Endovascular treatment of symptomatic high-grade vertebral artery stenosis

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Background: **The purpose of this study was to evaluate the initial and long-term results of endovascular treatment (EVT) in patients with symptomatic high-grade extracranial vertebral artery (VA) origin stenosis.**
Methods: **From February 2001 to March 2013, 73 consecutive patients (33 men with a mean age of 61.7 ± 8.8 years) underwent EVT for symptomatic high-grade VA stenosis. Preoperative evaluation included Duplex ultrasonography and arteriography. After successful treatment, all patients were followed up at 1, 3, 6, and 12 months after the procedure and every 6 months thereafter.**
Results: **Successful EVT of the VA stenosis was achieved in 68 patients (93.2%). All procedures were performed without use of cerebral protection. The early complication rate was 5.5%, which included one periprocedural transient ischemic attack, two hematomas at the puncture site, and one allergic reaction to the contrast agent. No in-hospital deaths occurred. During follow-up (mean, 44.3 ± 31.2 months; range, 2-144 months), the primary patency rates at 1, 3, 5, and 7 years were 98.4%, 87.3%, 87.3%, and 87.3%, respectively. Ultrasound Doppler controls during follow-up detected seven VA restenoses (10.3%). Univariate analysis failed to identify any variable predictive of long-term patency of successfully treated VA stenosis.**
Conclusions: **EVT of symptomatic VA origin stenosis is a safe and effective procedure associated with low risk and good long-term results, even without use of cerebral protection devices. (J Vasc Surg 2014;60:92-7.)**

Atherosclerotic vertebral artery (VA) stenosis is the second most common supra-aortic branch lesion after internal carotid artery (ICA) stenosis.[1,2] VA stenosis is a potential cause of posterior circulation ischemia, and about 20% to 25% of ischemic strokes occur in the vertebro basilar territory.[3,4] Approximately 30% of lesions of the VA are located either extracranially or intracranially; about 20% are at the basilar artery.[5] Another significance of the VA is that branches of both VAs make the anterior spinal artery, one of the main artery suppliers of the spinal cord. There are several management options for VA stenosis, including medical, surgical, and endovascular approaches. The current study was undertaken to review our 12-year experience of angioplasty and angioplasty with stenting of extracranial VA stenosis to evaluate the safety, short- and long-term patency, clinical success rates, and predictive risk factors in patients with VA stenosis.

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This manuscript was partly funded by the Serbian Ministry of Science and Technological Development, Project No 41002.
Author conflict of interest: none.
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The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.
0741-5214/$36.00

http://dx.doi.org/10.1016/j.jvs.2014.01.023

METHODS

From February 2001 to March 2013, 73 consecutive patients (33 men with a mean age of 61.7 ± 8.8 years) underwent endovascular treatment (EVT) of symptomatic high-grade VA stenosis (70%-99%) at the University Cardiovascular Clinic. Patients with VA occlusion and with the lesion distal to the V1 segment were not included in the analysis. Preprocedural evaluation included clinical examination and duplex ultrasound scanning of the extracranial carotid arteries, subclavian artery (SA), and VA. For the ultrasonic assessment of our patients, we used the European Carotid Surgery Trial method[6] to define the degree of VA stenosis. Medical records were reviewed for demographic data, procedural and lesion-specific factors, complications, and outcome variables. The neurologic examination was performed before and after the procedure by two experienced neurologists who were blinded for the study results. Neurologic symptoms were vertigo in 36 patients (49.4%), diplopia in 10 (13.7%), recurrent syncope in 9 (12.3%), speech disturbance in 3 (4.1%), headache in 2 (2.8%), and ataxia in 1 (1.4%). Of these, 14 were classified as a posterior circulation transient ischemic attack (TIA) by a neurologist (8 cases of diplopia, 2 cases of vertigo, 3 cases of speech disturbance, and one case of ataxia). TIA was defined as a brief episode of neurologic dysfunction caused by a focal disturbance of brain ischemia without imaging evidence of infarction. The remaining 12 patients (16.3%) had prior stroke in the posterior circulation in the past 6 months (four recurrent strokes), which classified them as symptomatic. Because all patients underwent brain computed tomography (CT) before intervention and final diagnosis, the stroke in the anterior

circulation was found in 10 patients. Other possible causes of the presenting symptoms, such as hypotension and otogenic and cardiac disorders, were excluded. The status of the contralateral VA was graded as follows: mild stenosis (<50%), 34 patients (46.6%); moderate stenosis (50%-69%), eight patients (11%); and severe stenosis (70%-99%), four patients (5.5%). Contralateral VA occlusion was found in 22 patients (30%), whereas it was absent in two patients (2.7%), and three patients (4.1%) had an atretic (<2 mm) contralateral VA.

Diagnosis of the VA stenosis was confirmed by digital subtraction angiography in nine patients from 2001 to 2005 by quantitative stenosis analysis. After 2005, multislice CT angiography (Lightspeed VCT; GE Healthcare, Milwaukee, Wisc) was used in 64 patients. Diagnosis of VA stenosis by multislice CT was made with Advantage Workstation software AW 4.3. VA anatomy was analyzed by a volume rendering three-dimensional protocol. Stenosis analysis was performed with the curved multiplanar reconstruction protocol, and the VA lumen was measured with a digital ruler (1-mm resolution). The degree of stenosis was calculated with the following equation: stenosis = (1 − minimal residual lumen/distal VA diameter) × 100%. In our center, the agreement between color Doppler ultrasound and digital subtraction angiography is 98%; between color Doppler ultrasound and CT angiography, it is 97%. All patients signed the informed consent for use of their data for the analysis. The study was approved by our local ethical committee.

Interventional procedure and administration of drugs. After the diagnosis of VA stenosis was made, every patient was seen by the neurologist and the vascular surgeon. Best medical therapy was prescribed in all the patients, except in the patients with posterior circulation TIAs and patients with simultaneous carotid artery and VA near-total occlusion, which required immediate treatment. If there was no symptom improvement under best medical therapy for at least 2 months, the indication for EVT was made by an interdisciplinary group (vascular surgeon, neurologist, and interventional radiologist). All procedures were performed by interventional vascular specialists in a Siemens AXIOM Artis dFA (Siemens Medical Solutions, Malvern, Pa) angiography suite. In every consecutive patient, at least 3 days before the intervention, acetylsalicylic acid (100 mg/d) and either ticlopidine (250 mg twice daily) or clopidogrel (75 mg/d) were administered. Since 2002, after the intervention, dual antiplatelet therapy was administered to all patients for 12 months, and acetylsalicylic acid (100 mg/d) was continued. Statins were administered in 61 of 73 patients (83.6%) on discharge. All procedures were performed under local anesthesia (lidocaine 1%). The procedure was performed under systemic anticoagulation (heparin in doses of 100 units/kg) to have the activated clothing time between 250 and 300 seconds. Selection of the puncture site was tailored to the individual patient's anatomy; it was the common femoral artery in 87% of patients, followed by the radial artery (8%) and brachial artery (5%). A 6F Judkins right, VA, or internal mammary artery catheter was used to engage the SA. A 6F or 7F guiding catheter was advanced to the stenosis over a 0.035-inch wire. Sometimes we used a buddy wire positioned in the distal SA to provide additional stability for the guiding catheter. The lesion was traversed with a 0.014-inch steerable guidewire, usually BMW Universal or Whisper (Abbott, Abbott Park, Ill). Depending on the severity of stenosis, predilation was performed with a balloon that was undersized compared with the reference vessel diameter. Selection of balloon size, stent type, and stent size was left to the discretion of the interventionist. The stents most often used were low-profile balloon-expandable coronary stents: Driver (Medtronic, Santa Clara, Calif), 16 (25.8%); Tsunami (Terumo Corp, Tokyo, Japan), 14 (22.7%); FlexMaster F1 (Abbott), 13 (21%); Multilink Vision (Abbott), 6 (9.7); Liberté (Boston Scientific Corp, Natick, Mass), 4 (6.5%); Integrity (Medtronic, Minneapolis, Minn), 4 (6.5%); and peripheral Palmaz Blue stent (Cordis Corp, Warren, NJ), 5 (8%). The proximal portion of the stent was positioned with one or two cells protruding into the SA to prevent prolapse of SA plaque into the VA. The degree of residual stenosis in the stented VA was measured by quantitative stenosis analysis on a post-treatment catheter angiogram. In six patients, only balloon dilation was used when the response to predilation was a stent-like result without any residual stenosis. All procedures were performed without use of cerebral protection.

Follow-up and definitions. During follow-up, patients were examined by the attending surgeon, and the duplex ultrasound controls were performed at 1, 3, and 6 months in the first year and every 6 months thereafter or whenever new symptoms appeared. Technical success was defined as a reduction in stenosis severity to <20% luminal narrowing with symptom resolution. Clinical success was defined as technical success related to periprocedural events from the initiation of the procedure through the first 24-hour postoperative period[7] and with symptom resolution beyond 24 hours after the procedure. Clinical failure was defined as a resumption of clinical symptoms with recurring stenosis (>50%) at 1 year after the index procedure confirmed by duplex ultrasound or arteriography. Ischemic cerebrovascular events (strokes, TIA) and worsening of symptoms were assessed.

Statistical analysis. Standard descriptive statistics were used. Kaplan-Meier curves were constructed to assess patency as well as to assess survival during the follow-up period. Cox univariate and multivariate analyses were performed to assess predictors of survival. Patency rates and mortality were calculated only for patients in whom initial EVT was successful. Individual differences were considered to be statistically significant for $P < .05$. SPSS version 17.0 (SPSS Inc, Chicago, Ill) was used for all statistical calculations.

RESULTS

Initial results. All lesions were located in the ostial part of the VA (V1). Technical success was achieved in 68 patients (93.2%), whereas the percutaneous approach

Table. Demographic characteristics of enrolled patients, indication for treatment, and lesion characteristics

Variable	*n = 73*	*%*
Median age, years	61.7 ± 8.8	
Male sex	33	45.2
Smoking	52	71.2
HTN	68	93.2
HLP	61	83.6
DM	26	35.6
Family	39	53.4
CAD	33	45.2
ICAD	14	19.2
Prior CEA	35	48
SAD	11	15.1
PAD	21	28.8
Prior TIA	14	19.2
Prior stroke	22	30.1
Mean VA stenosis	—	85.7 ± 9.2
Lesion side, left	35	47.9
Average lesion length, mm	16.2 ± 7.3	

CAD, Coronary artery disease; *CEA,* carotid endarterectomy; *DM,* diabetes mellitus; *Family,* family history of atherosclerotic disease; *HLP,* hyperlipoproteinemia; *HTN,* hypertension; *ICAD,* internal carotid artery disease; *PAD,* peripheral artery disease; *SAD,* subclavian artery disease; *TIA,* transient ischemic attack; *VA,* vertebral artery.

failed in five patients (6.8%) because of severe artery calcification in four and tortuosity in one. Direct stenting was performed in 50 cases (68.5%) with bare metal stents (mean stent diameter, 4.37 ± 0.64 mm; mean stent length, 16.57 ± 7.6 mm). Two stents were used in five lesions (7.3%). In 12 patients (16.4%), balloon angioplasty was used for predilation for very tight stenosis to allow later passage of the stent. Six patients (8.2%) were treated with percutaneous transluminal angioplasty alone. Baseline demographic characteristics of enrolled patients, indication for treatment, and lesion characteristics are shown in the Table.

Additional endovascular procedures were performed in 11 patients (15.1%). SA occlusion was found in five (6.9%), whereas six patients (8.2%) had SA stenosis. These patients received EVT (recanalization and stenting) in the same session, followed by ostial VA stenting. In nine patients (12.3%), we performed combined EVT (for VA stenosis) and open surgical carotid artery procedures because of high-grade ICA stenosis and contralateral ICA occlusion. To prevent an ischemic event, we first performed VA stenting to enable adequate cerebral perfusion, and carotid endarterectomy (CEA) was done in the next step.

No in-hospital deaths occurred. A neurologic complication, periprocedural TIA, was noted in one patient. This patient complained of diplopia during balloon dilation. The patient fully recovered after 60 seconds, and the postprocedural intracranial angiogram and brain CT scan were unremarkable. No specific therapy was given.

Other complications included hematoma at the puncture site in two patients (one required surgical treatment) and one allergic reaction to the contrast material. These complications were successfully resolved in all cases. After the initial 30-day periprocedural period, there was no death

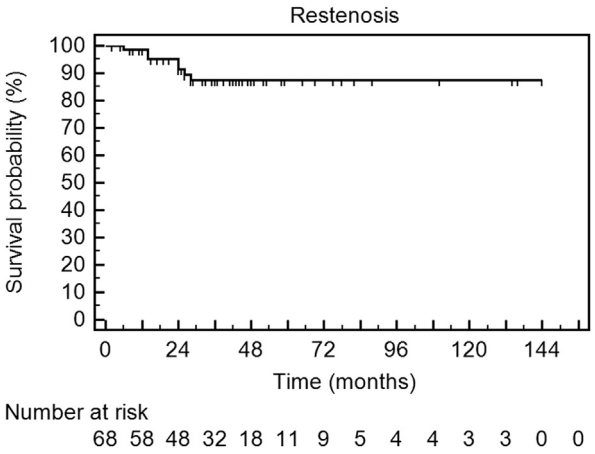

Fig 1. Kaplan-Meier curves for the presence of restenosis for the patients with successful endovascular treatment (EVT). The standard error is <10% throughout the graph.

or neurologic, vascular access site, or other complication. None of the symptoms worsened, including in nine patients (12.4%) with ICA stenosis and contralateral ICA occlusion.

In patients with EVT failure, the severe artery calcification was found in the target vessel in all four patients. Besides target vessel calcification, one patient had severe calcification of all the supra-aortic branches and aortic arch. In these four patients, the lesion was refractory to balloon inflation, and because of the possibility of plaque rupture or vessel dissection, the intervention was aborted. The tortuosity in the fifth patient was located directly to the SA, and the intervention failed because the balloon could not cross the tortuous lesion. This patient and two patients with severe artery calcification were switched to surgical treatment (one transposition and two bypass grafting procedures). A patient with severe calcification of the supra-aortic branches and aortic arch was unsuitable for the surgical treatment, and the last one refused surgery. These two patients died during follow-up (after 30 months and 89 months).

Follow-up data. The median follow-up period was 44.3 ± 31.2 months (range, 2-144 months). Four patients (5.5%) were lost during the follow-up period. Ultrasound Doppler controls during follow-up detected seven restenoses (10.3%). Four secondary endovascular repeated interventions were performed because of symptomatic moderate restenosis at 6, 14, 24, and 24 months, respectively (median, 17 months), after the index procedure. The recurrent symptoms were similar to those before intervention (vertigo, three patients; headache, one patient). Before reintervention, the same examinations as before the index intervention were performed to exclude other possible causes.

Another three patients had asymptomatic mild to moderate restenosis and were treated by drug therapy and controlled every 3 months with ultrasound Doppler examination. Fig 1 shows Kaplan-Meier curves for the presence

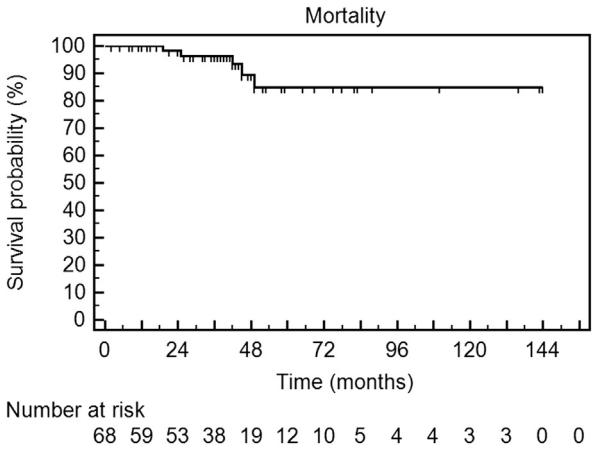

Fig 2. Kaplan-Meier curves depicting mortality for all the patients with successful endovascular treatment (EVT). The standard error is <10% throughout the graph.

of restenosis for the patients with successful EVT. Seven patients (9.6%) died during follow-up: 4 patients from cardiac causes (all had a prior history of ischemic heart disease), 2 patients from fatal carotid territory stroke of uncertain cause, and 1 patient as a result of malignant disease. Fig 2 shows Kaplan-Meier curves for mortality for all of the patients with successful EVT. After the index procedure, 27 patients (including nine with scheduled CEA) underwent various cardiovascular interventions: 2 patients underwent carotid angioplasty; 3 patients, SA angioplasty; 4 patients, coronary angioplasty; 4 patients, aortocoronary bypass grafting; 4 patients, CEA; and 1 patient, aortobifemoral bypass grafting.

Univariate analysis evaluating the following factors failed to identify any variable predictive of successful EVT: age; sex; risk factors for vascular disease; presence of carotid, subclavian, cardiac, and peripheral artery diseases; length and side of the occlusion; and stent used.

DISCUSSION

In current clinical practice, EVT of a symptomatic high-grade (>70%) VA stenosis is a reasonable therapeutic option to improve the vertebrobasilar blood supply. Numerous previous published studies have shown the results of EVT of extracranial VA stenosis. However, one of the limitations of these studies is the relatively short follow-up.[8,9] The current study shows the results of our 12-year experience of angioplasty and angioplasty with stenting of extracranial VA stenosis. The main finding of our study is that patients with symptomatic VA stenosis have low procedural risk and good long-term results. Patency rates at 1, 3, 5, and 7 years were 98.4%, 87.3%, 87.3%, and 87.3%, respectively. In addition, during follow-up (mean, 44.3 ± 31.2 months; range, 2-144 months), seven patients developed restenosis. The univariate analysis failed to identify any variable predictive factor associated with restenosis after EVT.

Medical treatment is not well established in the literature. Also, there is a lack of data for medical therapies related to VA restenosis after EVT. Optimal medical therapy for patients with VA stenosis should include antiplatelet medication for first-line prevention of stroke, risk factor modifications, and statin therapy.[10] To date, there have been no randomized trials of the use of different antiplatelet therapies or anticoagulation vs antiplatelet therapy in patients with extracranial VA stenosis. Sivenius et al[11] found in the European Stroke Prevention Study that a combination of aspirin and dipyridamole significantly reduced the rate of stroke in the patients with vertebrobasilar insufficiency compared with placebo. In the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS), Coward et al[12] compared endovascular and best medical treatment in patients with symptomatic VA stenosis. This trial failed to show a benefit of EVT for VA stenosis, with the limitation of small numbers of patients included (n = 16). However, the investigators found that no patient in either group experienced a vertebrobasilar stroke during a mean follow-up period of 4.7 years, but the initial results were better in the medical treatment group; two patients (25%) had TIAs at the time of EVT.

There are several surgical techniques for the treatment of VA stenosis; but in clinical practice, surgical treatment is technically demanding because of difficult access to the vessel origin, and it requires experienced surgeons. In addition, the combined morbidity and mortality rates after surgery range from 10% to 20%, and the risk of cranial neuropathies (such as Horner syndrome) and nonneurologic complications (lymphocele, wound infection, and pneumothorax) is high.[13-17] Also, long-term results are not promising; the incidence of vertebrobasilar stroke and TIA rates in several series during the follow-up period (mean time, 37 and 86 months) were 9.4% to 11.7%, and the incidence of restenosis ranged from 19% to 33%.[16,18,19] On the other hand, the study of Berguer et al[20] published in 2000 compared surgical results of patients treated before 1991 (n = 215) and after 1991 (n = 154). Surgical outcome after 1991, supported with digital arteriography in the operating theater, a trained anesthesia team, and established uniform management protocols, showed significant improvement. The vascular and neurologic complication rates and death rates were significantly lower in the patients operated on after 1991. However, it appears that the 5-year primary patency rates were similar in both groups (80%).

Surgical treatment may be the only viable treatment option in those patients who fail to respond to medical therapy and have lesions or anatomy unfavorable to EVT. In clinical practice, vascular reconstruction by EVT is logically a reasonable option to improve the vertebrobasilar blood supply in patients with VA stenosis. The first case of VA origin angioplasty was published in 1981 by Motarjeme et al.[21] Until the mid-1990s, angioplasty with no stent implantation was the treatment option for patients with VA stenosis, with low complication rates and low incidence of restenosis.[22]

A meta-analysis performed by Borhani Haghighi et al[8] in 2011 comprised 27 case series and showed a technical success rate similar to that of our study, with low periprocedural complication, mortality, and morbidity. In contrast, the restenosis rate in this meta-analysis was 20.8% vs 10.3% in our series.

Another review[9] published in 2012 that comprised 690 patients (737 lesions) with extracranial VA stenosis treated endovascularly showed similarly low technical and clinical complication rates. In this review, the rate of restenosis was significantly higher than in our series, especially after implantation of a bare metal stent (mean, 27%; range, 3%-48%), during the follow-up period (mean, 12.8 months; range, 6-36 months). In the same review, in the drug-eluting stent (DES) series, the restenosis rate was lower (mean, 14%; range, 0%-63%) during an average follow-up period of 5.7 months.

One of the possible explanations for the low restenosis rate might be SA revascularization. In our group, 17 patients (25%) had SA treatment: 3 patients had a prior VA angioplasty, 11 patients had a simultaneous procedure (SA and VA stenting), and 3 patients received SA stenting after VA treatment (after 12, 16, and 17 months). Werner et al[23] found that SA stenosis is a significant predictor of VA restenosis. A second potential explanation may be the extensive and prolonged use of high-dose statins in 83.6% of patients. Another advantage of our study is a long surveillance period; however, as can be seen from Kaplan-Meier curves, all restenosis occurred in a period of almost 2 years after EVT (range, 6-28 months). After this period, there was no evidence of VA restenosis. The cited meta-analysis[8] and review article,[9] which comprised all high-volume studies of EVT of VA stenosis, showed a higher restenosis rate, but all were limited with a short follow-up period (mean, 12.8 months; range, 6-36 months). These facts lead to the possible important conclusion that the peak incidence of VA restenosis is during 2 to 3 years after EVT.

In recent years, most series[24-26] have reported predominantly use of the DES for treatment of VA stenosis. Akins et al[27] suggested that placement of a DES reduces in-stent restenosis, but it is difficult to draw lessons from this study because of the small number of patients (n = 12). However, DES studies[24-26] showed technical and clinical complication rates similar to those in our study, and the rate of significant restenosis ranged from 7% to 17% during a follow-up period of 6, 7, and 12 months, respectively.

In the case of a concomitant lesion of the ipsilateral SA and VA, our practice is to treat both lesions in the same session. There are several advantages to this approach: complete revascularization in one session; SA treatment allows an adequate approach to and technically easier treatment of the VA stenosis; reduction in the rate of embolization; and improvement in the left internal mammary artery graft perfusion in the patients with coronary artery bypass grafts.[28] Also, as reported by Werner et al,[23] VA restenosis occurs significantly more often in patients with an ipsilateral SA stenosis.

Another important message from this study is that EVT of VA stenosis allows safe revascularization of the multiple occlusive lesions of the supra-aortic arteries. In nine patients (12.3%), EVT of the VA stenosis was performed before CEA and enabled adequate cerebral perfusion during surgical treatment of a single ICA in the next step.

During the procedure, we did not use cerebral protection in any patients. The role of distal embolic protection devices in VA stenting is unclear. Mintz et al[29] showed that only low numbers of microemboli signals were detected during VA stenting. However, the study performed by Qureshi et al[30] showed that stenting of the VA orifice with use of an embolism protection device is feasible and safe. In addition, during 1-month follow-up, no stroke or death was observed in 12 patients. On the other hand, the use of embolic protection devices is difficult in cases with high-grade stenosis and small diameter of the VA. Wehman et al[31] made a similar recommendation: the use of an embolic protection device for a larger VA (diameter > 3.5 mm) and in patients who have a favorable angle of the VA orifice and for the treatment of ulcerated lesions. Nevertheless, only one patient in our study had TIA during the intervention.

Limitations of the study. The treatment period was long, from 2001 to 2013, but all patients are consecutive. During the study period, the evolution of endovascular tools contributed to good initial results. Our study showed a good long-term result and additionally confirmed the benefit of EVT.

The use of different stents did not allow evaluation of different stent types with respect to early and long-term results. The conduct of randomized trials seems to be impossible, so that clinical series, like ours, may contribute to a better understanding of the value of EVT for VA symptomatic stenosis. Also, because of the small number of patients treated with angioplasty only (n = 6; 8.2%), we did not perform subgroup analysis (ie, percutaneous transluminal angioplasty alone vs stent placement). In addition, no restenosis occurred in these six patients during the follow-up period.

CONCLUSIONS

EVT of symptomatic VA origin stenosis is a safe and effective procedure associated with low risk and good long-term results, even without use of cerebral protection devices.

AUTHOR CONTRIBUTIONS

Conception and design: DR, SB
Analysis and interpretation: DS, ST, VK
Data collection: ST
Writing the article: SB, VK, PO
Critical revision of the article: ZR
Final approval of the article: PO, ZR
Statistical analysis: SB, PO
Obtained funding: Not applicable
Overall responsibility: DR, DS

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Submitted Nov 21, 2013; accepted Jan 9, 2014.