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Severe symptomatic intracranial internal carotid artery stenosis treated with intracranial stenting: a single center study with 58 patients

Zi-Liang Wang*
Bu-Lang Gao*
Tian-Xiao Li
Dong-Yang Cai
Liang-Fu Zhu
Jiang-Yu Xue
Wei-Xing Bai
Zhao-Shuo Li

PURPOSE
We aimed to investigate the safety and effectiveness of intracranial stenting in a population with severe (≥70%) symptomatic intracranial internal carotid artery (ICA) atherosclerotic stenosis.

METHODS
Fifty-eight patients with severe intracranial ICA atherosclerotic stenosis were prospectively enrolled. The baseline data, cerebral angiography, success rate, perioperative complications, clinical and imaging follow-up were prospectively analyzed.

RESULTS
All patients had successful intracranial stenting (100%), and the mean degree of stenosis was improved from 84.3%±7.5% to 23.5%±5.1% after the stent procedure. During the 30-day perioperative period, only one patient (1.7%) had ischemic stroke. Seven patients (12.1%) had headache and dysphoria. Thirty-six patients (62.1%) had clinical follow-up for 6–68 months after stenting. Five female patients (13.9%) had ipsilateral stroke including one death, but no disabling stroke, while three other patients (8.3%) had ipsilateral temporary ischemic attack (TIA). The recurrent stroke rate was higher in patients presenting with stroke (4/17, 23.5%) than in patients presenting with TIA (1/19, 5.3%), with no statistical significance ($P = 0.33$). Thirteen patients (22.4%) had imaging follow-up of 5–12 months following stenting, five of whom (38.5%) had in-stent restenosis.

CONCLUSION
Intracranial stenting for patients with intracranial ICA atherosclerotic stenosis has a low perioperative stroke rate and decent outcome on long-term follow-up, despite a relatively high in-stent restenosis rate.

Intracranial atherosclerotic stenosis is the leading cause of recurrent ischemic stroke in the Chinese population (1). Although the effect of anticoagulation has been greatly improved, the two-year cumulative rate of any stroke or death from symptomatic intracranial atherosclerotic stenosis treated with intensive medicines still reached 19.8% with a 4.5% death rate in a large randomized controlled study comparing the Wingspan stenting versus intensive medical treatment (SAMMPRIS) (2). As a complementary therapy to anticoagulation, intracranial stenting has emerged as an effective approach for intracranial atherosclerotic stenosis, with the clinical effect proven by some studies (3–5). Even though the SAMMPRIS study disfavors the use of Wingspan stent for intracranial stenosis (2), it is only one of many trials in the initial stage of intracranial stenting, similar to the initial circumstances of carotid stenting. It should not prevent further trials of intracranial stenting for atherosclerotic stenosis involving different populations with different baseline characteristics of intracranial atherosclerosis. This study was performed to investigate the effect of the Wingspan stent (Stryker Neurovascular) in treating a Chinese subpopulation with intracranial internal carotid artery (ICA) atherosclerotic stenosis at a large-volume center in China.

Methods

Between July 2007 and April 2013, 58 consecutive patients with severe (≥70%–99%) symptomatic intracranial ICA stenosis, 41 of whom (70.7%) presenting with recurrent isch-

*These authors contributed equally to this work.

Stroke Center, Henan Provincial People's Hospital, Zhengzhou University (Z.L.W., T.X.L. ✉ *litianxiaod@163.com*, D.Y.C., L.F.Z., J.Y.X., W.X.B., Z.S.L.), Henan, China; the Department of Medical Research (B.L.G.), Shijiazhuang First Hospital, Hebei Medical University, Hebei, China.

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emic events despite regular antiplatelet therapy, were managed with the Wingspan stent at our center (Table 1). This was a prospective study approved by the institutional ethics committee for scientific research and signed informed consent was obtained from all patients for the stenting procedure. Inclusion criteria for the study were ≥70% stenosis of the ICA with symptomatic ischemic stroke or a transient ischemic attack (TIA), length of each stenosis ≤15 mm, 18–85 years of age, over 24 hours from the final TIA event, and over seven days from the final stroke. Patients with the following features were excluded: nonatherosclerotic stenosis, potential source of cardiac embolism, combined intracranial pathology (tumors, aneurysms, or arteriovenous malformation), and contraindication to antiplatelet therapy.

The Wingspan stenting (Stryker Neurovascular) procedure was performed under general anesthesia with access through the common femoral artery using a long-sheath system (Boston Scientific). A targeted activated coagulation time of 250–300 s was achieved by heparinization. A microcatheter (SL-10, Boston Scientific; or Prowler-10, Cordis) was navigated through the target lesion using a 0.014-inch microwire (Boston Scientific) and was then exchanged over a 0.014-inch microwire for a Gateway angioplasty balloon (Stryker Neurovascular), with the microwire tip placed at the relatively straight segment of M3 of the middle cerebral artery. The Gateway balloon was inflated to 80%–90% of the "normal" parent artery diameter proximal or distal to the stenosis, with its length matching the stenosis length, and navigated to the stenosis for angioplasty with a slow graded inflation of the balloon to the pressure of 6 atm for approximately 10–20 s. Then, the Wingspan delivery system (Stryker Neurovascular) was advanced over the exchange wire to the target stenosis and the stent was deployed. The stent diameter was chosen to exceed that of the normal parent artery by 0.5–1.0 mm and the length to completely cover the entire stenotic segment. The microcatheter and the guiding catheter (Stryker Neurovascular) were withdrawn to end the procedure if the residual stenosis was ≤30% compared with the normal diameter proximal to the lesion and no occlusion was present in the distal arterial branches.

Main points

- Severe symptomatic atherosclerotic intracranial internal carotid artery stenosis can be treated with intracranial stenting.
- The perioperative stroke rate of intracranial stenting for patients with atherosclerotic intracranial internal carotid artery stenosis is low.
- Intracranial stenting for atherosclerotic intracranial internal carotid artery stenosis can prevent long-term ischemic stroke.
- The in-stent restenosis rate is relatively high in patients with digital subtraction angiography follow-up.

Antiplatelet agents (aspirin 100 mg/day and clopidogrel 75 mg/day, Bristol-Myers Squibb and Sanofi Pharmaceuticals) were prescribed for all patients at least 3–5 days before stenting. In emergency procedures, a loading dose of 300 mg of aspirin and 300 mg clopidogrel was administered once within 24 hours. Nimodipine (Huabei Pharmaceuticals) was administered to control the blood pressure two hours before stenting. Immediately following stenting, computed tomography (CTSOMATOM, Siemens Medical Systems) was performed to check for possible intracranial hemorrhage. Nimodipine was further prescribed for 1–3 days after stenting for blood pressure control at the lower limit. If there was no intracranial hemorrhage, low-molecular-weight heparin (4000–6000 U/12 hours, Huabei Pharmaceuticals) was injected subcutaneously. The dual antiplatelet regimen was maintained for six months, and then all patients were prescribed aspirin (325 mg daily) indefinitely. Meanwhile, all patients were educated regarding control of other atherosclerotic risk factors.

During the 30-day perioperative period, stroke, death, and TIA were recorded in all patients. The modified Rankin Scale (mRS) score and the National Institute of Health Stroke Scale (NIHSS) score were used to assess the neurologic deficits in all patients before and after stenting, at discharge, and 1, 3, 6, and 12 months later. After 12 months, clinical follow-up was scheduled once per year. Head CT, magnetic resonance imaging (Signa HDXT 1.5 T, GE Healthcare) or digital subtraction angiography (DSA, ARTIS FA, Siemens) were performed for patients suspected of having a recurrent stroke. Imaging follow-up was performed six months after stenting for in-stent restenosis, which was defined as >50% stenosis compared with baseline at a site within the stent or within 5 mm immediately adjacent to the stent and >20% of absolute luminal loss since stenting (6, 7).

The primary endpoint was ischemic stroke or death within and beyond 30 days after stenting. The secondary endpoint was the disabling or fatal stroke rate throughout the study and the status of the stented segment on imaging at one or two years in terms of change in luminal diameter.

Statistical analysis

Data were presented as mean±standard deviation for continuous variables and number/frequency for categorical data. The baseline, imaging, and procedural data were statistically analyzed using student's t test on SPSS version 13.0 (SPSS Inc.). The *P* value was considered significant at <0.05.

Results

Fifty-eight patients with severe intracranial ICA stenosis were enrolled for Wingspan stenting, including 28 males and 30 females (mean age, 55.1±9.6 years; range, 34–80 years) (Table 1). Presenting symptoms were TIA in 36 patients and ischemic stroke in 22. Forty-one patients (70.7%) had recurrent stroke or TIA despite anticoagulation, whereas 17 patients (29.3%) had a good response to anticoagulation therapy with no symptoms. The characteristics of the stenosis are presented in Table 2.

The Wingspan stent was successfully deployed in all 58 patients (100%), and the mean stenosis rate was improved from 84.3%±7.5% to 23.5%±5.1% after stenting (Table 2, Fig. 1). During the 30-day perioperative period, only one patient (1.7%) had ischemic stroke. In this patient, difficulty in navigating the stent to the lesion and multiple adjustments of the stent led to thrombosis within the stent and in the trunk of the middle cerebral artery. The thrombus in the middle cerebral artery trunk was compressed by a Solitaire AB stent (4×15 mm, ev3), and Tirofiban Wuhan Landmark Co.) was pumped into the trunk leading to good recovery of blood flow, and complete recovery of the patient.

No hemorrhagic stroke occurred in the perioperative period; however, seven patients (12.1%) had headache and dyspho-

Table 1. Baseline characteristics

Variables	
Age (years), mean±SD	55.1±9.6
Sex ratio (M/F), n (%)	28 (48.3) /30 (51.7)
Presenting symptoms	
TIA, n (%)	36 (62.1)
Ischemic stroke, n (%)	22 (37.9)
Hypertension, n (%)	42 (72.4)
Diabetes, n (%)	16 (27.6)
Hyperlipemia, n (%)	16 (27.6)
Smoking, n (%)	10 (17.2)
Coronary heart disease, n (%)	2 (3.4)
mRS Score 0–2/3	44/14

SD, standard deviation; M, male; F, female; TIA, temporary ischemic attack; mRS, modified Rankin Scale.

Table 2. Stenosis characteristics and imaging

Variables	
Stenosis location: left/right	36/22
Stenosis length before stenting, n (%)	
>10 mm	18 (31.0)
5–10 mm	38 (65.5)
<5 mm	2 (3.4)
Interval between presenting symptoms and stenting (days), mean (range)	21 (8–40)
Stenosis before stenting (%), mean±SD (range)	84.3±7.5 (70–99)
Residual stenosis after stenting (%), mean±SD (range)	23.5±5.1 (15–27)
Interval between stenting and in-stent restenosis (months), mean (range)	13.2 (6–21)

SD, standard deviation.

ria, including one patient with headache, transient unconsciousness, and temporary ipsilateral limb weakness. Head CT demonstrated no abnormality in these seven patients, and hyperperfusion was thought to account for the symptoms, which were resolved by administration of nimodipine to strictly control the blood pressure.

Thirty-six patients (62.1%) had clinical follow-up for 6–68 months (mean, 24.4±16.4 months) after stenting (Fig. 2). Some patients were lost to follow-up due to uncontrollable reasons like moving away from the local area, or alteration of their home address and phone number. Among 36 patients with follow-up, five female patients (13.9%) had ipsilateral stroke, including one death but no disabling stroke, and three other patients (8.3%) had ipsilateral TIA. The resulting total ischemic event rate was much lower than the ischemic event rate before stenting (22.2% vs. 70.7%, $P = 0.032$) (Fig. 3). The rate of stroke was not statistically significant between men and women ($P = 0.21$). The rate of recurrent stroke was higher in patients with before stenting stroke (4/17, 23.5%) than in patients with TIA (1/19), although the difference was not statistically significant ($P = 0.33$).

Thirteen patients (22.4%) had DSA follow-up for 5–12 months (mean, 8.8±2.6 months) following stenting. Five patients (38.5%) had in-stent restenosis: two patients had stent occlusion and three patients had symptomatic restenosis, including two patients (15.4%) with recurrent stroke and one patient with TIA. The two patients with stent occlusion were successfully re-treated using balloon angioplasty, with no procedure-related complications.

Discussion

Symptomatic intracranial ICA atherosclerotic stenosis is an important reason for recurrent ischemic stroke in the anterior circulation and responds poorly to anticoagulation therapy (1, 2, 8). Intracranial angioplasty and stenting has become an important approach in combination with intensive medications to treat intracranial stenosis (3, 5). Compared with extracranial ICA stenting (9, 10), stenting in the intracranial ICA segments is relatively immature with more perioperative complications, higher long-term in-stent restenosis rates, and higher recurrent rates of ischemic stroke (11, 12). However, our study demonstrated that the Wingspan stenting for the intracranial ICA atherosclerotic stenosis has a very low perioperative stroke rate and an acceptable long-term recurrent stroke rate, despite a relatively high in-stent restenosis rate.

The perioperative complications of stenosis in intracranial atherosclerotic stenosis stenting include perforator stroke, operation-related vascular injury and tear, and post-stenting hyperperfusion (3–5, 11, 13). Since the approval of the Wingspan stent by the U.S. FDA, some Wingspan registry studies revealed the perioperative 30-day stroke or death rate as 4.5%–9.6% (3, 4, 13). To date, no studies have investigated stenting in the intracranial ICA segments alone. Our study showed a lower perioperative complication rate of 1.7%, which was caused by longer stent navigation in one patient due to a tortuous siphon segment. However, appropriate management left no neurological deficits in this patient. Compared with other intracranial arteries, the intracranial ICA segments are more tortuous and can thus make navigation of endovascular devices difficult or lead to incomplete expansion of the stent during deployment, resulting in thrombus formation. The intracranial ICA has fewer tenuous perforators and thus fewer complications associated with perforator occlusion or injury. However, the ICA is much larger than other intracranial arteries like the middle cerebral artery and can readily bring about hyperperfusion syndrome after the stenotic lumen is resolved by stenting. Hyperperfusion is thought to occur more frequently after carotid endarterectomy and carotid

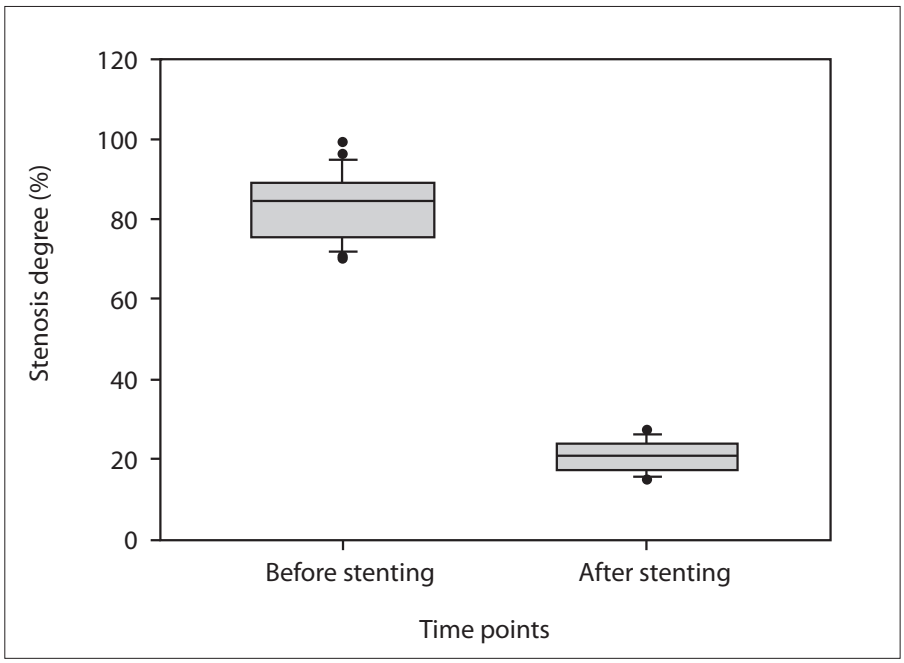

Figure 1. The degree of stenosis of the intracranial internal carotid artery before and after stenting. The mean degree of stenosis was 84.3%±7.5% before stenting but improved to 23.5%±5.1% after stenting.

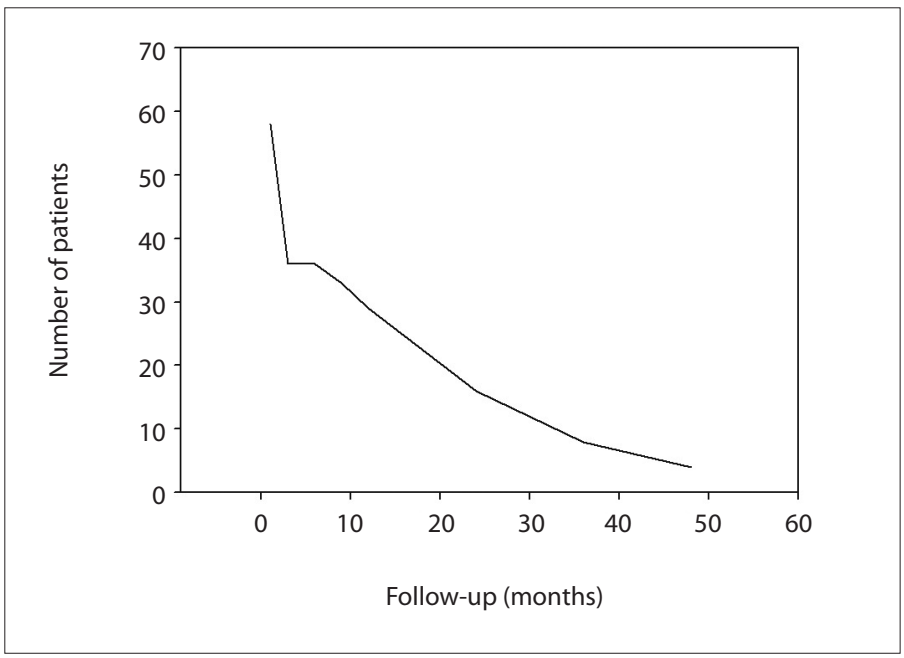

Figure 2. Follow-up curve at different time points. At 1, 3, 6, 9, 12, 24, 36, and 48 months, 58, 36, 36, 33, 29, 16, 8, and 4 patients were followed up, respectively.

stenting (14, 15); however, in our study, seven patients (12.1%) had headache and dysphoria after stenting, which was probably related to post-stenting hyperperfusion despite normal cranial CT findings.

Atherosclerotic stenosis in intracranial ICA is prone to high recurrent stroke rate in spite of intensive medication, and the WASID study revealed that patients with intracranial ICA stenosis had an endpoint event rate of 20% either with aspirin or warfarin treatment over a 1.8-year follow-up period (8). The study by Turk et al. (7) demonstrated that stenosis lesions in the ICA supraclinoid segment responded particularly poorly to interventional stenting, and many patients developed in-stent restenosis and recurrent ischemic symptoms. Consequently, they suggested that the Wingspan stent system might not be an optimal choice for patients with intracranial ICA stenosis, who should be excluded from future trials of drug therapy versus percutaneous transluminal angioplasty and stenting with Wingspan stent until more data are available. Of 58 patients included in this study, 41 (70.7%) had recurrent ischemic events including ischemic strokes and TIA despite regular antiplatelet treatment before stenting. Nonetheless, during a mean post-stenting follow-up period of 24.4 months, the ischemic events were reduced to five ipsilateral strokes including one death, yielding a stroke and death rate of 13.9%, a much lower rate than the stroke and death rate in the SAMMPRIS study (19.8%) (2) or the WASID study (20%) (8) with similar durations of follow-up. Our results indicate that the Wingspan stenting can provide additional benefit for symptomatic patients with intracranial ICA atherosclerotic stenosis receiving anticoagulation therapy. If the perioperative complication rate can be effectively controlled, the intracranial stenting can certainly benefit patients with severe symptomatic intracranial ICA stenosis by decreasing the rate of recurrent ischemic strokes or TIA despite regular anticoagulation. Usually, randomization and control are necessary to test the effect of a measure in managing a disease. However, it would be very dangerous to randomize patients with severe symptomatic ICA atherosclerotic stenosis into a stenting group and a medication alone (control) group. In these patients the severity of stenosis has already caused insufficient blood supply to the intracranial cerebral tissue. Without mechanical expansion of the stenosis, the patients will suffer ischemic strokes at any time because medications alone cannot improve the situation completely. In this study, 41 of 58 patients (70.7%) had recurrent ischemic strokes or TIA despite intensive medications. Thus, it would be unethical to set up a control group just for the purpose of scientific research. Severe stenosis has to be treated despite some risk of procedure-related stroke. Our study showed that after stenting, the rate of ischemic events have reduced considerably, yielding a stroke and death rate of 13.9%. This is why in the current era, very few studies have adopted the randomization and control policies in treating pa-

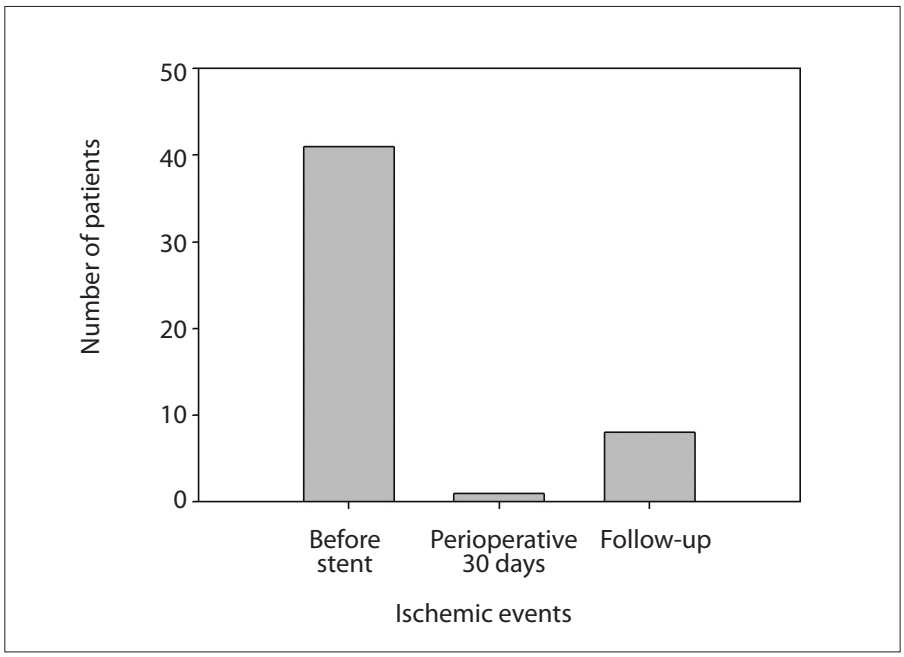

Figure 3. Ischemic events at different time points. Before stenting, 41 patients had recurrent stroke or temporary ischemic attack despite intensive medications. During the perioperative period within 30 days after stenting, one patient had ischemic stroke (perioperative stroke or death rate, 1.7%). At follow-up of 36 patients up to 68 months, five patients had ipsilateral stroke and another three had ipsilateral temporary ischemic attack (total rate of ischemic events, 22.2%).

tients with this kind of severe intracranial arterial stenosis. The perioperative stroke rate is extremely low (1.7%) in this study. If the perioperative complication rate can be effectively controlled, the intracranial stenting can certainly provide additional benefit for patients with severe symptomatic intracranial ICA stenosis who cannot benefit sufficiently from intensive medications alone.

A previous study showed that recurrent stroke after Wingspan stenting was associated with discontinuation of antiplatelet therapy as well as in-stent restenosis (12). However, our study confirmed the association of recurrent stroke with in-stent restenosis rather than discontinuation of antiplatelet therapy. Among eight patients (five patients had imaging check-up) with ischemic events during follow-up, three had in-stent restenosis; however, all these eight patients had regular antiplatelet therapy after stenting. Although not statistically significant, recurrent stroke after stenting was more frequent in women and in patients whose presenting event was ischemic stroke, consistent with previous studies (2, 8, 16). In-stent restenosis is an important reason for recurrent stroke following stenting, which is usually used as an important index for evaluating the long-term stenting effect (12). In-stent restenosis is caused by excessive intimal hyperplasia resulting from inflammatory reaction of vascular wall to stenting (17, 18). It is often present in the anterior circulation and in younger patients (<55 years) (6, 7, 19) and may not be caused by atherosclerosis as in older patients. In our study, five of 13 patients with imaging follow-up (38.5%) had in-stent restenosis. However, our study had a higher symptomatic restenosis rate (23.1%, 3/13) and the ischemic symptoms may have been caused by hypoperfusion in the intracranial ICA stenosis.

In this study, some patients were lost to follow-up because they lived far away from the hospital, or they changed their addresses or phone numbers. Most patients in China do not have health insurance, and they have to pay for their healthcare. If they do not have symptoms, they will not come to see the doctors. This is usually the reason for a high drop-out rate during follow up course in China.

The main limitation of our study is the absence of a control group and randomization. Other limitations include presence of a single center, limited number of patients enrolled, inclusion of Chinese patients only, and low imaging follow-up rate. In addition, responsiveness to aspirin and clopidogrel was not tested in this study. In the future, a randomized, controlled study with multiple large-volume centers involved has to be conducted to confirm the effect of Wingspan stenting on preventing long-term recurrent stroke rate.

In conclusion, this study demonstrates that Wingspan stenting for the intracranial ICA atherosclerotic stenosis has a low perioperative stroke rate and decent long-term outcome in spite of a relatively higher in-stent restenosis rate.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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