Higher Risk of Recurrent Ischemic Events in Patients With Intracranial In-Stent Restenosis

Min Jin, MD*; Xian Fu, MD*; Yuzhen Wei, MD; Bin Du, MD; Xiao-Tong Xu, MD; Wei-Jian Jiang, MD

Background and Purpose—Reliable data concerning prognosis of patients with intracranial in-stent restenosis (ISR) is lacking. We prospectively studied long-term outcomes of patients with and without a catheter angiography-verified ISR.

Methods—Between September 2001 and May 2009, 540 consecutive patients with symptomatic intracranial atherosclerosis received stenting treatment at our institute. Of them, 226 patients with 233 stented arteries had catheter angiography follow-up after stenting and were enrolled into this study. They were clinically followed up until the end of December 2011. Primary end point was ischemic stroke or transient ischemic attack in the territory of the stented artery after the catheter angiography follow-up. ISR was defined as a catheter angiography-verified stenosis of ≥50% within or immediately adjacent (within range of 3 mm) to the implanted stent.

Results—During a mean follow-up of 38.9 months, 27 (11.6%, 27/233) primary end point events were recorded. The risk of primary end point in ISR group was higher compared with non-ISR group (21.1% [12/57] versus 8.5% [15/176]; hazard ratio, 2.94; 95% confidence interval, 1.37–6.30; P=0.005). Multivariable analysis showed that the ISR was an independent risk factor for the primary end point (hazard ratio, 2.79; 95% confidence interval, 1.20–6.49; P=0.017). The median occurrence time of primary end point was 9.9 (interquartile range, 5.0, 21.1) months in ISR group, earlier than that in non-ISR group (26.6 [13.1, 52.9] months; P=0.01).

Conclusions—In-stent restenosis after stenting of intracranial atherosclerosis is significantly associated with an increased risk and an earlier occurrence of recurrent ischemic events in the territory of the stented intracranial artery.

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Key Words: angioplasty ■ intracranial arterial disorders ■ natural history ■ outcome measures

Intracranial artery stenosis (ICAS) is a common cause of ischemic stroke worldwide.1 In the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial, 13.5% of 569 patients had recurrent ischemic stroke in the territory of the symptomatic ICAS ≥50%, while being on antithrombotic treatment and standard management of vascular risk factors during the follow-up of 1.8 years, and the severe stenosis (diameter stenosis degree of ≥70%) was detected to be the strongest predictor of the ipsilateral ischemic stroke.2,3 During the past decade, percutaneous transluminal angioplasty and stenting (PTAS) has been evolving as a possible treatment option for ICAS patients at particularly high risk for recurrent stroke.4-18 However, a higher risk of major complications including periprocedural stroke or death and intracranial in-stent restenosis (ISR) limited its use in clinical practice. Only when those 2 are controlled to an enough small rate will PTAS be a promising option for symptomatic ICAS. Numerous studies have discussed periprocedural complications of PTAS for ICAS. However, reliable data concerning prognosis of ISR patients are lacking so far. Thus, we prospectively studied long-term outcomes of patients with and without a catheter angiography-verified ISR after intracranial stenting.

Patients and Methods

Patients

Between September 2001 and May 2009, 561 consecutive procedures of stenting for symptomatic intracranial atherosclerosis in 540 patients were recorded in our intracranial stenting database. Of them, 238 stented arteries had catheter angiography follow-up after stenting. Five of the 238 stented arteries underwent restenting treatment for ISR. Thus, 233 stented arteries in 226 patients were enrolled into this prospective study. Written informed consent for this study was obtained from each patient or his or her family member. The ethics committee of our institute approved the study protocol, Good Clinical Practice guidelines in accordance with the Declaration of Helsinki were used, and the privacy of patients was strictly protected.

Data Collection and Follow-Up

Catheter angiography follow-up was scheduled at 3 to 6 months on a voluntary basis or when in-stent restenosis was suspected clinically after PTAS. The method used for determining percentage of stenosis of

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From the New Era Stroke Care and Research Institute, the Second Artillery General Hospital PLA, Beijing, China (M.J., B.D., W.-J.J.); Institute of Neurosciences, the Second Affiliated Hospital of Guangzhou Medical University, Guangzhou, China (X.F.); and the Department of Interventional Neuroradiology, Beijing Tiantan Hospital, the Capital Medical University, Beijing, China (Y.W., X.-T.-X.).

*Drs Jin and Fu contributed equally.

Correspondence to Wei-Jian Jiang, MD, New Era Stroke Care and Research Institute, The Second Artillery General Hospital PLA, Beijing 100088, China. E-mail cj.r.jiangweijian@vip.163.com

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an intracranial stented artery was the same as that used in the WASID trial.\textsuperscript{7} ISR was defined as an angiographically verified $>50\%$ stenosis within the stent or at the edge of the stent in the range of 3 mm. Data on baseline were prospectively recorded. All patients were followed every 3 months by telephone or clinic visit with the use of a uniform questionnaire to the date of the occurrence of the primary end point, or lost contact, or until the end of December 2011. Brain CT or MRI was performed if the patient had a new neurological event. The primary end point was independently assessed by stroke neurologists, who did not know the stenosis degree of the stented artery. Primary end point was lesion-related ischemic event, consisting of ischemic stroke or transient ischemic attack (TIA). Ischemic stroke was traditionally defined as a new focal neurological deficit of sudden onset that lasted at least 24 hours and that was not caused by hemorrhage on brain CT. TIA was defined as an acute onset of a focal neurological deficit lasting $<24$ hours. Ischemic event was considered to be (1) definitely lesion-related when the neurological symptoms and signs were localized to the stented artery territory but without a new infarct in any area on CT or MRI; (2) probably lesion-related when the neurological symptoms and signs were localized to the stented artery territory but without a new infarct in any area on CT or MRI; (3) indeterminate when the neurological symptoms and signs were localized to $\geq 2$ distinct vascular territories without new infarct on CT or MRI; or (4) definitely or probably non-lesion-related.\textsuperscript{2,3,10} Lesion-related ischemic events included definitely and probably lesion-related ones, and non–lesion-related ischemic events consisted of other ischemic events.

**Medical Treatments**

The PTAS was performed as described previously.\textsuperscript{9,10} Three types of stents (coronary balloon-expandable stents, or Apollo balloon-expandable intracranial stents \cite{MicroPort Medical, Shanghai, China}, or Wingspan self-expanding stents \cite{Stryker Neurovascular, formerly Boston Scientific Neurovascular}) were used in the 233 stented arteries (Table 1). After the initial catheter angiography follow-up, patients verified with ISR were typically maintained on dual antiplatelet therapy for 3 months, then single antiplatelet therapy and single antiplatelet therapy was used in patients with no in-stent restenosis (NISR). Atherosclerotic risk factors of both groups were managed in the same way according to the American Heart Association guidelines.\textsuperscript{19}

**Statistical Analysis**

Values are reported as mean±SD, median (interquartile range), or number (percentage) of subjects. Baseline characteristics were compared for statistical difference using 2-tailed unpaired Student $t$ tests or Wilcoxon tests for continuous variables, and $\chi^2$ tests for categorical variables. Log-rank test were used to detect the difference in the rate of the primary end point between the 2 groups. Univariate Cox regression analyses were first conducted for factors associated with the primary end point, followed by multivariate analysis adjusted for age, sex, hypertension, diabetes mellitus, hyperlipidemia, smoking, prior stroke, prior coronary artery disease, and stent types, which may be related to the prognosis of patients. Wilcoxon test was used to detect the difference in median (interquartile range) occurrence time of primary end point between ISR and non-ISR group. Statistical significance was established at $P<0.05$. Statistical analyses were performed using the SPSS software for Windows, version 16.0.

### Results

**Baseline Characteristics**

This study enrolled 226 patients (189 males, 37 females) with 233 stented arteries, who had catheter angiography follow-up (Figure 1). The mean time for catheter angiography follow-up after stenting was 10.1±1.0 months. The mean age was 52.9±9.9 years. Of 233 stented arteries, 24.5% (57/233) lesions were classified into ISR group, and 176 lesions into NISR group. In ISR group, 15 lesions were symptomatic, and 42 were asymptomatic. Baseline characteristics were compared between 2 groups in Table 1. The proportion of patients with diabetes mellitus was higher in ISR group (42.1% [24/57] versus 26.6% [45/169]; $P=0.03$). The proportion of men (86.4% [146/169] versus 75.4% [43/57]; $P=0.03$) and smokers (71% [120/169] versus 75.4% [43/57]; $P=0.05$) and smokers (71% [120/169] versus 75.4% [43/57]; $P=0.05$) and smokers (71% [120/169] versus 75.4% [43/57]; $P=0.05$) and smokers (71% [120/169] versus 75.4% [43/57]; $P=0.05$) were more in ISR group (56.1% [32/57] versus 56.1% [32/57]; $P=0.04$) were more in ISR group (56.1% [32/57] versus 56.1% [32/57]; $P=0.04$) were more in ISR group (56.1% [32/57] versus 56.1% [32/57]; $P=0.04$) were more in ISR group (56.1% [32/57] versus 56.1% [32/57]; $P=0.04$) were more in ISR group (56.1% [32/57] versus 56.1% [32/57]; $P=0.04$) were more in ISR group (56.1% [32/57] versus 56.1% [32/57]; $P=0.04$).

**Table 1. Comparison of Baseline and Clinical Characteristics Between In-Stent Restenosis (ISR) and No In-Stent Restenosis (NISR) Groups (N=226, Lesions=233)***

<table>
<thead>
<tr>
<th>Variables</th>
<th>ISR (n=57, Lesions=57)</th>
<th>NISR (n=169, Lesions=176)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>52.9±11.5</td>
<td>52.9±9.4</td>
<td>0.97</td>
</tr>
<tr>
<td>Male</td>
<td>43 (75.4)</td>
<td>146 (86.4)</td>
<td>0.05</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>43 (75.4)</td>
<td>119 (70.4)</td>
<td>0.47</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>24 (42.1)</td>
<td>45 (26.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>45 (78.9)</td>
<td>138 (81.7)</td>
<td>0.65</td>
</tr>
<tr>
<td>Smoking</td>
<td>32 (56.1)</td>
<td>120 (71.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>10 (17.5)</td>
<td>22 (13.0)</td>
<td>0.40</td>
</tr>
<tr>
<td>Prior coronary artery disease</td>
<td>9 (15.8)</td>
<td>22 (13.0)</td>
<td>0.60</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial internal carotid artery</td>
<td>7 (12.3)</td>
<td>29 (16.5)</td>
<td>0.45</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>28 (49.1)</td>
<td>79 (44.9)</td>
<td>0.58</td>
</tr>
<tr>
<td>Intracranial vertebral artery</td>
<td>15 (26.3)</td>
<td>35 (19.9)</td>
<td>0.30</td>
</tr>
<tr>
<td>Basilar artery</td>
<td>7 (12.3)</td>
<td>33 (18.8)</td>
<td>0.26</td>
</tr>
<tr>
<td>Stent type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apollo</td>
<td>24 (42.1)</td>
<td>63 (35.8)</td>
<td>0.39</td>
</tr>
<tr>
<td>Wingspan</td>
<td>17 (29.9)</td>
<td>52 (29.5)</td>
<td>0.97</td>
</tr>
<tr>
<td>Coronary stent</td>
<td>16 (28.1)</td>
<td>61 (34.7)</td>
<td>0.36</td>
</tr>
<tr>
<td>Stent sum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>53 (93.0)</td>
<td>173 (98.3)</td>
<td>0.11</td>
</tr>
<tr>
<td>Two</td>
<td>4 (7.0)</td>
<td>3 (1.7)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

*Values are reported as mean±SD or number (percentage) of subjects; all risk factors based on both self report and diagnosis in-hospital.

**Figure 1. Study flow chart. Seven patients each had 2 lesions in NISR group. AISR indicates asymptomatic in-stent restenosis; ISR, in-stent restenosis; NISR, no in-stent restenosis; SISR, symptomatic in-stent restenosis.**
group than ISR group. At baseline, 99% (224 of 226) patients took a statin, 96% (66 of 69) of patients with diabetes mellitus were prescribed insulin or an oral hypoglycemic agent, and 100% (162 of 162) of patients with hypertension were prescribed an antihypertensive agent.

**Primary End Point Event**
During a mean follow-up of 38.9 (range, 1–107) months, we observed 27 (12%) primary end point events (9 strokes and 18 TIs). The mean time to the occurrence of primary end point after catheter angiography follow-up was 25.3±20.7 (range, 0.1–73.5) months. There are 12 primary end points (terminal internal carotid artery 2, middle cerebral artery 5, vertebral artery 4, and basilar artery 1) in ISR group and 15 events (terminal internal carotid artery 3, middle cerebral artery 3, vertebral artery 1, and basilar artery 8) in NISR group developed from the ipsilateral lesion arteries. The occurrence of primary end point in ISR was earlier compared with NISR group (median [interquartile range], 9.9 [5.0, 21.1] months versus 26.6 [13.1, 52.9] months; \( P = 0.01 \)).

**Risk Factor Associated With Primary End Point**
Log-rank test (Figure 2A) revealed that the incidence of the primary end point in ISR group was higher than that in NISR group: 21.1% (12/57) versus 8.5% (15/176; hazard ratio [HR], 2.94; 95% confidence interval [CI], 1.37–6.30; \( P = 0.005 \)). However, there was no difference between symptomatic and asymptomatic ISR group: 25% (3/12) versus 20% (9/45; HR, 1.03; 95% CI, 0.28–3.83; \( P = 0.96 \); Figure 2B). Univariate Cox regression analysis showed ISR to be associated with primary end point (Table 2). Multivariable Cox model still revealed that ISR was the only factor associated the primary end point (HR, 2.79; 95% CI, 1.20–6.49; \( P = 0.017 \); Table 2).

**Discussion**
This study showed that intracranial ISR, whether being or not symptomatic at the time of initial angiography follow-up, is an independent risk factor for recurrent ischemic stroke or TIA in the territory of the stented artery. In our patients with catheter angiography follow-up after stenting, intracranial ISR rate was 26.1% (62/238), being within the range of reported ISR rate (14.4% to 30%).\(^\text{11-13}\) the ISR significantly brought a higher risk (21.1% versus 8.5%) and an earlier occurrence time (9.9 months versus 26.6 months) of recurrent ischemic events in the territory of the stented artery. Therefore, reducing the occurrence of ISR should be targeted in future research to improve the efficacy of intracranial PTAS.

Specific risk factors in the development of ISR after intracranial stenting had been described, such as age, diabetes mellitus, stent type, and lesion location.\(^\text{7,8,11,12}\) In this study, we did find the proportion of patients with diabetes mellitus in ISR group was higher compared with non-ISR group. We interestingly found that there were more smokers in NISR group than ISR group, which indicated that smoking might be a beneficial factor for NISR. Smokers paradox was repeatedly mentioned in recent studies, which suggested that smokers not only had dramatically lower periprocedural ischemic events in Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) than nonsmokers, but also had a better outcome than nonsmokers after intravenous tissue plasminogen activator in patients with
Another interesting finding that women were at increased risk of ISR, although this was of borderline significance, is not readily explained. Women may have smaller intracranial arteries, which could pose a greater ISR risk. However, these results should be further verified in succedent studies.

In the GESICA study, 38.2% of patients with symptomatic ICAS of ≥50% experienced a cerebrovascular event in the territory of the stenotic artery during a mean follow-up of 23.4 months. In contrary, the rate of 12% in this study population during a mean follow-up of 38.9 months seems lower than the GESICA’s. These data suggest that when the periprocedural major complication risk is controlled low enough (such as 6%), PTAS is a promising option of treatment for patients with symptomatic ICAS, especially for those at high risk for stroke recurrent or who fail to medical therapy. Therefore, control of the periprocedural major complication risk of PTAS should be an important issue needed to be resolved first before starting a study to test the efficacy of PTAS on patients with ICAS.

The present study has several limitations. First, this study was event sourcing by a single center. Second, although this represents one of the largest cohort of patients with intracranial ISR analyzed, the absolute numbers of ISR lesions included are still relatively small compared with similar studies of coronary ISR. As such, the statistical power is not sufficient to perform detailed subset analyses. Meanwhile, because the main focus of the registry was to collect preliminary data on the periprocedural complications and their long-term outcome after intracranial PTAS, detailed information on medical treatment and improvement results of the controllable risk factors was not sufficiently collected during the clinical follow-up. This limits our ability to correlate them with long-term outcome of intracranial ISR. Finally, most of the patients who met the primary end points in this study were not investigated with telemetry and echocardiography to rule out other potential causes for stroke/TIA, which would lead to the overestimation of the rate of lesion-related events.

Conclusions
ISR, a frequent complication of intracranial PTAS, is significantly associated with an increased risk and an earlier occurrence of recurrent ischemic events in the territory of the stented intracranial artery. Promising options for prevention and treatment of the ISR need to be further discussed in future trials of intracranial stenting.

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Disclosures
None.

References


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