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Full Title

Endovascular Stenting for Atherosclerotic Subclavian Artery Stenosis in Patients with Other Craniocervical Artery Stenosis

Running Head

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ABSTRACT

Atherosclerotic subclavian artery stenosis (SAS) accompanied with other craniocervical artery stenosis (OCAS) is not uncommon in practice. We sought to investigate the safety and efficacy of endovascular stenting for SAS in patients with OCAS. Between January 2004 and February 2012, 71 consecutive atherosclerotic SAS patients who underwent primary stenting in our medical center were included. The enrolled patients were divided into combined-SAS group (n=51) and solitary-SAS group (n=20) depending on the presence or absence of OCAS. Data of demographics, procedure, and the followed-up were retrieved and analyzed. The technical success rate was 95.8%; the clinical success rate was 90.1%. There was no catheter-related major stroke or death. The immediate outcomes had no statistical difference between groups. During a mean of 27±20 months (range 2-88 months) followed-up, 7(10.3%) restenoses and 12(17.6%) clinical events were identified. The primary patency rate was 95.3%, 84.9% and 84.9% at 12 months, 24 months, and final followed-up respectively, which had no statistical difference between groups (Odds ratio (OR), 2.60; 95% confidence interval (CI), 0.54-12.53; P=0.232). The overall clinical event-free survival rate was 93.5%, 86.2% and 54.6% respectively, where the result of combined-SAS group was inferior to that of the solitary-SAS group (OR, 3.34; 95% CI, 1.02-11.00; P=0.047). Endovascular stenting was safe and feasible for atherosclerotic SAS in patients with OCAS, although the combined OCAS may have a significant influence on the long-term outcome. Further studies are warrant to investigate the effects of revascularization for MCAS on the cerebral hemodynamics and long-term outcomes.

Key words: subclavian artery stenosis; multiple craniocervical artery stenoses;

atherosclerosis; endovascular treatment; stenting

Introduction

Subclavian artery stenosis (SAS) is a common lesion of the aortic arch branches [1]. The left subclavian artery (LSA) appears to be more frequently involved [1]. Atherosclerosis is an important underlying aetiology of SAS that is often associated with involvement of other vessel beds [2, 3]. Severe SAS may lead to subclavian steal syndrome (SSS) and coronary-subclavian steal syndrome [4]. Although medical therapy is advocated as the first line treatment, endovascular revascularization is emerging as an alternative [5, 6].

Previous studies indicated the feasibility and safety of endovascular angioplasty and stenting for atherosclerotic SAS [7-12]. Most of the studies focused on patients with solitary SAS. In fact, atherosclerotic SAS accompanied with other craniocervical artery stenoses (OCAS) is relatively common in clinical practice. Patients with combined OCAS have a more severe load of atherosclerosis than patients with solitary SAS, thus they may have an inferior result of recanalization for SAS. However, there were few published data on endovascular stenting in this special patient population. Herein, we conducted a retrospective analysis to investigate the results of endovascular stenting for SAS in patients with OCAS.

Patients and Methods

Patient population

Between January 2004 and February 2012, patients who underwent endovascular stenting for SAS were retrieved from the Nanjing Stroke Registry Program (NSRP) [13]. Inclusion criterion was a symptomatic atherosclerotic stenosis or total occlusion (≥70% angiographic

diameter reduction), or part of high grade asymptomatic stenosis (≥80% angiographic diameter reduction) that had been intervened. We excluded all patients who had a history of disabling stroke [14] or had non-atheromatous causes such as Takayasu's arteritis, fibromuscular dysplasia, dissection and radiation-induced craniocervical arteriopathy. This study was approved by the local institutional review board, and informed consent was obtained from all patients.

Seventy-one patients (52 men and 19 females; median age 65 years [range 45–80 years]) were included. Each patient was evaluated by independent neurologists for a complete medical history collection and neurologic examinations before and after the procedure. All patients were routinely performed cerebral MR imaging before the procedure, and underwent computed tomography scan or MR imaging whenever indicated after stenting. Patients who had a history of nondisabling stroke [14] within 2 weeks to 6 months before procedure were evaluated of symptoms and brain imaging to identify the location of cerebral ischemia. Patients were confirmed as having SAS and OCAS based on the digital subtraction angiography (DSA) by using the method of NASCET [15] or WASID [16]. OCAS was defined as steno-occlusive lesions in the major extra- and intracranial arteries with a luminal diameter reduction > 50%. Patients with combined OCAS were classified into the combined-SAS group (51 patients), otherwise were assigned into the solitary-SAS group (20 patients).

Procedural techniques

All patients were pretreated with 100 mg aspirin and 75 mg clopidogrel daily for at least 3 days before the intervention, and were required to continue the dual anti-platelet regiments for at least 3 months after the procedure; thereafter, aspirin would continue lifelong. Procedures were performed under local anesthesia and conscious sedation. Patients were heparinized with a target activated clotting time of 250-300 s.

Two patients were performed the procedure by brachial access due to the severe atherosclerosis of iliac artery and common femoral artery, and 7 patients with a total occlusive lesion were treated by a combination of femoral and brachial access; the remaining patients were treated via the femoral artery approach alone. Unless otherwise indicated, an 8F arterial sheath was introduced into the right common femoral artery. For the brachial approach, a 5 F or 6 F vascular sheath was used. Angiography was performed to visualize the type of aortic arch and features of the target lesions. An 8F multipurpose guiding catheter was introduced into the aortic arch via a 0.035 inch superslide hydrophilic guidewire to be placed proximal to the SA lesion. The guidewire was then passed through the guiding catheter and crossed the lesion. A 0.014 inch micro-guidewire was exchanged for the 0.035 inch guidewire, and was deployed into the distal portion of the subclavian artery. Predilation was performed with an appropriate size balloon before self-expandable stent (SES) placement, depending on the extent and severity of the target lesions.

The total occlusive lesion was crossed via the brachial and femoral approach with a 0.014 inch micro-guidewire. In the situation of sub-intimal placement of the guidewire, attempts

were repeated until engagement with true luminal passage was achieved. Predilation with a small coronary balloon was performed to provide a channel for passing the delivery systems of the balloon or stent through the femoral approach. A secondary predilation was performed before stent placement using a peripheral balloon of 7-9 mm in preparation for placement of an SES. Poststent balloon dilatation was performed to ensure optimal stent expansion depending on the remaining stenosis after primary angioplasty.

No emboli protective device was used for the procedure of SAS revascularization. Only one patient with left SAS required two SESs to cover the entire lesions. Altogether 54 SESs and 14 balloon expanding stents (BES) were used for SAS, including 21Wallstents (Boston Scientific, Natick, Massachusetts), 20 Precise stents (Cordis, Warren, New Jersey), 11 Acculink stents (Abbott, Chicago, Illinois), 2 Protégé stents (ev3, Plymouth, MN), 14 Genesis stents (Cordis, Miami Lake, Florida).

One hundred and three OCAS were identified in 51 combined-SAS patients, including 38 internal carotid artery (ICA) lesions in 30 patients, 36 vertebral artery (VA) ostial lesions in 29 patients, 3 common carotid artery (CCA) lesions in 3 patients, and 26 intracranial artery lesions in 19 patients. Altogether, 28 additional stents were successfully implanted for extracranial symptomatic OCAS in a single procedure of SAS, including ICA (n=15), VA ostium (n=10), and CCA (n=3). A carotid lesion was usually treated after SAS stenting as previous described [17]. For the tandem lesions of SA and ostium of ipsilateral VA, we usually managed SA lesion initially with a balloon angioplasty, and then advanced a 0.014

micro-guidewire into V2 segment of ipsilateral vertebral artery, deploying a balloon-expandable stent in the ostium of VA; an appropriate stent was finally placed into the SA lesion.

Clinical and angiographic followed-up

Followed-up was conducted in the clinic or during hospital admission, and was scheduled at 1, 3, 6, and 12 months after procedure, and annually thereafter. Imaging workup was scheduled at 6 months after procedure with an interval of 6-12 months thereafter. DSA was recommended when the patient developed recurrent symptoms or the noninvasive workup suggested restenosis.

Definitions

Technical success was defined as < 30% residual stenosis confirmed by posttreatment DSA. Clinical success was defined as the resolution of the symptoms with the condition of technical success. Restenosis was defined as > 50% diameter reduction after primary stenting. Primary patency was defined as the uninterrupted vessel patency with no procedure performed on the treated SA segment. The primary clinical event was defined as the recurrent clinical symptoms originating from recurrent obstruction of SA. The secondary clinical event was defined as other cardio-cerebrovascular events including additional stent implantation, and various deaths during followed-up.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation and analyzed with Student's t-test. Enumerable data were presented as the numbers and percentages of patients or lesions, and were analyzed with the Fisher exact test. Kaplan-Meier analysis was performed to evaluate the rate of event-free survival and the primary patency. All reported probability values were 2-sided, and a value of $P < 0.05$ was considered to be statistically significant. Statistical analysis was performed with SPSS version 17.0 (SPSS; Chicago, IL, USA).

Results

The details of the risk factors for SAS intervention are shown in **Table 1**. No significant difference was found in respect to age, gender, or the incidence of hypertension, diabetes, hyperlipidemia, smoking, alcoholism, cardiac disease, and indications between the SAS-combined and SAS-solitary group. Thirty-two (45.1%) patients had a history of nondisabling stroke/transient ischemic attack (TIA). There was a significant difference in the incidence of history of stroke/TIA between the 2 groups (56.9% vs 15.0%; P=0.002). Of the 10 (14.1%) asymptomatic patients, 9 with a high grade stenosis were treated during endovascular therapy for other vascular territories; the remaining one was treated with the aim of reserving left internal mammary artery for coronary surgical bypass.

Sixty-four stenoses and 7 totally occlusive lesions were scheduled to perform stent implantation (left 65 and right 6). All the targeted SAS were proximal to the origin of the VA. The details of the characteristics and procedural data of SAS, including lesion length, the

incidence of the subclavian steal phenomenon (SSP), calcification, ulceration, or the extent of stenosis, mean difference of bilateral systolic blood pressure (SBP), the number of different stents, were shown in **Table 2**. The combined-SAS group had a lower incidence of SSP than the solitary-SAS group (39.2% vs 70%; *P*=0.03). No significant difference was detected with respect to the other above-mentioned variables between subgroups.

Perioperative outcomes

The detailed periprocedural outcomes of the study patients were listed in **Table 2**. The overall technical success was 93.4% (68/71), including 98.4% (63/64) for stenosis and 71.4 % (5/7) for total occlusion. Of the 3 technical failures, one was the above-mentioned patients with intraprocedural stroke; the second one was due to unable to cross the total occlusive lesions despite of repeated attempts; and the third had a remaining stenosis >30% after multiple postdilatations due to elastic recoil of the severe calcified stenotic lesion. Of the 7 patients who did not achieve clinical success, three were technical failures and four patients with OCAS of ipsilateral vertebral had persistent symptoms of vertebral basilar ischemia (VBI), resulting in an overall clinical success rate of 90.1% (64/71). Four (5.6%) complications were encountered in patients of combined-SAS group. In addition to 3 complications of puncture side hematomas, one patient suffered from embolic stroke during the repeated attempts to cross the total occlusive lesion, resulting in the procedure termination and technical failure. No significant difference was found with respect to technical success, clinical success, and incidence of complications between subgroups.

Mid-and long-term outcomes

Sixty-eight patients with technical success had been followed after procedure, with a mean time of 27±20 months (ranged 2 to 88 months). There were 3 patients lost to follow up with a censored value of 12 months. Sixty-four (94.1%, 64/68) patients had a followed-up time of 6 months or more.

Restenoses were found in 7 (10.3%, 7/68) patients, of whom 3 symptomatic restenosis received further balloon angioplasty due to recurrent VBI, 4 asymptomatic restenoses didn't need any further intervention. A typical patient underwent endovascular stenting for LSA, left VA, and right ICA in one procedure, and was identified with restenosis at 6 months (**Fig 1)**. The overall primary patency rate for subclavian stenting was 95.3%, 84.9% and 84.9% at 12 months, 24 months, and final followed-up, respectively. The combined-SAS patients had a lower long-term primary patency than solitary-SAS patients, but it did not reach statistical difference (OR, 2.60; 95% CI, 0.54-12.53; *P*=0.232).

Twelve clinical events (17.6%) were identified during a mean followed-up of 26 ± 20 months (ranged 2 to 88 months). Of the 12 clinical events, 3 (25.0%, 3/12) primary clinical events were symptomatic restenosis as just mentioned, the remaining 9 (75%, 9/12) were secondary clinical events: cerebral infarction or TIA (n=5), stents implantation in other vessel bed (n=3), died of acute pancreatitis (n=1). A marginal statistical difference was detected in the incidence of secondary clinical events between subgroups (*P*=0.053). The overall event-free survival rate was 93.5%, 86.2% and 54.6% at 12 months, 24 months, and final followed-up,

respectively. The combined-SAS group had a significant inferior clinical event-free survival rate to the solitary-SAS group (OR, 3.34; 95% CI, 1.02-11.00; *P*=0.047) (**Fig 2**).

Discussion

In the present case serial study of endovascular stenting for SAS, most enrolled patients were accompanied with OCAS. We achieved a high technical success rate and a satisfied immediate clinical success, with only a few minor complications. These figures were equivalent with most of recent reports, where the technical success rate ranged from 94.4% to 98.3%, and the clinical success rate was about 93.4% [7, 8, 18]. Moreover, we detected no significant difference in respect to these immediate outcome variables of SAS revascularization between the combined-SAS group and solitary-SA group. Therefore, our study demonstrated that endovascular stenting could achieve an excellent immediate outcome for atherosclerotic SAS in patients with OCAS.

Restenosis is a common concern of stent implantation. In the present study, seven (10.3%) restenoses were identified, and only three symptomatic restenoses needed further intervention. The primary patency rate was not inferior to some previous studies where it was ranged from 87% to 98% at 12 months, and about 84% at 24-78 months [8, 18, 19]. Of note, a 10-year primary patency of 85.2% and primary assisted patency of 92.6% has been reported recently with prevertebral subclavian artery angioplasties, and no restenosis occurred after the 25th month of the followed-up [12]. Similarly, we found that all our restenoses occurring within 24 months after procedure, which indicated that followed-up for restenosis of SAS

recanalization should be continued at least for 2 years. Surgical bypass of SAS had also revealed a superior long-term patency, but it was usually reserved for only low risk patients due to more invasive , inconvenient[9, 20], and especially not suitable for patients with OCAS. Accordingly, endovascular recanalization for SAS can achieve an acceptable long-term primary patency.

We found no significant difference in the incidence of restenosis and the corresponding primary patency rate between groups, which indicated that multiple craniocervical artery stenoses (MCAS) might be not a predictor for SAS restenosis. In contrast to Miyakoshi study that indicated that SES could provide long-term support and prevent restenosis [11], we did not find the same result despite we used SES for most patients. The selection of stent in our institution depended on the location and characteristics of the target lesion and experience of the operators. Most studies reported predominantly using BES for treatment of SAS [7, 8, 10, 21, 22]. However, some recent studies have also achieved high technical success by using SES [10, 11, 18]. Schillinger et al. found that long lesions, residual stenosis, and stent implantation independently correlated with restenosis [23].We observed one patient with restenosis had obvious intimal hyperplasia and stent shrunk (**Fig 1**), but no confirmative predictors were identified because of a small sample size and a relative low incidence of restenosis.

The long-term event-free survival rate in the current study was lower than that of previous studies [7, 18], which may be related to a high proportion of patients with MCAS. The

combined-SAS group had a significant higher incidence of history of stroke/TIA than the solitary-SAS group at baseline. Also, the former was slightly more prone to the clinical events during followed up (P=0.053). It is conceivable that patients with MCAS had a higher risk of cardio-cerebrovascular events than solitary-SAS patients. We further compared the event-free survival rate between groups, and found that the combined-SAS group had a significant inferior result to the solitary-SAS group (**Fig 2**). The result indicated that patients with MCAS may have an inferior long-term outcome of SAS recanalization, which should be evaluated more carefully before intervention.

In this study, the incidence of SSP was lower than many previous reports [19, 24, 25] because the combined-SAS patients had a significant lower incidence of SSP than the solitary-SAS patients (P=0.03), which indicated that patients with MCAS might have a more complex change of cerebral hemodynamics. Nevertheless, it remains controversial on treating several vessels in a single procedure for patients with MCAS. Valerio N et al. showed that surgical treatment can improve or normalize cerebral hemodynamic abnormalities and relieve nonhemispheric symptoms caused by severe multiple lesions of supraaortic trunks [26]. Klijn CJ did not find an association between symptoms and a poor cerebral hemodynamic or metabolic state in the patients with carotid artery occlusion [27, 28]. In our study, along with SAS revascularization, we implanted twenty-eight additional stents for symptomatic extracranial OCAS, and no related clinical events were encountered during followed up. These results indicated that endovascular treatment for one or more craniocervical arteries in one procedure was technologically feasible, and could relieve the related symptoms in most

of the study patients. Nevertheless, no cerebral perfusion imaging was available in this study to show the changes of cerebral hemodynamics before and after revascularization.

Our study had primary limitations of its retrospective nature and the relative short followed-up time, which did not allow for drawing a firm conclusion. A multicenter registry and prospective study with 5- to 10-year followed-up would be of greater scientific value.

In conclusion, our study demonstrated that endovascular stenting was safe and feasible for atherosclerotic SAS in patients with OCAS, although the combined OCAS may have a significant influence on the long-term clinical outcome. Further prospective studies are warranted to investigate the effects of one or more vessel revascularizations in patients with MCAS, especially on the cerebral hemodynamics and long-term outcomes.

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Disclosure of Interest Conflicts

We have no interest of conflicts to disclosure.

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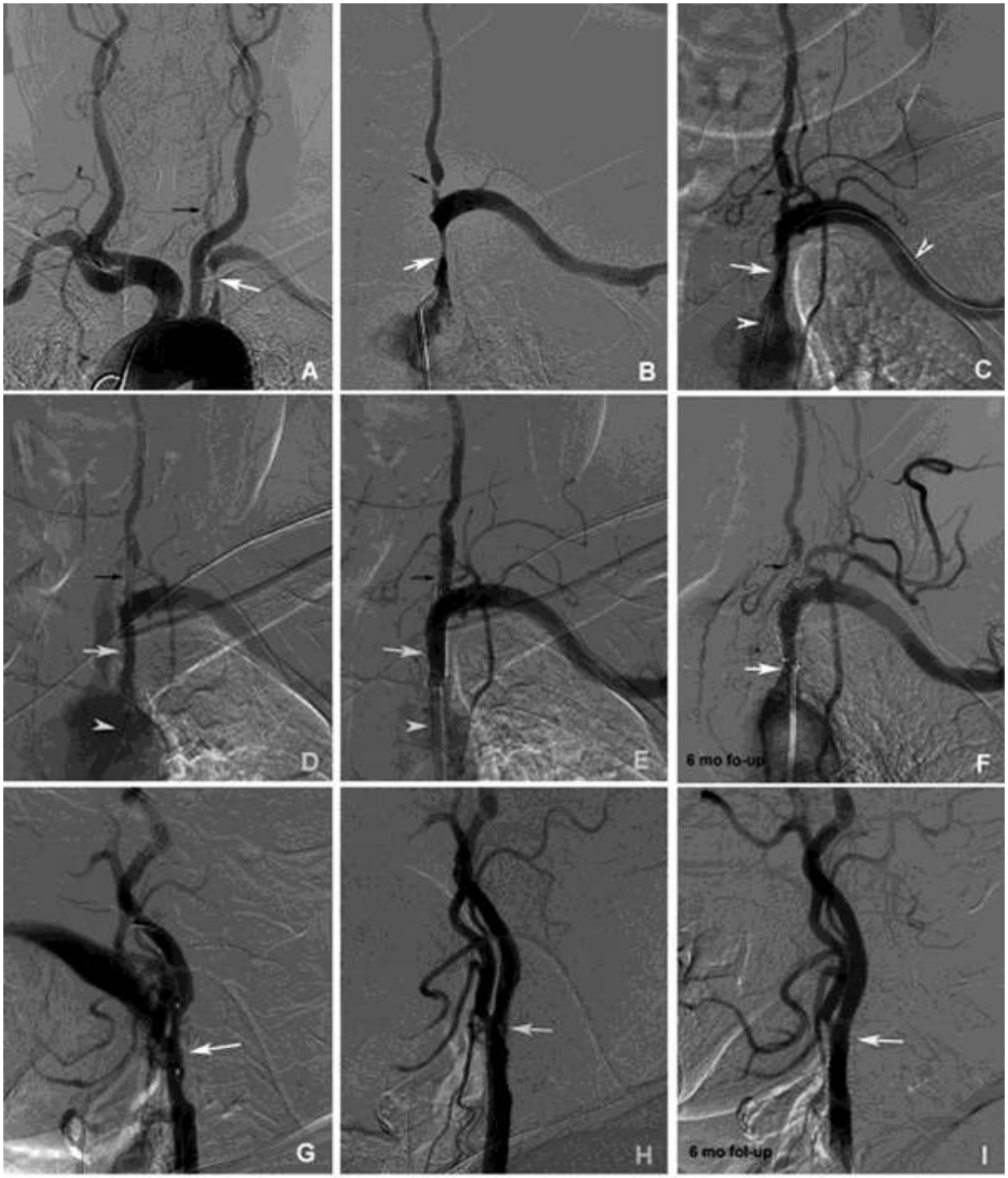
Figure Legends

Fig 1 Endovascular stenting in a patient with multiple craniocervical artery stenoses

A 65-year-old woman developed symptoms of vertebrobasilar insufficiency followed by left hemiparesis and dysarthria. (A) Aortic arch angiography shows a severe stenosis of left subclavian artery (LSA, white arrow), antegrade opacification of left vertebral artery (LVA, black arrow), and non-opacification of right vertebral artery; (B) Tandem lesions of LSA and LVA ostium; (C, D, E) Stenting of LVA and LSA at one session, with a mild remaining stenosis of LSA; (F) Intimal hyperplasia within stents of LSA and LVA with consequent moderate restenosis at 6-month followed-up; (G, H) Stenting of severe stenosis of origin of right internal carotid artery (RICA, white arrow) with mild residual stenosis; (I) No evidence of in-stent restenosis of RICA at 6-month followed-up.

Fig 2 Kaplan–Meier analysis of the clinical event-free survival

There was a statistically significant difference in the rate of clinical event-free survival between the 2 groups (OR, 3.34; 95% CI, 1.02-11.00; *P*=0.047, by log-rank test).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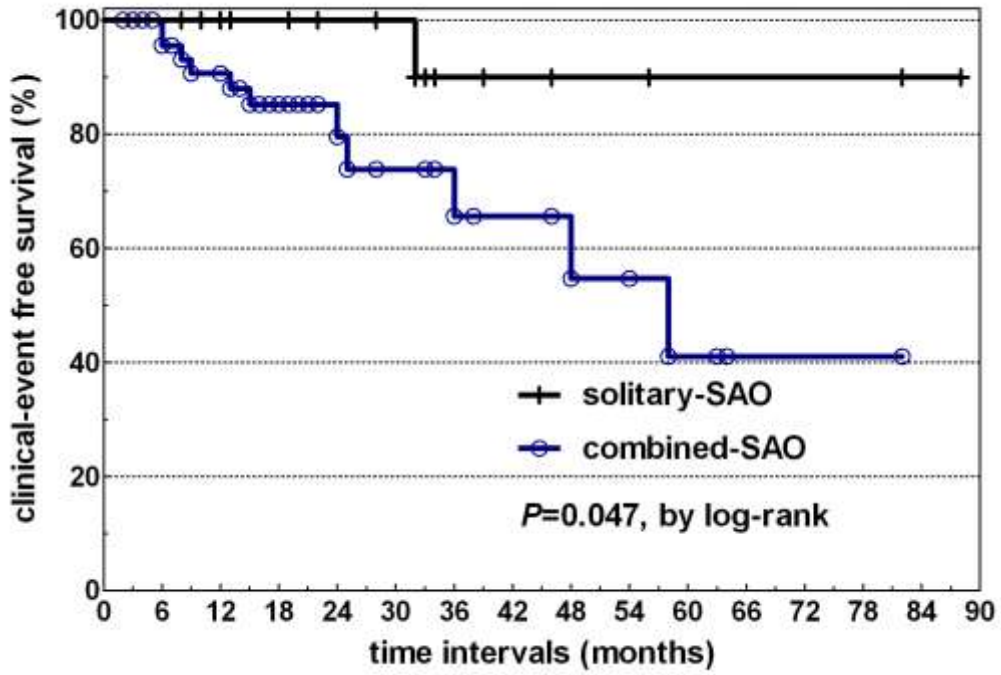

Table 1 Baseline Data Stratified to Subgroups

	All patients (N=71)	Combined-SAS group (N=51)	Solitary-SAS group (N=20)	*P*
Ages (years)	64.8±9.1	65.8±9.0	62.3±9.0	0.134
Male gender (n, %)	52(73.2)	38(74.5)	14(70.0)	0.77
Comorbidities and history				
Hypertension (n, %)	44(61.9)	31(60.7)	13(65.0)	0.79
Diabetes mellitus (n, %)	18(25.0)	12(23.5)	6(30.0)	0.56
Dyslipidemia (n, %)	15(21.2)	9(17.6)	6(30.0)	0.33
Smoking (n, %)	37(52.1)	27(52.9)	10(50.0)	1.00
Alcoholism (n, %)	20(28.1)	14(27.5)	6(30.0)	1.00
CAD and PAD (n, %)	12(16.9)	9(17.6)	3(15.0)	1.00
History of Stroke/TIA (n, %)	32(45.1)	29(56.9)	3(15.0)	0.002
Anterior circulation	21(29.6)	21(41.2)	0(0.0)	
Posterior circulation	11(15.5)	8(15.7)	3(15.0%)	
Indications and symptoms				

Symptomatic	61(85.9)	42(82.4)	19(95.0)	0.26
VBI	23(32.4)	15(29.4)	8(40.0)	0.41
Upper limber ischemia	18(25.4)	12(23.5)	6(30.0)	0.56
VBI + Upper limber ischemia	14(19.7)	10(19.6)	4(20.0)	1.00
Angina pectoris	6(8.5)	5(9.8)	1(5.0)	0.67
Asymptomatic or for CABG	10(14.1)	9(17.6)	1(5.0)	0.26

SAS subclavian artery stenosis, OCAS other craniocervical artery stenosis, TIA transient ischemia attack, CAD coronary artery disease, PAD peripheral artery disease, VBI vertebrobasilar insufficiency, CABG coronary artery bypass grafting

Table 2 Procedural Data and Outcomes

Variable	All patients (N=71)	Combined-SAS group (N=51)	Solitary-SAS group (N=20)	*P*
Left Sided (n, %)	65(91.5)	47(92.2)	18(90.0)	0.61
Total occlusive lesions	7(9.9)	5(9.8)	2(10.0)	1.00
SSP (n, %)	34(47.9)	20(39.2)	14(70.0)	0.03
Stenosis (%)				
Pre-intervention	83.8±9.0	83.7±9.3	84.2±8.4	0.83
Post-intervention [a]	6.8±7.6	7.1±7.8	6.1±7.2	0.60
Length (mm)	22.6±6.5	22.3±6.6	23.3±6.3	0.58
Calcification (n, %)	26(36.6)	21(41.2)	5(25.0)	0.86
Ulceration (n, %)	18(25.4)	15(29.4)	3(15.0)	0.52
Mean of bilateral SBP difference (mmHg)				
Pre-procedure	30.6±8.4	30.1±7.9	32.0±9.8	0.40
Post-procedure [a]	4.1±5.4	3.8±5.3	4.7±5.7	0.51
Type of stent (n, %) [a]				0.60
BES	14(20.6)	10(20.4)	4(21.1)	
SES	54(79.4)	39(79.6)	15(78.9)	
Immediate outcomes (n, %)				
Technical success	68(95.8)	49(96.1)	19(95.0)	0.89
Clinical success	64(90.1)	45(88.2)	19(95.0)	0.26
Complications	4(5.6)	4(7.8)	0(0.0)	0.31
Long-term outcomes (n, %) [a]				
Restenosis	7(10.3)	6(12.2)	1(5.3)	0.66
Clinical events	12(17.6)	11(22.4)	1(5.3)	0.16
Primary	3(4.4)	2(4.1)	1(5.3)	1.00

secondary	9(13.2)	9(18.4)	0(0.0)	0.053

SSP subclavian steal phenomenon, SBP systolic blood pressure, BES balloon-expanding stent, SES Self-expandable stent;

[a] Excluded 3 technical failure cases