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;38:1526-1530.)

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 artery 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, e.g., 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. 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
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 postrandomization 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 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 difference was statistically significant.

### TABLE 2. Comparison of Outcome Events 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>Outcome events during follow-up beyond 30 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<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.
ment alone. Previous case series showing a low rate of
lar territory stroke, even when treated with medical treat-
CAVATAS may have a low risk of recurrent vertebrobas-
with clinical features similar to those randomized in
Hence, our findings suggest that vertebral stenosis patients
outcome after endovascular treatment with best medical
CAVATAS is the only randomized study to compare the
stroke recurrence.
larger randomized trials to determine whether vertebral artery
prevention.
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 se-
vere carotid stenosis, who have a 5-year risk of recurrent
ipsilateral carotid territory stroke of \( \sim 27\% \).\cite{24} 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 vertebrobas-
lar territory stroke, even when treated with medical treat-
ment alone. Previous case series showing a low rate of
recurrent stroke after endovascular treatment of symptom-
atic vertebral stenosis have been interpreted as demonstrat-
ing effective stroke prevention,\cite{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 possi-
bility 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 re-
cently symptomatic carotid stenosis.\cite{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 vertebro-
basilar 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 endovascu-
larly 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 periprocedural stroke or death in a recent review
of nonrandomized case series of endovascular treatment of
vertebral artery stenosis was 3.2%.\cite{26}
Despite the high initial technical success rate, 3 of 6 endo-
vascular 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 vertebral artery origin
stenosis.\cite{11} 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 com-
ment 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

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J. Beard, T. Buckenham, M.M. Brown, A. Clifton.

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Queen’s Medical Center, Nottingham, England: D. Jefferson, N. McConachie.


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