leaving 8 patients allocated to endovascular treatment and 8 patients allocated to best medical treatment alone. All patients had cerebrovascular symptoms attributed to the vascular territory of the stenosed vertebral artery (Table 1). Fifteen of 16 patients had symptoms within 6 months of randomization, and 1 patient in the endovascular treatment arm had a TIA 12 months before randomization. The mean time interval between symptom onset and randomization was 92 days (range, 5 to 376), and the mean interval between randomization and endovascular treatment was 45 days (range, 7 to 148 days). No patients in the endovascular group experienced any cerebrovascular symptoms between randomization and treatment.

There were no significant differences in age, demographic or vascular risk factor profiles, or median baseline stenosis severity between the treatment groups (Table 1). The randomized stenosis affected the distal intracranial vertebral
TABLE 1. Comparison of Baseline Clinical Characteristics Between Groups

<table>
<thead>
<tr>
<th></th>
<th>Endovascular Treatment (n=8)</th>
<th>Best Medical Treatment (n=8)</th>
<th>Significance (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>5/3</td>
<td>7/1</td>
<td>0.57</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>64 (7.2)</td>
<td>63 (10.2)</td>
<td>0.91</td>
</tr>
<tr>
<td>Most severe prerandomization cerebrovascular symptom</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>4</td>
<td>5</td>
<td>1.0</td>
</tr>
<tr>
<td>Posterior circulation stroke</td>
<td>4</td>
<td>3</td>
<td>1.0</td>
</tr>
<tr>
<td>Minor</td>
<td>1</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Major, nondisabling</td>
<td>3</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>Major, disabling</td>
<td>0</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Vascular risk factors at randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>5</td>
<td>5</td>
<td>1.0</td>
</tr>
<tr>
<td>SBP, mean (SD), mm Hg</td>
<td>147.5 (15.5)</td>
<td>143.8 (19.2)</td>
<td>0.67</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean (SD), mm Hg</td>
<td>82.1 (11.7)</td>
<td>84.3 (10.1)</td>
<td>0.70</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>2</td>
<td>4</td>
<td>0.61</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>3</td>
<td>1</td>
<td>0.57</td>
</tr>
<tr>
<td>Insulin-dependent diabetes</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Non-insulin-dependent diabetes</td>
<td>0</td>
<td>2</td>
<td>0.47</td>
</tr>
<tr>
<td>Current smoker</td>
<td>3</td>
<td>4</td>
<td>1.0</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>3</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>Cholesterol &gt;6.5 mmol/L</td>
<td>5</td>
<td>2</td>
<td>0.24</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0</td>
<td>1</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Values are No. of patients, except where stated. No individual difference was statistically significant.

artery in 1 patient in the medical group and the origin of the vessel in the remaining 15 patients. All patients had at least moderate (>50%) vertebral stenosis, with a median baseline stenosis of 73% (range, 58% to 92%) in the endovascular group and 74% (range, 53% to 95%) in the medical group. In 1 case with distal collapse of the vertebral artery, the degree of stenosis was arbitrarily determined to be 95%.

Patients were followed up for a mean of 4.5 years in the endovascular group and 4.9 years in the medical group. One patient in the endovascular group died 5 months after randomization of a myocardial infarction, but the duration of follow-up in the other 15 patients ranged from 2.8 to 8.2 years. There was no significant difference in the 30-day risk of cerebrovascular symptoms between the groups (P=0.47; Table 2). After the initial 30-day periprocedural or po randomization period, 2 patients from each group had at least 1 additional posterior circulation TIA, with a mean time interval to symptom onset of 10.8 months (range, 6 to 13.6 months), but no patient experienced the primary outcome event of vertebrobasilar territory stroke after randomization. Two patients had a fatal myocardial infarction at 5 months and 5.6 years after randomization, respectively. Both had a prior history of ischemic heart disease. One patient died suddenly of a presumed vascular cause. One patient had a fatal carotid territory stroke of uncertain cause, and 1 patient had a nondisabling carotid territory stroke attributed to 70% stenosis of the common carotid artery. Both of these strokes occurred in the endovascular treatment arm. Overall, there were significantly more secondary end points (vertebrobasilar TIA, carotid territory stroke, and fatal myocardial infarction or vascular death) in the endovascular arm (log-rank statistic comparing risk of any secondary end point in the 2 arms, P=0.035).

There were no significant differences in the medical therapy used in the 2 arms. At the time of last follow-up, 7 patients in the endovascular arm were receiving antiplatelet therapy compared with 6 in the medical treatment arm. The other 3 patients were being anticoagulated with warfarin. Antihypertensives were prescribed in 6 and 5 patients in each arm, respectively. Five patients in the endovascular arm and 3 in the medical arm received statins.

In the endovascular group, 6 patients underwent PTA alone, and 2 had primary stenting. Endovascular treatment was technically successful in all 8 patients at the first attempt. The severity of vessel stenosis was reduced immediately after angioplasty or stenting, from a median of 73% to a median of 25% (interquartile range, 0% to 50%; P=0.003). One patient who was treated with primary stenting died 5 months after randomization and did not have follow-up imaging. Of the 7 remaining endovascular patients, 6 who were treated with balloon angioplasty alone underwent catheter angiography, and the surviving patient who was treated with stenting had a Doppler ultrasound scan after treatment. The mean time interval between treatment and last follow-up imaging was 9.6 months (range, 3 to 15 months). The median stenosis severity of the treated vertebral artery in the 6 endovascular patients who had follow-up catheter angiography was 49% (interquartile range, 9% to 63%). Three of the 6 PTA patients had restenosis on follow-up angiography (restenosis rate of 50%). Two of these 6 patients had additional posterior circulation TIAs during follow-up (median stenosis severity,

TABLE 2. Comparison of Outcome Events Between Groups

<table>
<thead>
<tr>
<th>Outcome events within 30 days of treatment or randomization</th>
<th>Endovascular Treatment (n=8)</th>
<th>Best Medical Treatment (n=8)</th>
<th>Significance (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebrobasilar territory TIA</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Any arterial territory stroke</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Combined “30-day risk”</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Outcome events during follow-up beyond 30 days

<table>
<thead>
<tr>
<th>Outcome events during follow-up beyond 30 days</th>
<th>Endovascular Treatment (n=8)</th>
<th>Best Medical Treatment (n=8)</th>
<th>Significance (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebrobasilar territory TIA</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Vertebrobasilar territory stroke</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nonfatal carotid territory stroke</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Fatal carotid territory stroke</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Fatal myocardial infarction/vascular death</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Values are No. of patients. No individual difference was statistically significant.
60%), and 4 had no further TIAs (median stenosis severity, 59%; P=0.64). One of the patients who had recurrent posterior circulation TIA underwent successful vertebral artery stenting 16 months after randomization. The 1 surviving patient who underwent primary stenting did not have restenosis on Doppler ultrasound imaging 11 months after treatment. Only 1 patient randomized to best medical treatment had follow-up imaging. This took place after the patient had a recurrent posterior circulation TIA 14 months after randomization, and the patient subsequently received successful vertebral artery stenting. The type and manufacturer of the stents used were Palmaz-Schatz (Cordis), NIR (Boston Scientific), and AVE (Medtronic).

Discussion

CAVATAS is the only randomized study to compare the outcome after endovascular treatment with best medical treatment alone for patients with vertebral artery stenosis. However, only 16 patients with vertebral artery stenosis were included in CAVATAS, compared with 504 patients with carotid stenosis randomized between endovascular treatment and endarterectomy in the study during the same 5-year time interval.27 The small numbers of patients with vertebral artery stenosis demonstrates the low rate of diagnosis of symptomatic vertebral artery stenosis. The trial failed to show a benefit of endovascular treatment for vertebral artery stenosis because no patient in either arm had a recurrent vertebrobasilar territory stroke up to 8 years after randomization. The study was therefore severely underpowered to demonstrate a benefit of treatment, but the results emphasize the need for much larger randomized trials to determine whether vertebral artery stenting is justified in patients at higher risk of vertebrobasilar stroke recurrence.

In contrast to the zero rate of vertebrobasilar stroke during follow-up, 3 patients in each treatment arm died of myocardial infarction, vascular death, or carotid territory stroke, and 1 endovascular patient had a nonfatal carotid territory stroke during follow-up. This suggests that the long-term outcome of patients with symptomatic vertebral artery stenosis depends more on the severity of coexistent atherosclerotic disease in other territories. Treatment of patients with symptomatic vertebral artery stenosis should therefore focus on a global reduction in vascular risk and the investigation and treatment of associated carotid and coronary artery stenosis to prevent long-term stroke and myocardial infarction.

The fact that none of the patients, whether treated medically or by endovascular intervention, experienced another vertebrobasilar territory stroke during a mean follow-up period of 4.7 years contrasts with the findings in medically treated patients with recently symptomatic severe carotid stenosis, who have a 5-year risk of recurrent ipsilateral carotid territory stroke of ≈27%.28 If the rate of stroke in our patients with symptomatic vertebral artery stenosis had been similar, we would have expected at least 3 or 4 vertebrobasilar territory strokes during follow-up. Hence, our findings suggest that vertebral stenosis patients with clinical features similar to those randomized in CAVATAS may have a low risk of recurrent vertebrobasilar territory stroke, even when treated with medical treatment alone. Previous case series showing a low rate of recurrent stroke after endovascular treatment of symptomatic vertebral stenosis have been interpreted as demonstrating effective stroke prevention,13,15 but this conclusion must be open to question if our findings in the medical arm are a reflection of the true risk. However, it is possible that our results have been unduly affected by chance because of the small numbers of patients randomized. Another possibility is that the interval between the presenting event and randomization (mean, 92 days) may have resulted in selecting patients with a benign prognosis. A systematic review suggested that patients with symptomatic vertebral artery stenosis may have a higher risk of recurrent stroke in the first 7 days after symptom onset than patients with recently symptomatic carotid stenosis.30 Therefore, it is possible that if patients could be randomized and treated within 7 days of first symptom onset, one might demonstrate a beneficial effect of endovascular treatment in terms of vertebrobasilar stroke prevention.

There was no significant difference in the 30-day risk of vertebrobasilar TIA or stroke, any stroke, or death between the treatment groups, and we did not observe any strokes or deaths in this period at all. However, 2 of the 8 endovascularly treated patients experienced a TIA in the immediate postprocedural period, and thus, one cannot conclude that vertebral artery endovascular therapy is necessarily safe. The incidence of peri-procedural stroke or death in a recent review of nonrandomized case series of endovascular treatment of vertebrobasilar stenosis was 3.2%.26

Despite the high initial technical success rate, 3 of 6 endovascular patients treated with PTA alone developed restenosis of the treated artery on follow-up catheter angiography. These data are in keeping with case series that reported a high rate of restenosis after endovascular treatment of vertebrobasilar artery origin stenosis.31 It was not possible to compare the risk of restenosis after PTA alone with that after stenting because only 1 stented patient had follow-up imaging. Furthermore, we cannot comment on the relation between stenosis severity and the risk of experiencing recurrent symptoms after endovascular treatment because of the small number of outcome events. The technology and protocol used for angioplasty changed during the course of the trial, from balloon angioplasty alone to primary stenting as the method of choice. The recent development of stents designed specifically for use in the cerebral vasculature may result in superior early outcomes after vertebral artery stenting. Thus, the significance of the restenosis we detected remains unclear, and further studies are required.

Appendix

CAVATAS Collaborators

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Trial Statistician
J.M. Bland.
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CAVATAS Centers
The following investigators contributed patients with vertebral artery stenosis to CAVATAS:
Hospital Clinic i Provincial, Barcelona, Spain: A. Chamorro, F. Vasquez, N. Vila (deceased).
Kuopio University Hospital, Finland: H. Manninen, J. Sivenius, T. Saari.
Policlinico St. Marco, Zingonia, Italy: M. Porta.
Queen’s Medical Center, Nottingham, England: D. Jefferson, N. McConachie.

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Disclosures
None.

References
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