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# Simultaneous Bilateral Carotid Stenting for Symptomatic Bilateral High-Grade Carotid Stenosis: A Retrospective Clinical Investigation

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**Background:** This retrospective clinical investigation aimed to evaluate the short-term effectiveness and safety of SBCAS for symptomatic bilateral high-grade CS.

**Material/Methods:** From 2009 to 2014, 145 patients were recruited. Among them, 70 underwent SBCAS, and other 75 patients underwent SAMM and served as controls. The immediate postprocedural complications and postprocedural neurological evaluation, as well as restenosis at 6-month and 1-year follow-ups in the SBCAS group are reported. Additionally, baseline risk factors for ischemic stroke, adverse effects of drugs, and outcomes at 30-day, 6-month, and 1-year follow-ups were compared between the 2 groups.





**Results:** Our data did not reveal significant differences between the 2 groups in baseline risk factors for ischemic stroke. In the SBCAS group, both HPS (5.7%) and HD (40%) occurred, but they were not very severe, and no patients had postprocedural neurological deficit. Moreover, restenosis only occurred in 3 patients at 3 stent placement sites (4.3%) at 1-year follow-up. Adverse effects of drugs did not occur in SBCAS group, but adverse effects of Bayer aspirin and Lipitor occurred in 4 patients (5.4%) and 18 patients (24.3%), respectively, at 6-month follow-up in the control group. Furthermore, there were significant differences in outcomes between the 2 groups at 30-day, 6-month, and 1-year follow-ups, in that NIHSS, CS ratio, and incidence of endpoint events, as well as 1-year cumulative probability of endpoint events, were all lower in the SBCAS group than in the control group ( $p < 0.05$ ).

**Conclusions:** Compared to SAMM, we found that SBCAS was more effective and safer for symptomatic bilateral high-grade CS.

**MeSH Keywords:** **Carotid Stenosis • Heart Defects, Congenital • Retrospective Studies**

**Abbreviations:** **SBCAS** – simultaneous bilateral carotid stenting; **CS** – carotid stenosis; **SAMM** – sole aggressive medical management; **HPS** – hyperperfusion syndrome; **HD** – hemodynamic depression; **CAS** – carotid stenting; **CEA** – carotid endarterectomy; **TIA** – transient ischemic attack; **DSA** – digital subtracted angiography; **NASCET** – North American symptomatic carotid endarterectomy trial; **NIHSS** – National Institute of Health stroke scale; **BP** – blood pressure; **CTP** – computed tomography perfusion; **PET** – positron emission computed tomography; **CTA** – computed tomography angiography; **OR** – odds ratio

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## Background

Stroke is a major cause of long-term disability and is the second leading cause of death in the world [1]. Also, stroke has brought about tremendous economic and social burdens on patients, families, and public health services, especially in low- and middle-income countries [2–4]. Ischemic stroke is a serious subtype of stroke due to its prompt onset without warning and great likelihood of recurrence after the initial episode, especially when patients have poorly controlled risk factors. For this reason, the first-level prevention of ischemic stroke, as well as better control of risk factors for ischemic stroke, is extremely significant.

CS – especially symptomatic, bilateral, and high-grade CS – is an important independent risk factor for ischemic stroke [5–10]. Both sole medical treatment and vascular surgical interventions have been recommended for symptomatic CS [11,12]. Since Kasner et al. reported the feasibility of sole medical treatment for symptomatic CS [13], some articles have been published in succession, trying to promote a better medical regimen (namely, SAMM) [14–20]. However, these results were divergent, and there was still a question of whether SAMM was superior to surgical intervention. Moreover, due to the consideration of likely poor outcomes at follow-ups, such patients with symptomatic bilateral high-grade CS have seldom been recruited into these clinical investigations. In addition, as both aspirin and statins have to be prescribed at above their routine dosages in SAMM, adverse effects of drugs may be a potential impediment that could reduce the therapeutic benefit from SAMM.

In spite of a controversial approach with regard to the optimal surgical intervention for symptomatic bilateral high-grade CS [21], CAS assisted by a distal protected device is more appropriate and advantageous than CEA [22–24], which is the criterion standard only for unilateral symptomatic high-grade CS [25–27]. Furthermore, in spite of concerns about greater likelihood of HPS and HD, such as severe brain edema, bradycardia and hypotension, SBCAS is still recommended for symptomatic bilateral high-grade CS. On the other hand, SBCAS could also eliminate a wider range of additional medical, physical, and economic burdens imposed by staged CAS on patients, such as later onset of severe postsurgical CS of the contralateral carotid artery, longer hospital stay, increased health care costs, and even scheduling inconveniences for those patients that may also require other potentially life-saving procedures like open heart surgery. Since Al-Mubarak et al. first reported the feasibility and theoretical advantages of SBCAS [28], some small retrospective clinical investigations have also been published, demonstrating that the SBCAS was effective and safe for symptomatic bilateral high-grade CS [29–36]. Nonetheless, most of them were just small series or lacked a control group, and an explicit, data-supported conclusion regarding SBCAS for symptomatic bilateral high-grade CS has not been reached.

Therefore, there is a clear need for larger investigations to firmly establish the superiority of SBCAS over SAMM, thus enriching the available clinical experience regarding use of SBCAS for treating symptomatic, bilateral, high-grade CS.

Thus, we retrospectively analyzed and compared short-term outcomes between a SBCAS group and a SAMM control group at 30-day, 6-month, and 1-year follow-ups in the present clinical investigation. Our aim was to preliminarily confirm the short-term effectiveness and safety of SBCAS for symptomatic bilateral high-grade CS. We also aimed to identify a more effective and safer regimen for patients with symptomatic bilateral high-grade CS.

## Material and Methods

### Patient population

From January 2009 to December 2014, 145 patients were recruited into this investigation. Inclusion criteria were: (1) 14–30 days after cerebral infarction onset and without previous history of TIA or ischemic stroke; (2) with a confirmed diagnosis of cerebral infarction via CT or MRI; (3) symptoms in accord with ischemic stroke; (4) presence of bilateral high-grade CS based on DSA examination (according to NASCET criteria: stenosis  $\geq 70\%$  and assumed to be a result of atherosclerosis); and (5) NIHSS  $\leq 22$ . Exclusion criteria were: (1) concurrent with severe neurological dysfunction; (2) multiple lines of severe stenosis in at least 1 lesion artery; (3) concurrent with stenosis of vertebral or basal artery; (4) undergoing acute myocardial infarction within 2 weeks of admittance; (5) concurrent with severe heart, liver, renal, or other systemic disease; or (6) incompleteness of medical history. All patients provided a complete medical history (Table 1) and underwent a systematic neurological examination by an independent neurologist who was not involved in follow-up evaluation. In addition, we extracted about 2 mL of vein blood from each patient for biochemical analysis the next morning. This retrospective clinical investigation was officially approved by the Medical Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (Nanning, Guangxi, China) and each patient provided written informed consent containing appropriate information on procedural complications and neurological disturbances [37] to aid patients in deciding which regimen to choose. Our protocol was approved by the Institutional Review Board of the First Affiliated Hospital of Guangxi Medical University.

### Interventions

#### SBCAS group

Patients were routinely prescribed oral dual-antiplatelet medication, including 75 mg Plavix and 100 mg Bayer aspirin for 3

**Table 1.** Comparisons of baseline characteristics between SBCAS group and control group.

Variables	SBCAS group	Control group	p values
Age (years)	70.81±5.55	70.97±6.11	0.618
Male gender (%)	39 (54.93%)	41 (57.75%)	0.735
Hypertension (%)	31 (43.66%)	28 (39.44%)	0.559
Hyperlipidemia (%)	44 (61.97%)	49 (69.01%)	0.377
Diabetes mellitus (%)	27 (38.03%)	21 (29.58%)	0.287
Coronary artery disease (%)	3 (4.23%)	5 (7.04%)	0.467
Current smoking (%)	29 (40.85%)	33 (46.48%)	0.499
Pulmonary disease (%)	1 (1.41%)	0 (0)	0.316
Previous PCI* (%)	5 (7.04%)	3 (4.23%)	0.467
Renal failure (creatinine ≥120 μmol/L) (%)	0 (0)	2 (2.82%)	0.154
Alcohol intake (%)	33 (46.48%)	37 (52.11%)	0.502
Hyperhomocysteinemia (%)	19 (26.76%)	22 (30.99%)	0.579
Abdominal obesity (%)	14 (19.72%)	11 (15.49%)	0.509
NIHSS (points)	3.94	3.13	0.938
Left CS (%)	80.55±5.69	80.41±5.02	0.959
Right CS (%)	80.48±5.51	81.24±5.10	0.335
mRS** ≥2 ratio (%)	70 (100%)	75 (100%)	1.000

\* PCI – percutaneous coronary intervention; \*\* mRS – modified Rankin scale.

successive days leading up to the procedure. Patients with hypertension were instructed to continue their regular medication on that morning. Patients with diabetes were instructed to keep their blood glucose level within an acceptable range. The whole procedure was carried out under general anesthesia monitored by an experienced anesthesiologist. Throughout the whole procedure, electrocardiography, hemodynamics, and intraarterial pressure were continuously monitored. The BP before and during the procedure were maintained at between 120 and 130 mmHg (systolic) and between 80 and 90 mmHg (diastolic). Intravenous antihypertensive medications were administered if necessary. Systemic heparinization was performed via intravenously administering a single bolus of heparin (3000–5000 units in total, according to body weight) after the procedure onset, to ensure an activated clotting time of approximately 250–300 seconds was maintained at all times. First, we treated the dominant lesion artery, defined as the artery with a further reduction in its lumen diameter. Percutaneous access of Seldinger technique was achieved through right femoral artery route and then an 8F sheath was placed into this artery. With the help of interchangeable guidewires, the 8F MP-A1 guiding catheters were positioned into the proximal

side of the common carotid artery. A distal embolic protection device, the Spiders (EV3, Plymouth, Minnesota), was placed into the C1 segment of the internal carotid artery and then deployed. Then atropine (0.5mg) was intravenously administered. Next, the lesion artery was predilated with a balloon 1 or 2 times, for 3–5 s each time. Then we implanted a self-expandable stent, the Precise (Cordis, Warren, New Jersey), into the stenotic portion with the help of microguidewires and then deployed the stent. We repeated the postdilation if necessary. After stent deployment, the final angiograph was carried out to assess the lumen of the carotid artery and intracranial vessels. Finally, the protection device was retrieved. We followed the same procedure a second time for another lesion artery. After the whole procedure was completed, every patient was transferred to the neuro-intensive care unit for an additional successive 24-h monitoring. Heparin was tapered off first. Rigid hemodynamic observation, especially of BP, was implemented in order to maintain systolic BP between 120 and 130 mm Hg and diastolic BP between 80 and 90 mmHg. Frequent neurological examinations were conducted. After the procedure, patients have to routinely continue to orally accept 75 mg Plavix, 100 mg Bayer aspirin, and 20 mg Lipitor every day

for 3 successive months. At 3 months later, Plavix was discontinued, while Bayer aspirin and Lipitor were maintained.

### Control group

Patients were prescribed oral doses of 75 mg Plavix, 325 mg Bayer aspirin, and 40 mg Lipitor (to lower LDL level to less than 1.81mmol/L) to be taken daily for 3 successive months. Moreover, individualized secondary regimens were also provided for each patient for aggressive control of risk factors for ischemic stroke [38]. These were antihypertensive treatment (to lower systolic BP to lower than 140 mmHg), strict blood glucose control, lipid profile regulation, giving up smoking, decreasing alcohol intake, getting appropriate exercise, and losing weight, as well as changes in lifestyle [18]. In the later stage of SAMM 3 months later, Plavix was discontinued from SAMM, the Bayer aspirin dose was decreased to 100 mg, and both Lipitor and individualized secondary regimens were maintained the same.

### Evaluations

#### Postprocedural complications

Primary technical success was defined as less than 20% residual stenosis in each artery after stent placement, according to the final DSA examination. One major immediate complication, HPS, was diagnosed in the presence of ipsilateral throbbing headache concurrent with/without nausea, vomiting, or ipsilateral focal seizures at the corresponding treated side, or occurrence of a focal neurological dysfunction without any neuroimaging evidence of cerebral infarction [39]. CTP or PET was carried out for patients whose symptoms did not conclusively diagnose HPS. Patients with symptomatic or asymptomatic hypotension (systolic BP  $\leq$ 90 mm Hg) or bradycardia (heart rate  $\leq$ 50 beats/min), regardless of whether normal saline infusions or atropine were required, were diagnosed with HD [40], another major immediate complication. In addition, each patient also had to accept a postprocedural neurological evaluation by a neurologist not involved in the SBCAS within 24 h and on the day of discharge. In-stent restenosis was diagnosed if there was a stenosis of more than 50% according to the NASCET criteria, confirmed by CTA [41].

#### Side effects of drug application

At 30-day, 6-month, and 1-year follow-ups, we extracted about 2 mL of vein blood from each patient for blood routine, liver function, renal function, and myocardial enzymes examinations. In addition, a stool sample was obtained for routine examination. A complete medical history was taken and a systemic physical examination was performed.

#### Follow-up outcomes

Neurologists carried out the evaluations of short-term outcomes at 30-day, 6-month, and 1-year follow-ups. NIHSS and CS ratios were evaluated. Comprehensive evaluation of neurological symptoms was performed by NIHSS, and evaluation of curative effect used the CS ratio. The primary clinical endpoint events were any occurrence of minor stroke, TIA, or death within 30 days. Minor stroke was defined as a new occurrence of nondisabling neurological dysfunction or a transient increase in NIHSS score of at least 3 points [42]. Death from any cause, including stroke, other vascular diseases, or other diseases, was considered a valid primary endpoint. The main secondary clinical endpoint event was major stroke, defined as a new neurological dysfunction or disability with an increase in NIHSS score of at least 4 points [43]. Other secondary clinical endpoint events included local and systemic complications, such as myocardial infarction, cranial-nerve injury, or upper gastrointestinal hemorrhage. All patients underwent an independent CTA examination at 6-month and 1-year follow-ups.

#### Statistical analysis

The present investigation involved both quantitative and qualitative variables. All quantitative variables (except demographics) are shown as interquartile range OR ( $=P_{75}-P_{25}$ ), due to their non-normal distribution. The quantitative demographics data are showed as mean  $\pm$ SD. All qualitative variables are shown as n%. The 2-sample t-test was used to compare demographic data. For other quantitative variables, the matched t-test was used for within-group comparisons, while the Kruskal-Wallis equality of populations rank test was used for between-group comparisons in other quantitative variables. The chi-squared test or Fisher's exact test was used for comparisons of qualitative variables. All statistical results are reported as a 2-tailed *p*-value, and *p*<0.05 was regarded as a statistically significant difference. All statistical analysis was carried out using SPSS software (Version 13.0).

## Results

### Baseline risk factors of ischemic stroke

Table 1 shows the detailed baseline risk factors for ischemic stroke of the 2 groups, including demographic, clinical characteristics, and atherosclerosis risk factors, as well as the *p*-value of each comparison. There were no statistically significant differences in demographics, clinical characteristics, or atherosclerosis risk factors between the 2 groups. There were also no significant differences in NIHSS or CS ratio between these 2 groups prior to our trial (all *p*>0.05). Moreover, every patient finished the complete follow-up.

**Table 2.** Comparisons of evaluated measures CS and NIHSS in SBCAS group.

	Before trial	Follow-up			<i>p</i> values		
		30-day N=70	6-month N=70	1-year N=70	30-day	6-month	1-year
Left CS (%)	80.55±5.69	13.83±4.82	11.68±3.96	11.10±4.08	<0.001	<0.001	<0.001
Right CS (%)	80.41±5.02	13.82±3.36	11.73±3.25	11.01±3.41	<0.001	<0.001	<0.001
NIHSS (points)	3.94	3.01	1.96	1.10	0.000	0.000	0.000

**Table 3.** Comparisons of evaluated measures CS and NIHSS in control group.

	Before trial	Follow-up			<i>p</i> values		
		30-day N=75	6-month N=74	1-year N=72	30-day	6-month	1-year
Left CS (%)	80.48±5.51	80.67±5.45	80.16±5.44	79.57±5.53	0.852	0.754	0.365
Right CS (%)	81.24±5.10	81.63±5.03	81.30±5.12	80.68±5.02	0.682	0.970	0.485
NIHSS (points)	3.13	2.83	2.31	1.72	0.534	0.155	0.136

### Postprocedural complications

Overall, 140 stents were implanted into 140 arteries in 70 patients, with 2 stents for each patient. Every patient had the potential to receive a technically successful procedure, as final DSA examination showed the residual stenosis of each artery to be less than 20%. We observed only 4 cases of HPS (5.7%, 4/70), all of which occurred within 48 h after SBCAS. The 4 cases of HPS manifested as elevated blood pressure, headache, and nausea, and were confirmed by CTP of anterior circulation edema. With the help of meticulously controlling BP and cautious hemodynamic monitoring after SBCAS, each patient could potentially achieve a full recovery without obvious sequelae. Although HD occurred in 28 patients (40%, 28/70), 26 (92.9%, 26/28) were just transient manifestations and spontaneously resolved without additional therapeutic necessity, leaving 2 relatively severe cases in need of further medical therapy. One case was manifested as a sustained low heart rate within 24 h after SBCAS, and this patient received a second dose of intravenous atropine (0.5 mg) to achieve a full recovery. The other case was more severe and presented with a sustained low BP; the patient required an infusion of normal saline and intravenous dopamine (10 mg) but still achieved a full recovery. No patients required more extreme rescue measures, such as transcutaneous or transvenous cardiac pacing. In addition, no patient suffered from a neurological deficit after SBCAS, with an NIHSS similar to the preprocedural value. Moreover, restenosis was found at just 3 stent placement sites in 3 patients (4.3%, 3/70) at 1-year follow-up.

### Side effects of drug use

At 30-day, 6-month, and 1-year follow-ups, adverse drug effects, including Plavix, Bayer aspirin, and Lipitor, did not occur in the SBCAS group. In the control group, adverse effects of drugs did not occur at 30-day follow-up. Nonetheless, adverse effects of Bayer aspirin occurred in 4 patients (5.4%, 4/74) at 6-month follow-up; they all manifested as a little melena, and the melena disappeared at 1-year follow-up after Esomeprazole application. In addition, adverse effects of Lipitor occurred in 18 patients (24.3%, 18/74) at 6-month follow-up; they all manifested as obvious muscular damage, including myosalgia and elevated creatine kinase. However, the muscular damage disappeared at 1-year follow-up after coenzyme Q10 application.

### Follow-up outcomes

At 30-day, 6-month, and 1-year follow-ups, NIHSS and CS ratio were all significantly lower than their preprocedural values in the SBCAS group (all  $p < 0.05$ ) (Table 2); however, NIHSS and CS ratio were all similar to their preprocedural values in the control group (all  $p > 0.05$ ) (Table 3).

At 30-day follow-up, there was just 1 case of new minor stroke (1.4%, 1/70) in the SBCAS group. In the control group, however, there were 8 adverse events in total, including 2 cases of minor stroke (2.7%, 2/75) and 6 cases of TIA (8%, 6/75) in the control group. These cases mainly manifested as weakness and numbness of the ipsilateral limb and transient aphasia. No case of major stroke, death, or other complications was observed in either group. The total incidence of endpoint

**Table 4.** Comparisons of endpoint events at 30-day, 6-month and 1-year follow-ups between SBCAS group and control group.

	SBCAS group						Control group						p Values		
	30-day		6-month		1-year		30-day		6-month		1-year		30-day	6-month	1-year
Minor stroke	1 (1.4%)	3 (4.3%)	4 (5.7%)	2 (2.7%)	4 (5.4%)	10 (13.9%)	0.601	0.775	0.102						
TIA	0 (0)	0 (0)	0 (0)	6 (8%)	12 (16.2%)	14 (19.4%)	0.005	<0.001	<0.001						
Major stroke	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.4%)	2 (2.8%)	1.000	0.332	0.160						
Total death	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.4%)	2 (2.8%)	1.000	0.332	0.160						

was much higher in the SBCAS group (1.4%, 1/70) than in the control group (10.7%, 8/75), and a significant difference was found in between-group comparison of TIA ( $p < 0.05$ ) (Table 4).

At 6-month follow-up, there were 3 cases of minor stroke (4.3%, 3/70) that mainly manifested as new symptoms of paralysis in the ipsilateral limb in the SBCAS group. No case of major stroke, death, or other complications was observed in the SBCAS group. In the control group there were 18 adverse events, including 4 cases of minor stroke (5.4%, 4/74), 12 cases of recurrent TIA (16.2%, 12/74), 1 case of major stroke (1.4%, 1/74), and 1 death (1.4%, 1/74). The death was caused by a large-scale cerebral infarction in the ipsilateral frontal, parietal, and temporal lobes. This occurred 3 months after SMM onset and led to death 1 week later. The total incidence of endpoint was much higher in the SBCAS group (4.3%, 3/70) than in the control group (24.4%, 18/74), and a significant difference was found in between-group comparison of TIA ( $p < 0.05$ ) (Table 4).

At 1-year follow-up, there were 4 cases (5.7%, 4/70) of minor stroke in the SBCAS group. In the control group there were 28 adverse events, including 10 cases of minor stroke (13.9%, 10/72), 14 cases of TIA (19.4%, 14/72), 2 cases of major stroke (2.8%, 2/72), and 2 deaths (2.8%, 2/72). The 2 deaths were both caused by new acute myocardial infarction that occurred 10 months after SMM onset and led to death 3 days and 7 days later, respectively. The total incidence of endpoint was much higher in the SBCAS group (5.7%, 4/70) than in the control group (38.9%, 28/72), and a significant difference was found in between-group comparison of TIA ( $p < 0.05$ ) (Table 4). The 1-year cumulative probability of endpoint events in the SBCAS group and control group were 5.71% and 38.89%, respectively. A between-group comparison showed that the 1-year cumulative probability of endpoint events in the SBCAS group was significantly lower than in the control group ( $p < 0.05$ ).

## Discussion

To the best of our knowledge, this is the first retrospective clinical investigation on optimal therapeutic choice for symptomatic bilateral high-grade CS. The present investigation

retrospectively analyzed the adverse effects of drug application and short-term outcomes at 30-day, 6-month, and 1-year follow-ups between the SBCAS group and control group, as well as some major postprocedural complications. The results preliminarily established the superiority of SBCAS for symptomatic bilateral high-grade CS over SMM, as the former seemed to be more effective and safer.

### Short-term outcomes of follow-ups (effectiveness)

#### SMM

Chimowitz et al. were the first to show the effectiveness of SMM on high-grade intracranial CS by demonstrating that the actual incidence of endpoint events was lower than expected at both 30 days and 1 year [20]. Also, Zaidat et al. reported the incidence of endpoint events after SMM was 9.4% within 30 days and 15.1% within 1 year [17]. Furthermore, the final results of SAMM-PRIS [44], a multicenter prospective randomized controlled trial, reported that the incidence of endpoint events after SMM was just 5.8% within 30 days and 12.6% within 1 year. This was similar to the other 2 studies mentioned above. In the present investigation, however, worse outcomes were demonstrated in that there was little advantageous influence on symptomatic bilateral high-grade CS after SMM. In contrast to results of the 3 studies mentioned above, the present investigation shows an even higher incidence of endpoint events after SMM – up to 10.7% within 30 days and 37.8% within 1 year. In addition, the incidence of endpoint events within 6 months was also very high. Several factors may be regarded as contributing to the higher incidence of endpoint events involving SMM in the present investigation. The CS was not as severe as in the other 3 studies due to its bilateral high-grade lesion and this may have contributed to the higher incidence of endpoint events [17,20,44]. In addition, even if the CS severity was as similar to that in the other 3 studies, SMM designed for Westerners may have not been the best SMM regimen for Chinese. Nonetheless, we did not have enough prerequisites to ascertain the contribution made by population difference to these worse outcomes in the present investigation. Moreover, the higher incidence of endpoint events after SMM shown in the present investigation may,

in part, be attributed to the current lower dosage of Lipitor, which was necessary because Chinese are intolerant to higher doses of Lipitor. This may be related to the inherent population difference between Chinese and Westerners, and iterative trials are required to ascertain the role of population difference in the intolerance of Chinese to higher dosage of Lipitor in the future. Therefore, our present results are partially consistent with those reported by Brown [15].

### SBCAS

In the present investigation, our data further demonstrated that SBCAS was feasible and helpful in alleviating bilateral high-grade CS, as reported in other studies [28,32–36]. The immediate effectiveness of SBCAS are demonstrated by the final angiograms showing that the CS ratio was distinctly reduced and the branches of distal arteries were remarkably increased after SBCAS. These results were in accord with those reported by other investigations [28,32,36]. This suggests the technical success of SBCAS achieved in the present investigation. Our data also revealed that SBCAS may be an effective vascular surgical intervention for symptomatic bilateral high-grade CS.

As to the later effectiveness of SBCAS, both the lower NIHSS and CS ratio observed in the SBCAS group at all follow-ups suggested that SBCAS had a short-term positive effect on symptomatic bilateral high-grade CS and that these patients would likely benefit from this kind of vascular surgical intervention during a relatively long period. On the other hand, although we initially thought that the SBCAS would give rise to an increased risk for stroke owing to its more severe CS nature in the present investigation, our data finally revealed that the incidence of endpoint events at 30-day follow-up was similar to or even lower than the incidence reported in other investigations [29,32,33,35,36]. Thus, our data supported the fact that the SBCAS helped alleviate symptomatic bilateral high-grade CS within 30 days. Moreover, our incidence of endpoint events at 6-month follow-up was similar to that reported by Liu et al. [35], although 2 cases of minor stroke were observed in the present investigation. This similarity suggests that our outcome at 6-month follow-up was not as severe as in Liu's investigation. Instead, a higher incidence of endpoint events was found at 6-month follow-up, along with more severe outcome profile characterized by more deaths and acute myocardial infarctions observed in Dong's investigation [30]. A possible explanation of the difference in demographic characteristics is that more patients with high risk for ischemic stroke and myocardial infarction (e.g., elderly, hypertension, and diabetes) were recruited. SBCAS would not increase the incidence of endpoint events within 6 months. At 1-year follow-up, however, a higher incidence of endpoint events reported by both Chimowitz et al. and Zaidat et al. may be attributed to insufficient operator experience, inherent imperfection of protected device, and lack of better pressure control [17,20]. Instead,

their potential shortcomings of operator, technical, and periprocedure factors were almost eliminated in the present investigation, which is why we found a lower incidence of endpoint events. Overall, the adverse outcome profile at all follow-ups and the 1-year cumulative probability of endpoint events were acceptable in the SBCAS group. For this reason, SBCAS could be regarded as an effective regimen for symptomatic bilateral high-grade CS, at least within a short period.

### SAMM vs. SBCAS

In their randomized controlled trials, Chimowitz et al., Zaidat et al. [17,20], and the final results of SAMMPRIS did not support the idea that CAS was superior to SAMM for symptomatic high-grade stenosis, because the incidence of endpoint events after CAS was much higher than after SAMM [44], both within 30 days and within 1 year. Therefore, we initially did not think that the SBCAS would be more effective and safer for symptomatic bilateral high-grade CS than SAMM. In fact, however, our data showing that the incidence of endpoint events and adverse outcome profile were both lower in the SBCAS group than in the control group further established the superiority of SBCAS over SAMM for symptomatic bilateral high-grade CS. A few factors may play key roles in creating this difference. For instance, in contrast to the aforementioned studies [17,20], the qualified operational experience was ensured as much as possible in the present investigation with the help of self-expanding stents rather than stents for cerebral aneurysm but coiled to CS. On the other hand, in light of the previous protected device's technical limitation [20], an improved protected device was used in the present investigation. Moreover, some meaningful periprocedural factors, such as adequate timing of SBCAS intervention since ischemic stroke onset, appropriate choice of anesthesia pattern, and better management of BP, were all cautiously considered prior to SBCAS and carried out throughout the whole procedure. For these reasons, the effectiveness of SBCAS was so greatly improved that the effectiveness of SAMM was lower relative to SBCAS.

Furthermore, the worse CS ratio and bilateral-lesion nature in the present investigation may make SAMM have more difficulty in alleviating or even reversing lesions than SBCAS, at least in the short term. As a result, this also stands out the short-term superiority of SBCAS over SAMM for symptomatic bilateral high-grade CS.

### Adverse effects of both interventions (safety)

#### *Procedural complications of SBCAS*

One of the most important complications following the SBCAS is HPS. Usually, cerebral blood flow increases by 20–40% after CAS; however, patients will inevitably undergo HPS due to

severe brain edema or intracranial hemorrhage once the cerebral blood flow increases by more than 100% [45]. Therefore, HPS may be more remarkable following SBCAS, as the cerebral blood flow often undergoes a relatively greater increase owing to resolution of both arteries. While typically occurring within 36 h, HPS could occur at any time from several hours to 3 weeks after SBCAS [46,47]. Some risk factors, such as being elderly, peri-operational hypertension, diabetes mellitus, history of stroke, history of coronary artery surgery, and procedure technique, as well as bilateral high-grade CS, all increase risk of HPS [36,46,48,49]. Thus, 4 cases of HPS were observed in SBCAS group, a slightly higher incidence than in other previous investigations [30–36]. We hypothesized that the risk factors for HPS or percentage of patients at high risk for HPS in the present investigation were not significantly different from those in other investigations. The sole exception would be that our patients all had bilateral high-grade CS, whereas patients in other investigations just had unilateral or bilateral middle-grade CS. With this in mind, our incidence of HPS was, in fact, much lower than that reported by Liu et al. [33]. On the other hand, another characteristic difference between our study and Liu's investigation was their finding that HPS developed at between 11 days and 3 weeks after the SBCAS procedure. This difference may be predominantly attributed to strict BP management after SBCAS in the present investigation. Cautious control over the systolic BP ( $\leq 120\text{--}130/80\text{--}90$  mmHg) is a key factor for general prevention of HPS. In high-risk patients, even more precise management of blood pressure ( $\leq 120\text{--}130/80\text{--}90$  mmHg), as in the present investigation, has been shown to help lower incidence of HPS [30,50]. For this reason, the perioperative systolic BP should be reduced to the target level as much as possible, and maintained for at least 3–5 days, as in previous investigations [33,35], in order to avoid HPS.

HD may be another important SBCAS-related complication. HD is defined as persistent severe bradycardia (fewer than 60 beats/min) and hypotension (systolic pressure lower than 90 mmHg) following SBCAS [39], both of which are caused by activation of the carotid sinus reflex [33]. Most cases of HD occur after predilation of balloon or carotid stent implantation, since the carotid sinus is often activated at that time. The majority of patients recover within 3–5 days following infusion of normal saline or intravenous atropine, although a minority have to rely on extended dopamine use for recovery. Prophylactic use of atropine prior to balloon dilation or deployment of a carotid stent helps to reduce the incidence of HD, especially for those patients with bradycardia or second- or third-degree atrioventricular block [51]. Risk factors like stenosis of carotid bifurcation or contralateral carotid, length of CS, baseline BP, and heart rate, as well as balloon use, increase the risk of HD [51]. Theoretically speaking, SBCAS may bring about a higher incidence of HD and give rise to more severe, frequent, and long-lasting sequelae due to the procedure's bilateral nature

and more intense activation of carotid sinus right after balloon predilation or carotid stent implantation [35]. With this in mind, it is no wonder that we found a higher incidence of HD following the SBCAS relative to staged bilateral or unilateral CAS [18,30–33,35,36]. On the other hand, our incidence of HD following the SBCAS was also much higher than those reported by any other similar investigations [31–33,35–37]. This is possibly because all of our patients had bilateral high-grade CS, while patients in other investigations just had either unilateral CS or bilateral moderate- or middle-grade CS; therefore, the extent of stenosis in the present investigation was more severe than that in other investigations. As HD often lasts a long time and can result in renal failure, it usually requires careful observation and management [52], although usually the SBCAS-related HD is not very severe and commonly does not increase perioperative risk. Because we had no cases of HD developing secondary to cerebral ischemia or myocardial infarction, we believe that cautious perioperative management helps to effectively reduce the incidence of HD. In addition, we consider that prophylactic intravenous application of atropine is necessary during the perioperative period.

Restenosis is also a common CAS-related complication found at follow-up. The incidence of restenosis following CAS varies among different investigations, but few investigations have discussed the prevalence of SBCAS-related restenosis at follow-up [53]. Liu et al. [35] reported a restenosis incidence of 8.3% at 6-month follow-up, much higher than that reported in our investigation. In addition, our restenosis onset was 6 months later than that reported by Liu et al. We hypothesize that the additional use of Lipitor (a statin) may be the key explanation for the different restenosis incidences, because statins help ameliorate inflammatory and oxidative stress reactions [54,55], as well as to account for secondary lesions within plaques before and after SBCAS [56].

#### *Adverse effects of drug use*

The common adverse effect of aspirin is hemorrhage, especially in the upper gastrointestinal tract. The incidence of hemorrhage in the upper gastrointestinal tract caused by 100-mg aspirin varies widely, between 0.3% and 3.8% in Asians [57,58]. In present investigation, however, the cases of upper gastrointestinal tract hemorrhage were all observed when the dose of aspirin was 325 mg rather than 100 mg. Furthermore, the reported slightly higher incidence of aspirin-related upper gastrointestinal tract hemorrhage in the control group compared to the SBCAS group and in other relevant investigations, may be due to use of higher doses of aspirin; 100 mg is a safer dose of aspirin for symptomatic bilateral high-grade CS, regardless of routine procedural application or maintained application in SAMM.



The most common adverse effect of statins is statin-associated myopathy (SAM), manifested in a wide spectrum of muscular disorders, such as insignificant myalgia and mortal rhabdomyolysis. The incidence of SAM varies widely between 1% and 20%, and it may increase with higher doses of statins[59–61]. In the present investigation, the cases of SAM were all observed when the dosage of statin was 40 mg rather than 20 mg. Furthermore, the slightly higher reported incidence of SAM (only in the control group, not in the SBCAS group) may be due to higher doses of statins; 20 mg is a safer dose of statin for symptomatic bilateral high-grade CS, regardless of routine procedural application or for maintained application in SMM.

### Limitations

We are aware of 2 limitations in the present investigation worth mentioning. First, this was a retrospective clinical analysis. Second, the sample sizes were small. Therefore, randomized, controlled, prospective clinical investigations with large samples needed to establish the superiority of SBCAS for symptomatic bilateral high-grade CS over SMM.

### Conclusions

SMM has little positive effect on bilateral high-grade CS, whereas SBCAS is useful in treating symptomatic bilateral high-grade CS. Furthermore, our results suggest SBCAS is more

effective than SMM, because the SBCAS group had lower NIHSS, CS ratio, and incidence of endpoint events at 30 days, 6 months, and 1 year. Because all our patients had severe bilateral stenosis, the present study showed higher incidences of SBCAS-related HPS and HD compared to average reported rates. Fortunately, all cases of HPS and HD resolved without a concurrent increase in SBCAS-related risk. Furthermore, strict hemodynamic monitoring and cautious management of BP are indispensable for prevention of HPS and HD. The lower incidence of in-stent restenosis may be due to the addition of Lipitor before and after SBCAS. SMM is not as safe as SBCAS because SMM causes some adverse effects due to higher dosage of aspirin and statin. The present investigation lacks sufficient statistical power to draw definitive conclusions. Therefore, multicenter, prospective, randomized, controlled trials with larger sample sizes are required to further support the effectiveness and safety of SBCAS relative to SMM.

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### Conflicts of interest

None.

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