Collateral circulation is a predictor for in-stent restenosis after cerebral anterior circulation large artery stenting

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Research Article

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Abstract

Background-
In-stent restenosis (ISR) is a critical issue of endovascular therapy. The predictors for ISR are not fully explored. We aimed to investigate the predictors for ISR, especially the effect of collateral circulation on ISR after cerebral large artery stenting.

Methods-
From June, 2015 to June, 2018, a total of 312 patients, who performed stenting, with severe cerebral anterior circulation stenosis (≥ 70%), were enrolled. According to the flow velocity indicated by carotid artery ultrasound or Transcranial Doppler, the patients were divided into the ISR and no-ISR groups. Clinical data were collected, including age, sex, cerebrovascular risk factors, preoperative serum lipid, inflammatory markers, and platelet count, stent site, residual stenosis rate, drug therapy after stenting. The collateral circulation was graded according to digital subtraction angiography (DSA). Univariable and multivariable logistic regression analyses were performed to assess the potential risk factors related to restenosis in such patients.

Results-
Higher residual stenosis rate (median 11% vs 10%, p = 0.040), fewer patients received standard drug therapy (73.3% vs 89.4%, p = 0.001), more patients with poor collateral circulation (70.0% vs 41.0%, p = 0.007) were found in ISR group. Residual stenosis rate increased by 10% was associated with a 19.1% increase in restenosis risk. Good collateral circulation (OR 0.16, [95%CI, 0.04–0.49]; p = 0.002) and receiving standard drug therapy (OR 0.14, [95%CI, 0.05–0.58]; p = 0.002) were significantly related to the lower risk of ISR.

Conclusion-
Collateral circulation is an independent factor related with ISR after successful cerebral anterior circulation large artery stenting, and long-term standard drug therapy after stenting should be strictly carried out in such patients.

Introduction
About 22%-46% of ischemic stroke were caused by severe cerebral large artery atherosclerotic stenosis. Even though received normative medication, a high risk of progression and recurrence might have happened in such patients. Stent implantation is an effective method to achieve vascular remodel and blood flow recovery. The American Heart Association/ American Stroke Association guideline suggested
that if symptomatic cerebral large artery stenosis rate over 70%, the patients could be performed stenting, with the advantages of minor injury and rapid recovery\textsuperscript{3,4}.

However, it had been demonstrated that the patients who received cerebral large artery stenting have a risk of in-stent restenosis (ISR) about 2%-41\%\textsuperscript{5,6}; it was one of the main reason for stroke recurrence. Therefore, identifying the risk factors for ISR is very critical. As far as we know, the risk factors of ISR are various, including age, sex, cerebrovascular risk factors, multiple stenosis\textsuperscript{7}, stenosis site\textsuperscript{8}, plaque features\textsuperscript{9}, vessel tortuosity\textsuperscript{10}, length or diameter of stent\textsuperscript{11}, stent type\textsuperscript{11}, and the above factors have various effects in different studies.

Collateral circulation is the main predictor for stroke heterogeneity. It had been demonstrated that abundant collateral circulation was helpful to improve the prognosis in ischemic stroke. Some studies revealed that abundant collateral circulation would reduce ISR incidence after a percutaneous coronary intervention (PCI), but others showed the opposite results\textsuperscript{12-14}. To date, there is no conclusion about the effect of collateral circulation on ISR after cerebral large artery stenting. Our article analyzed the influence of collateral circulation and other factors on ISR after anterior cerebral circulation large artery stenting, then further provided more shreds of evidence to choose appropriate patients for stenting.

\textbf{Materials And Methods}

\textbf{Research population}

From June 2015 to June 2018, 312 patients who performed stenting in neurology department of the second hospital of Hebei Medical University were enrolled. These patients were satisfied with the inclusion criteria as follows: (1) cerebral anterior circulation atherosclerosis stenosis (cervical segment to communicating segment of the internal carotid artery, middle cerebral artery M1 segment) and recurrent ischemic stroke even with standard secondary prevention, however, all patients were in the non-acute stage; (2) DSA indicated severe stenosis (\geq 70\%); (3) willing to be follow-up, including carotid artery ultrasound or Transcranial Doppler; (4) mRS \leq 2 before stenting. The exclusion criteria as follows: (1) severe cerebral anterior circulation large artery stenosis caused by nonatherosclerotic, such as cardiogenic stroke, arterial dissection, vasculitis, fibromuscular dystrophy, and moyamoya disease; (2) history of cerebrovascular interventional treatment; (3) cerebral posterior circulation large artery stenting; (4) complicated with a tumor, autoimmune disease, liver or kidney dysfunction, and other serious diseases; (5) other intracranial diseases; (6) in a state of acute or chronic infection; (7) death after stenting. This retrospective study was performed and approved by the Institutional Ethics Committee of the Second Hospital of Hebei Medical University (Grant Number: 2020-R384). Informed consent was obtained from all patients or their relatives.

\textbf{Research design}

All the enrolled patients were divided into ISR group (n=30) and no-ISR group (n=282) according to the ultrasound or Doppler. ISR could be confirmed by ultrasound, Transcranial Doppler or DSA, and their
results have highly consistent\textsuperscript{15,16}. According to DSA, ISR was defined as more than 50% diameter stenosis within or immediately adjacent (within 5mm) to the implanted stent site\textsuperscript{5}. Our study included patients who were asked to receive carotid artery ultrasound or Transcranial Doppler at 1, 3, 6, and 12 months after stenting and then yearly after that; their follow-up data were collected in a clinic or by telephone. By carotid artery ultrasound, the peak systolic velocity in internal carotid artery\textsuperscript{\textless}1.3-2.1m/s, the end-diastolic velocity in internal carotid artery\textsuperscript{\textless}0.4m/s, peak systolic velocity in internal carotid artery/peak systolic velocity in common carotid artery\textsuperscript{\textless}3.2m/s, if any of the above criterion were met, then it was defined as ISR\textsuperscript{17}. By Transcranial Doppler, the mean velocity of cerebral middle artery\textsuperscript{\textless}1.0m/s was defined as ISR\textsuperscript{15}.

We collected their clinical data, including age, sex, cerebrovascular risk factors (hypertension, diabetes mellitus, coronary artery disease, current smoking or drinking), preoperative serum lipid (total cholesterol, triglycerides, low-density lipoprotein cholesterol), preoperative inflammatory markers (leukocytes, neutrophils, C-reactive protein), preoperative platelet count, stent site, residual stenosis rate, and drug therapy after the operation. Furthermore, we compared the above indexes between the two groups and analyzed the effect of collateral circulation on ISR in such patients.

**Stenting procedure**

All patients were managed with dual antiplatelet (aspirin 100mg and clopidogrel 75mg daily) for at least 3 days before stenting. A bolus of IV heparin (50IU/kg of body weight, 3000-5000IU) was injected after the guide catheter.

Intracranial segment of internal carotid artery and middle cerebral artery stenting: A guiding catheter was placed in the petrous or high cervical internal carotid artery via femoral access. The target stenosis segment was crossed with a microwire, the tip of which was placed into M3 or M4 segment of the middle cerebral artery. A suitable size of stent was placed in stenosis site. Balloon dilation in the stenosis site is required before the implantation of a self-expanding stent.

Terminal common carotid artery- initiation internal carotid artery stenting: A guiding catheter was placed into the common carotid artery. A protective umbrella and then a suitable size of the stent was implanted and released. Finally, the protective devices were removed.

**Grading of collateral circulation**

According to the grading of American Society for Interventional and Therapy Neuroradiology/ Society for Interventional Radiology (ASITN/SIR), cerebral collateral circulation was divided into 5 levels, 0 level: no collateral visible to the ischemic site; 1 level: slow collateral to the periphery of the ischemic site with the persistence of defect; 2 level: rapid collateral to the periphery of ischemic site with the persistence of defect and to only a portion of the ischemic territory; 3 level: collateral with slow but complete angiographic blood flow of the ischemic bed by the late venous phase; 4 level: complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion\textsuperscript{18}. 0–1
levels were defined as poor collateral circulation, and 2–4 levels were defined as good collateral circulation. All images were reviewed by two experienced independent observers who were blinded to the patients' information. If they had contrary opinions, a third neuro-interventional expert would be invited to participate in the evaluation.

**Drug therapy after operation**

Aspirin (100mg/day) and clopidogrel (75mg/day) were taken orally for 90 days after stenting, and then switch to aspirin (100mg/day) or clopidogrel (75mg/day) for lifelong. In the meanwhile, statins were also taken orally for a long-term after stenting. The above measures were defined as standard drug therapy. However, any discrepancy with the above measures was defined as no-standard drug therapy, for example, mono-antiplatelet therapy within 90 days after stenting, and no antiplatelet or statins were taken after stenting. Besides, all the patients were given a standardized prevention program, such as controlling cerebrovascular risk factors (hypertension, diabetes mellitus, coronary artery disease, current smoking or drinking, hyperlipemia and the like).

**Statistical analysis**

Statistical analysis was performed using SPSS (version 25.0.0, SPSS Inc. Chicago, Illinois). Data are expressed as mean ± standard deviation, medians with interquartile range, or numbers with percentages. Categorical variables were performed using the Chi-square statistics or Fisher’s exact test, as appropriate. Normality was assessed for continuous data using the Kolmogorov–Smirnov test. Continuous variables were compared using independent Student's t-tests. If data distributions were skewed, a non-parametric test was used for comparison.

To determine the independent risk factor for ISR, the results of univariate analysis, clinical experience and previous research conclusions were considered, and certain variables were further entered into multivariate regression. A p value < 0.05 was considered statistically significant, and the possible influencing factors of ISR were estimated according to odds ratios.

**Results**

**Baseline characteristics**

In our study, the enrolled patients were divided into ISR group (n = 30) and no-ISR group (n = 282). The median age was 63 years old and the median time from stenting to ISR was 18 months in both groups. There were 23 males (79.3%) in ISR group and 214 males (75.9%) in no-ISR group. Age, sex, hypertension, diabetes mellitus, coronary artery disease, current smoking or drinking had no significant difference in the two groups. For preoperative serum lipid, total cholesterol and triglycerides had no difference between the two groups, while low-density lipoprotein cholesterol was higher in no-ISR group (2.35mmol/L vs 2.05mmol/L, p = 0.038). Preoperative inflammatory makers, platelet count and C-reactive protein were
higher in ISR group, while leukocytes and neutrophils were higher in no-ISR group; however, the above indicators had not reach statistical difference. ISR was more likely to occur in the middle cerebral artery, compared to the internal carotid artery ($p = 0.059$). In the ISR group, the residual stenosis rate was higher ($p = 0.049$), more patients failed to receive standardized drug therapy after the operation ($p = 0.018$), and more patients with poor collateral circulation ($p = 0.007$). During the follow up period, more patients had recurrent ischemic stroke in ISR group (10.1% vs 4.3%, $p = 0.165$); however, the patients with recurrent ischemic stroke in both groups had a median mRS of 3 after 90 days. The above results were listed in Table 1 and a patient with ISR was shown by DSA (Fig. 1).
### Table 1
The baseline characteristics between ISR group and no-ISR group

|                               | ISR group (n = 30) | no-ISR group (n = 282) | P value |
|-------------------------------|--------------------|------------------------|--------|
| ISR after stenting (median, month) | 18 (13–21)         |                        |        |
| Baseline characteristics      |                    |                        |        |
| Age (median, year)            | 63 (59–67)         | 63 (58–69)             | 1.000  |
| Male( %)                      | 23 (79.3%)         | 214 (75.9%)            | 0.615  |
| TBIS (median, month)          | 1 (1.0–1.0)        | 1 (1.0–2.0)            | 0.056  |
| CRF (%)                       |                    |                        |        |
| Hypertension                  | 17 (58.6%)         | 205 (73.3%)            | 0.083  |
| Diabetes mellitus             | 12 (41.4%)         | 90 (32.3%)             | 0.321  |
| CAD                           | 6 (20.7%)          | 58 (20.8%)             | 0.990  |
| Current smoking               | 6 (20.7%)          | 90 (40.0%)             | 0.242  |
| Current drinking              | 5 (17.9%)          | 78 (28.1%)             | 0.247  |
| Preoperative serum lipid (median, mmol/L) |          |                        |        |
| Total cholesterol             | 3.45 (3.21–3.95)   | 3.82 (3.24–4.48)       | 0.112  |
| Triglycerides                 | 1.30 (1.04–1.99)   | 1.24 (0.96–1.87)       | 0.566  |
| LDL-C                         | 2.05 (1.61–2.33)   | 2.35 (1.80–2.93)       | 0.038  |
| Preoperative inflammatory markers |                    |                        |        |
| Leukocytes (median, *10^9/L)  | 6.04 (5.24–7.15)   | 6.67 (5.68–8.10)       | 0.121  |
| Neutrophils (median, *10^9/L) | 3.80 (3.30–4.63)   | 4.17 (3.33–5.10)       | 0.455  |
| CRP (median, mg/L )           | 11.35 (3.70–14.93) | 8.55 (1.60–15.48)      | 0.199  |
| Preoperative platelet count (median, *10^9/L) | 226 (198–269)      | 208 (179–246)          | 0.113  |
| Stent site (%)                |                    |                        | 0.059  |

Date are expressed as mean (SD), median (interquartile range), or number (%). ISR, in-stent restenosis; no-ISR, no in-stent restenosis; CRF, cerebrovascular risk factor; CAD, coronary artery disease; LDL-C, low density lipoprotein cholesterol; CRP, C-reactive protein; MCA, cerebral middle artery; TBIS, time between ischemic and stenting
| Predictor of ISR | ISR group (n = 30) | no-ISR group (n = 282) | P value |
|------------------|--------------------|------------------------|---------|
| Internal carotid artery | 22 (8.0%) | 242 (72.0%) |         |
| MCA (M1 segment) | 8 (17.6%) | 40 (83.8%) |         |
| Residual stenosis rate (%) | 11 (5–20) | 10 (5–16) | 0.049   |
| Drug therapy after operation (%) | | | 0.018   |
| Standard drug therapy | 22 (73.7%) | 252 (89.4%) |         |
| No-standard drug therapy | 8 (26.7%) | 30 (10.6%) |         |
| Recurrence of stroke (%) | 3 (10.0%) | 12 (4.3%) | 0.165   |
| Collateral circulation (%) | | | 0.007   |
| Poor | 21 (70.0%) | 113 (40.1%) |         |
| Good | 9 (30.0%) | 169 (59.9%) |         |

Date are expressed as mean (SD), median (interquartile range), or number (%). ISR, in-stent restenosis; no-ISR, no in-stent restenosis; CRF, cerebrovascular risk factor; CAD, coronary artery disease; LDL-C, low density lipoprotein cholesterol; CRP, C-reactive protein; MCA, cerebral middle artery; TBIS, time between ischemic and stenting

According to the univariate analysis results and clinical experience, we collected the data included collateral circulation, drug therapy after stenting, residual stenosis rate, and middle cerebral artery stenting into multivariate logistic regression analysis. The results implied that good collateral circulation (aOR 0.16, [95%CI, 0.04–0.49]; p = 0.002) and standard drug therapy after stenting (aOR 0.14, [95%CI, 0.05–0.58]; p = 0.002) would reduce the odds of ISR. Higher residual stenosis rate (aOR 1.110, [95%CI, 1.038–1.187]; p = 0.002) contributed to ISR and its 10% increase was associated with a 19.1% increase in restenosis risk. The above results were listed in Table 2. On the other hand, our study also observed no significant difference for ISR occurrence, no matter the stenosis was in left or in the right side of cerebral. Simultaneously, there was no statistical difference in ISR risk between intracranial and extracranial segment after anterior cerebral circulation large artery stenting. Above results were listed in Table 3.
Table 2
The independent risk factors of ISR after cerebral anterior circulation large artery stenting by multivariate regression analysis

| Variables                        | B value | OR value (95% CI) | P value |
|----------------------------------|---------|-------------------|---------|
| Good collateral circulation      | -1.967  | 0.140(0.039–0.496)| 0.002   |
| Standard drug therapy            | -1.807  | 0.164(0.047–0.576)| 0.005   |
| Residual stenosis rate           | 0.104   | 1.110(1.038–1.187)| 0.002   |
| MCA (M1 segment) stenting        | 0.766   | 2.151(0.496–9.322)| 0.306   |

MCA, cerebral middle artery.

Table 3
The stenosis sites and ISR

|                         | ISR group | no-ISR group | p value |
|-------------------------|-----------|--------------|---------|
| Internal carotid artery (no. %) | 9(45.0%)  | 110(45.8%) | 0.943   |
| left                    | 4(40%)    | 28(66.7%)   |         |
| right                   | 6(60%)    | 14(33.3%)   |         |
| Middle cerebral artery (no. %) |  |             | 0.156   |
| left                    |  | 4(40%)     | 28(66.7%) |
| right                   |  | 6(60%)     | 14(33.3%) |
| Cerebral anterior circulation large artery (no. %) | 18(60%) | 204(72.3%) | 0.155 |
| Extracranial segment    | 12(40%)   | 78(27.7%)   |         |
| Intracranial segment    |  |            |         |

ISR, in-stent restenosis.

Discussion

Even though the ISR is widely discussed in cerebral large artery stenting for a long period, the exact risk factors are still in debated. ISR involves many aspects, including age, sex, cerebrovascular risk factors, family history or hereditary factor, stenosis site, plaque features, length or diameter of stent, stent type, vessel tortuosity. As we all know, ISR signifies the increased odds of stroke recurrence, so it is necessary to take an in depth investigation to identify the related risk factors and take effective measures in advance.

It is believed that the pathophysiological mechanisms of ISR are referred to many factors. First, the elastic retraction of the vessel wall at the stent is the early factor for ISR after stenting. Second, the inflammation respond was a pivotal pathophysiological mechanism in ISR. The vessel wall's
inflammation promotes the proliferation and migration of vascular smooth muscle cells into the vessel intima, further leading to neointimal hyperplasia. Leukocytes and neutrophils could also be used as important biomarkers of the inflammatory response, and characterized by many influencing factors and lack of specificity. However, some blood cells ratios, like neutrophil/lymphocyte, could reflect the inflammation degree in vascular walls\(^\text{20}\). Our article demonstrates that platelet and C-reactive protein are higher in ISR group, which shows a trend of activated inflammatory status. However, the numbers of related blood cells did not reflect the difference between the two groups, which may be related to the relatively small sample size, especially in the ISR group. Third, during the stenting, stents would destroy the vascular endothelial cells, leading to release and aggregation of inflammatory mediators, such as platelets, macrophages and cytokines, which further remodel the vascular wall form ISR\(^\text{21}\). After stenting, chronic mechanical stimulation of vessel wall promotes vascular smooth muscle cells proliferation, contributes to extracellular matrix formation\(^\text{22}\), and ultimately leads to ISR\(^\text{7}\). As time goes on, the vascular wall at the stent site under an inflammatory status for a long time, the vascular endothelial cells would be dysplastic and the stents cannot be completely covered, which further intake lipid excessively and accelerate the formation of neoatherosclerosis\(^\text{23,24}\). Therefore, many studies had paid attention to the effect stent type, stent length, residual stenosis rate and stenosis sites on ISR. There was no consistent conclusion about the effect of stent type on IRS\(^\text{17,25,26}\), therefore, we did not include it as a variable. Also the diameters and hemodynamics states between intracranial and extracranial vessels might affect IRS. Kang et.al\(^\text{1}\) noted that ISR was more common after stenting in intracranial stenosis than extracranial stenosis. But there was no statistically significant difference in our study, because the sample size was small. After stenting, the higher residual stenosis rate would promote local thrombosis formation and result in lower vascular wall shear stress, which further activates the inflammatory response in the blood vessel wall. Oteros R et.al\(^\text{27}\) suggested that the risk of ISR was lowest when residual stenosis rate was no more than 30%. In our study, there was a significant difference in residual stenosis rate among the two groups, and it was an independent risk factor for ISR, which is agreed with previous studies. Our result implied that residual stenosis rate should be minimized after cerebral large artery stenting.

In recent years, collateral circulation is an important predictor of clinical outcome for acute ischemic stroke. Abundant collateral circulation could lessen disease severity, minimize infarct volume and improve clinical prognosis. Several studies suggested that the proximal anterior circulation stroke patients with poor collateral circulation would not benefit from stenting\(^\text{28}\). According to our knowledge, the correlation between collateral circulation and ISR had been reported more frequently in coronary artery PCI. Some researches revealed that poor collateral circulation was an important predictor of ISR after PCI, while others showed the opposite conclusion\(^\text{12,29,30}\). We speculate that this phenomenon is due to the different evaluation methods of collateral circulation, because the vascular perfusion pressure is usually used to evaluate the collateral circulation of the coronary artery in prior researches. However, it is indirect and imprecise\(^\text{13,14}\). Sometimes, the elevated perfusion pressure in ischemic cerebral tissue may be related to the recanalization of occluded vessels, but it does not refer to the abundant collateral circulation. Until now, few researches are found about the relationship between collateral circulation and
ISR after cerebral large artery stenting. In our research, we first reported that collateral circulation was an independent factor for ISR after cerebral anterior circulation large artery stenting. The mechanisms, we consider, may be due to the following reasons: first, after stenting the vascular wall shear stress dramatic decline in poor collateral circulation patients, which increases the expression of proinflammatory genes and leads to intimal hyperplasia\textsuperscript{22}. Second, the patients with poor collateral circulation after stenting have a greater change in blood flow in-stent sites, which leads to the activation of vascular endothelial cells, the releases of inflammatory cytokines, and remodelling of the blood vessels\textsuperscript{31}. Third, the patients with poor collateral circulation have higher vasoconstrictor peptide, which may increase vasoconstrictor force and promote restenosis\textsuperscript{14}. In brief, we hypothesize that hemodynamics changes, expression of inflammatory gene, and released of inflammatory cytokines in patients with poor collateral circulation would contribute to ISR. Therefore, we assume that the evaluation of collateral circulation before cerebral large artery stenting may help to predict the risk of ISR. Currently, there are lots of methods to evaluate the cerebral collateral circulation, including DSA, computed tomographic angiography, computed tomographic perfusion and some other magnetic resonance based methods. All of these methods have their own characteristics, but DSA is the gold standard for diagnosis\textsuperscript{18}. Because all the included patients in our study underwent DSA during stenting, so we used this method to evaluated cerebral collateral circulation. We found that many studies utilize the ASITN/SIR score to evaluate the collateral circulation that distal to severe carotid artery stenosis\textsuperscript{32,33}, basically the same way we did.

On the other hand, drug therapy after cerebral artery stenting involves a comprehensive management, including antiplatelet, lipid-lowering, and controlling other traditional vascular risk factors\textsuperscript{34,35}. The optimal treatment strategy after stenting remains controversial. The aggregation of platelets and the inflammatory response of vascular walls after stenting play a vital role in ISR. After stenting, platelet deposition in the injured vascular wall and promote the synthesis of extracellular matrix\textsuperscript{25}. Antiplatelet drugs and statins are the primary therapeutic medicine. However, their role in lowering the risk of ISR is still unclear. Akbulut M et al.\textsuperscript{36} observed that antiplatelet treatment would significantly lower the odds of intimal hyperplasia and ISR after PCI. Dual antiplatelet therapy might also play an important role in lowering the risk of ISR after cerebral artery stenting\textsuperscript{37}. Statins can lower the risk of ISR by inhibiting proliferation and migration of vascular smooth muscle cells\textsuperscript{34}. Leone AM et al.\textsuperscript{38} confirmed that statins should keep the low-density lipoprotein cholesterol\textsuperscript{2}70mg/dl to reduce the formation of neoatherosclerosis. Our study found that the combination of antiplatelet drugs and statins for long-term could effectively reduce ISR risk after anterior cerebral large artery stenting. Therefore, standard medicine treatment, the combination of antiplatelet and statins for more than 3 month, is recommended for such patients to reduce the risk of ISR. However, this was a retrospective study, and we did not collect the information about the dose of antiplatelet and statins agents, so it is impossible to determine the optimal oral dose to reduce the risk of restenosis. We hope this problem will be clear in our future research.

Currently, DSA is the gold standard for evaluation of intracranial artery stenosis. However, this method has lots of limitations, such as radiation damage and contrast agent allergy. It is not convenient for
follow-up, so we look forward to applying more accurate and less invasive methods. In our research, we used carotid artery ultrasound and Transcranial Doppler sonography to follow-up visit, and they are readily available and non-invasive diagnostic tools for evaluation of ISR. Compared with DSA, ultrasound was proved to have a high sensitivity (100%) and specificity (93.3%) in detecting of severe cerebral anterior circulation large artery stenosis\(^1\). Transcranial Doppler sonography is a real-time diagnostic tool for intracranial blood flow monitoring. Compared with DSA, it has higher consistency in evaluating of intracranial artery stenosis, and it could be used as a reliable tool for follow-up\(^1\).

There are some limitations to our study. First, it involved retrospectively observational research and the materials collection in a predetermined manner, so the information bias cannot be ruled out. Second, this research was a single centre study, and the selection bias may affect reliability. Third, a relatively limited proportion of the study population was involved, especially the ISR group. Although this situation was objective, it might affect the statistical results inevitably. A prospective systemic study would obtain more precise results based on our encouraging preliminary conclusion. Finally, carotid artery ultrasound and Transcranial Doppler were performed by different operators, and we collected clinical outcome via face to face or telephone interview, which may affect the homogeneity of examination and the accuracy of information.

**Conclusions**

Several factors are related with ISR, collateral circulation is independently associated with ISR in patients with cerebral anterior circulation large artery stenting. At the same time, regular oral antiplatelet and statins over a long term effectively to reduce the odds of ISR.

**Declarations**

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**Author Contributors**

L.L.: data analysis and interpretation, composition of manuscript, and critical revision of the manuscript for important intellectual content. X.S.: data analysis and interpretation, composition of manuscript, and critical revision of the manuscript for important intellectual content. Z.L.: data collection and collation. K.B.: data collection and collation. S.Y.: data collection and collation. Q.W.: data collection and collation. N.A: data collection and collation. Z.L.: image data analysis. C.Z.: image data analysis. J.Y.: image data analysis. G.T.: critical revision of the manuscript for important intellectual content. L.G.: critical revision of the manuscript for important intellectual content, and study supervision.

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Conflicts of interest

The authors declare no conflict of interest.

Ethical approval

The research was performed according to guidelines from Helsinki Declaration and was approved by Institutional Ethics Committee of the Second Hospital of Hebei Medical University (Grant Number: 2020-R384).

Patients consent for publication

Informed consent was obtained from all patients or their relatives.

Data availability

The data sets generated and analyzed during the current study are available on appropriate request made to the corresponding author.

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**Figures**
Figure 1

A 66-year-old woman, who occurred ISR one year after carotid artery stenting. A: severe stenosis in the C1 segment of the right internal carotid artery (arrow); B: there was no obvious stenosis after stenting (arrow); C: restenosis occurred in the stent after one year (arrow).