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Incidence and Risk Factors of In-Stent Restenosis for Symptomatic Intracranial Atherosclerotic Stenosis: A Systematic Review and Meta-Analysis

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ABSTRACT

BACKGROUND: In-stent restenosis affects long-term outcome in patients with intracranial atherosclerotic stenosis.

PURPOSE: The aim of this meta-analysis was to evaluate the incidence and risk factors of in-stent restenosis.

DATA SOURCES: All literature that reported in-stent restenosis was searched on PubMed, Ovid EMBASE and Ovid MEDLINE data bases.

STUDY SELECTION: Original articles about stents for symptomatic intracranial atherosclerotic stenosis were selected.

DATA ANALYSIS: Meta-analysis was conducted to derive the pooled in-stent restenosis using a random-effects model. Meta-regression was performed to explore the risk factors predisposing to in-stent restenosis.

DATA SYNTHESIS: In total, 51 studies with 5043 patients were included. The pooled incidence rate of in-stent restenosis was 14.8% (95% CI, 11.9%–17.9%). Among the lesions with in-stent restenosis, 28.8% of them led to (95% CI, 22.0%–36.0%) related neurologic symptoms. The series in the United States had a higher in-stent restenosis rate (27.0%; 95% CI, 20.6%–33.9%) compared with those from Asia (13.6%; 95% CI, 10.3%–17.2%) and other regions as a whole (7.6%; 95% CI, 1.1%–18.1%) ($P < .01$). Multiregression analysis revealed that younger patient age was related to high in-stent restenosis rates ($P = .019$), and vertebrobasilar junction location ($P = .010$) and low residual stenosis ($P = .018$) were 2 independent risk factors for symptomatic in-stent restenosis rate.

LIMITATIONS: The heterogeneity of most outcomes was high.

CONCLUSIONS: Our study showed promising results of in-stent restenosis for symptomatic atherosclerotic stenosis. Studies are needed to further expatiate on the mechanisms by which younger patient age, vertebrobasilar junction location, and low residual stenosis could increase in-stent restenosis and symptomatic in-stent restenosis, respectively.

ABBREVIATIONS: ISR = in-stent restenosis; MINORS = Methodological Index for Non-Randomized Studies; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SAMMPRIS = Stenting vs. Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis; SES = self-expandable stent

Intracranial atherosclerotic stenosis leads to a remarkable decrease of cerebral perfusion and is responsible for approximately 8%–10% of all ischemic strokes.[1,2] According to the results of several randomized clinical trials, including the Warfarin-Aspirin Symptomatic Intracranial Disease Study (WASID), Stenting vs. Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS), and VISSIT Intracranial Stent Study for Ischemic Therapy (VISSIT), the annual rate of recurrent strokes of patients with intracranial atherosclerotic stenosis could be as high as 12.2%–20.4% despite aggressive medical treatment.[3-5] Stent placement as a major technique of endovascular treatment can reduce the stroke recurrence in patients who were refractory to aggressive medical treatment. The Wingspan Stent System Post Market Surveillance Study (WEAVE) has shown that the incidence of perioperative complications can be reduced to 2.6%.[6] In-stent restenosis (ISR) is another important risk factor for long-term stroke recurrence in the patients with stents. Patients with ISR had an approximately

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10% higher risk of an ischemic event, which occurred earlier simultaneously than those without ISR after stent implantation.[7,8] The incidence of ISR differs among the available studies, varying from 5% to 30%, and reliable analyses of risk factors of ISR are still lacking until now.[8-11] In this meta-analysis, we aimed to evaluate the incidence of ISR and identify the relative risk factors.

MATERIALS AND METHODS

Literature Search

We searched the literature (last search August 30, 2019) via the databases PubMed, Ovid EMBASE, and Ovid MEDLINE and following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12] The inclusion criteria were stents for symptomatic intracranial atherosclerotic stenosis. The following key words were used and limited to the title and abstract: ("stent" or "stents" or "angioplasty") and ("stenosis" or "atherosclerosis" or "atherosclerotic" or "occlusion") and ("cerebral" or "intracranial"). The studies included had data of ISR as one of the outcomes. Exclusion criteria were the following: 1) articles written in languages other than English; 2) reviews, comments, protocols, editorials, letters, case reports, or animal trials; 3) studies with multiple treatments like primary balloon angioplasty or with extracranial artery stenosis in which data could not be separated; 4) studies on the treatment of complex cerebral artery stenosis; 5) studies on imaging evaluation or treatment of ISR; and 6) series with sample sizes of <20.

Data Extraction and Quality Scoring

We extracted the following data: 1) patient characteristics, including age, sex, hypertension, diabetes, hyperlipemia, smoking, coronary heart disease, ischemic stroke or TIA as a qualifying event, and duration from symptom to treatment; 2) lesion characteristics, including lesion location (internal carotid artery, middle cerebral artery, anterior cerebral artery, vertebral artery, basilar artery, vertebrobasilar artery, and posterior cerebral artery), degree of preprocedural stenosis, length and Mori type of lesion; 3) procedure-related characteristics, including stent type, procedural success, degree of residual stenosis, and periprocedural complications; and 4) image follow-up characteristics, including image follow-up rate, mean image follow-up time, ISR rate, and symptomatic ISR rate. ISR was defined as an angiographically verified >50% stenosis within or at the edge of the stent. All the included cohort studies were assessed by the Newcastle-Ottawa Scale and single-arm studies assessed by the Methodological Index for Non-Randomized Studies (MINORS) (On-line Tables 1 and 2).[13,14] Studies with a Newcastle Ottawa Scale score of >5 and a MINORS score of >10 were considered high-quality studies.

Statistical Analysis

Statistical heterogeneity of the data was measured by the Higgins index (I^2), and the DerSimonian and Laird random-effects model was used. I^2 < 60% was considered as little-to-moderate heterogeneity, while I^2 > 60% was considered substantial heterogeneity. The pooled ISR was represented on a forest plot with 95% CI. The publication bias was assessed by the Egger test and was illustrated on a funnel plot (On-line Figs 1 and 2). All *P* values were 2-sided, and a statistically significant difference was $P < .05$. All analyses were performed with the "meta" and "metafor" packages in R statistical and computing software, Version 3.4.3 (http://www.r-project.org/).

RESULTS

Description of Studies

There were 646 studies found in the first search. After screening the article and assessing the full text, a total of 51 studies met the inclusion and exclusion criteria, and 5043 patients with 5168 lesions were included in our analysis.[4,7-11,15-59] Among these, 4 studies were prospective multicentric, 7 were single-center prospective, 8 were retrospective multicentric, and 32 were retrospective single-center series. The PRISMA flow diagram of our analysis is shown in On-line Fig 3.

Patient Population and Characteristics

The mean age of patients was 60.1 years (range, 48.1–70.5 years), and the proportion of male patients was 73.6% (3712/5043; 95% CI, 71.1%–76.1%; $I^2 = 71\%$). The most common risk factors were hypertension (3772/5043 = 74.8%; 95% CI, 70.9%–78.7%; $I^2 = 87\%$), hyperlipidemia (2416/5043 = 47.9%; 95% CI, 42.1%–54.6%; $I^2 = 95\%$), smoking (2073/5043 = 41.1%; 95% CI, 34.9%–47.3%; $I^2 = 93\%$), diabetes (1725/5043 = 34.2%; 95% CI, 30.0%–38.4%; $I^2 = 88\%$), and coronary artery disease (908/5043 = 18.0%; 95% CI, 15.0%–20.9%; $I^2 = 69\%$). As the qualifying agent, 57.2% of patients (2885/5043; 95% CI, 50.8%–63.6%; $I^2 = 94\%$) had ischemic stroke, while 41.2% patients (2078/5043; 95% CI, 34.2%–48.3; $I^2 = 94\%$) had transient ischemic attack as the qualifying event.

On the whole, 57.1% of lesions (95% CI, 44.9%–68.8%; $I^2 = 98.5\%$) had anterior circulation artery stenosis, while 43.8% (95% CI, 31.9%–56.0%; $I^2 = 98.5\%$) were posterior circulation lesions. According to Mori type, Mori A was 24.1% (95% CI, 17.6%–31.1%; $I^2 = 86.6\%$), Mori B was 55.1% (95% CI, 48.1%-62.0%; $I^2 = 74.7\%$), and Mori C was 21.5% (95% CI, 14.7%–29.2%; $I^2 = 84.1\%$). Among these patients, balloon-mounted stents were used in 31.7% (95% CI, 16.3%–49.3%; $I^2 = 99.3\%$) of patients, and self-expandable stents were used in 68.3% (95% CI, 50.7%–83.7%; $I^2 = 99.3\%$).

ISR and Its Risk Factors

A total of 3652 lesions (70.7%) had imaging follow-up. The mean image follow-up time was 17.8 months (range, 5.9–180.0 months). For lesions with at least 1 imaging follow-up, the rate of ISR amounted to 14.8% (95% CI, 11.9%–17.9%; $I^2 = 82\%$) (On-line Fig 4).

The ISR rate was lower in older patients ($P = .009$) (On-line Fig 5). Prospective studies had higher ISR rates than retrospective studies (20.9%; 95% CI, 16.0%–26.3%; $I^2 = 69\%$ versus 13.2%; 95% CI, 10.0%–16.7%; $I^2 = 82\%$; $P = .02$) (On-line Fig 6). Series in United States had higher ISR rates (27.0%; 95% CI, 20.6%–33.9%; $I^2 = 30\%$) compared with those from Asia (13.6%; 95% CI, 10.3%–17.2%; $I^2 = 83\%$) and other regions as a whole (7.6%; 95% CI, 1.1%–18.1%; $I^2 = 80\%$; $P < .01$) (On-line Fig 7). Meanwhile, the ISR rate was significantly higher in studies with imaging follow-up rates below 60% than in the studies with image follow-up rates above 60% (21.6%; 95% CI, 16.1%–27.6%; $I^2 =$

Analysis of meta-regression with in-stent restenosis according to patient population and characteristics

	No. of Studies	*P* Value	Heterogeneity I^2 (%)
Patient characteristics			
Mean age	46	.009	78.4
Male %	47	.752	82.8
Hypertension	34	.710	84.2
Diabetes	34	.267	83.5
Hyperlipemia	32	.054	78.1
Smoking	34	.946	83.7
IS as the qualifying event	36	.513	84.2
TIA as the qualifying event	33	.621	81.0
Duration from symptom to treatment	20	.489	82.3
Lesion characteristics			
Anterior circulation	47	.995	82.2
ICA	44	.956	81.4
MCA	44	.924	81.4
ACA	44	.161	80.4
Posterior circulation	47	.998	82.2
VA	42	.122	80.8
BA	42	.208	80.4
VBJ	42	.232	81.0
PCA	43	.951	81.1
Preprocedural stenosis degree	42	.368	81.4
Length of stenosis	17	.731	79.0
Mori type			
Mori A	13	.955	72.1
Mori B	12	.705	52.3
Mori C	12	.987	53.3
Procedure-related characteristics			
Procedural success rate	42	.052	80.1
Stent type (BMS or SES)	47	.817	83.6
Mean degree of residual stenosis	38	.778	80.9
Periprocedural complication rate	43	.699	82.5
Image follow-up characteristics			
Image follow-up time (mo)	46	.404	83.1
Image follow-up rate >60%	51	.004	81.2

Note:—IS indicates ischemic stroke; ACA, anterior cerebral artery; VA, vertebral artery; BA, basilar artery; VBJ, vertebrobasilar junction; PCA, posterior cerebral artery; BMS, balloon-mounted stent.

73% versus 12.2%; 95% CI, 9.1%–15.7%; $I^2 = 83\%$; $P < .01$) (On-line Fig 8). Overall, the ISR rate was not statistically related to hypertension, diabetes, lesion location, length of stenosis, procedural success rate, degree of residual stenosis, and other variables (Table). Results of multiregression analysis showed that younger age was the only independent risk factor that predicted high ISR rates ($P = .019$).

Risk Factors for Symptomatic ISR

Among the lesions with ISR at follow-up, 28.8% (95% CI, 22.0%–36.0%; $I^2 = 44\%$) were symptomatic. Meanwhile, the symptomatic ISR rate was 4.3% (95% CI, 3.0%–5.7%; $I^2 = 53\%$) in the total study population.

First, symptomatic ISR was correlated to the sample size of the series. Symptomatic ISR increased as the sample enlarged ($P = .001$) (On-line Fig 9). Second, according to the results of subgroup analysis, the studies in the United States had higher symptomatic ISR rates (8.7%; 95% CI, 5.0%–13.2%; $I^2 = 0\%$) than those in Asia (4.3%; 95% CI, 3.1%–5.6%; $I^2 = 30\%$) and other regions (0.0%; 95% CI, 0.0%–2.3%; $I^2 = 0\%$) ($P < .01$). Third, older individuals also had lower symptomatic ISR rates ($P = .046$) (On-line Fig 10). Fourth, the symptomatic ISR rate was also lower in studies with an imaging follow-up rate of >60% than in the studies with an image follow-up rate of <60% (3.4%; 95% CI, 2.1%–5.1%; $I^2 = 58\%$ versus 6%; 95% CI, 4%–9%; $I^2 = 28\%$, $P = .02$). In multivariate regression analysis, vertebrobasilar junction location ($P = .010$) and low residual stenosis ($P = .018$) were independent risk factors for the symptomatic ISR rate (On-line Figs 11 and 12).

Heterogeneity

Moderate heterogeneity between effect estimates was observed for Mori B and Mori C lesions. Substantial heterogeneity between effect estimates was observed in the following variables: age, male sex, hypertension, diabetes, hyperlipemia, smoking, ischemic stroke or TIA as the qualifying event, duration from symptom to treatment, lesion location, peristenosis, length of stenosis, Mori A lesion, procedural success rate, stent type, and image follow-up rate (Table).

DISCUSSION

Our meta-analysis showed that 14.8% of symptomatic patients with intracranial atherosclerotic stenosis after stent implantations may experience ISR. Among these patients with ISR, 28.8% would have symptoms. The symptomatic ISR rate was 4.3% in the whole patient population, which was much lower than that in the SAMMPRIS trial.[60]

The SAMMPRIS trial is a prospective randomized controlled trial whose subgroup analysis of symptomatic ISR included 183 patients, and the image follow-up rate was <60%. The result of our meta-analysis showed that prospective studies had higher ISR rates than retrospective studies due to younger age (58.8 ± 5.2 versus 60.4 ± 4.8 years, $P = .37$) in prospective studies, which was the risk factor for ISR. The symptomatic ISR rate was higher in the studies with relatively low image follow-up rates as well. Meanwhile, the subgroup analysis of SAMMPRIS of symptomatic ISR enrolled 4 patients with primary balloon angioplasty; therefore, this meta-analysis excluded it.

In our study, we found that the reported ISR rate decreased as the image follow-up rate increased because the low image follow-up rate reflected the overall patient compliance with physicians' suggestions. The patients would not consider an invasive DSA follow-up until there were new-onset postprocedural symptoms. Therefore, in the series with a lower image follow-up rate, most of the patients came back only when they were symptomatic due to ISR. On the contrary, a higher image follow-up rate can reduce follow-up bias, and the ISR rate would be much closer to the real

situation. Our study showed that when the rate of image follow-up was higher than 60%, the incidence of ISR and symptomatic ISR was significantly lower. The total image follow-up rate of this meta-analysis was 77.3%; among these studies, 35 studies (68.6%) had image follow-up rates above 60%, with ISR rates of 12.2% and symptomatic ISR rates of 3.4%. This finding might have certain guiding significance for further study designs.

Lesion location as one of risk factors of ISR has been described previously. In the series of Turk et al,[58] the supraclinoid segment of the ICA tended to have higher ISR. In our study, the incidence of ISR and symptomatic ISR showed no notable difference between the anterior and posterior circulation, but a higher rate of symptomatic ISR was noticed in the lesions at the vertebrobasilar junction. Parent vessel tortuosity is more commonly seen in this location, thus hampering the apposition of the stent to the vessel wall and predisposing this location to higher risk of ISR.

Moreover, we also identified a disparity of reported ISR rates among different regions. Higher incidences of ISR and symptomatic ISR were observed in patients in the United States compared with patients in Asia and other areas like Germany, Italy, Turkey, and Argentina. There was no significant difference in procedural success rates and residual stenosis rates among different regions. The mean image follow-up rate of studies in the United States was 65.2%, lower than that of studies in other regions (79.7%) ($P = .08$). The studies in the United States also had lower residual stenosis rates (14.8% ± 5.2% versus 16.7% ± 8.2%, $P = .654$) and a higher proportion of vertebrobasilar junction locations (2.8% ± 4.3% versus 2.0% ± 7.7%, $P = .038$) than in other regions. Although without a statistical difference, these might have caused higher rates of ISR and symptomatic ISR in the studies in the United States.

Several studies have demonstrated that larger residual stenosis may be a predictor of restenosis after stent placement, especially when residual stenosis is >30%.[45,51,52] This finding is in accordance with our instincts, because larger residual stenosis might reflect lesions not being adequately treated. What if the lesions are adequately treated? Should we more aggressively minimize the residual stenosis to the best result possible? In our analysis, most of the included studies (36/38, 94.7%) had a residual stenosis of under 30%, indicating that most of the lesions were properly handled. However, the multivariate regression analysis suggested that lower residual stenosis was related to higher symptomatic ISR rates. This result is surprising, but it might hint that treating the lesions more aggressively added no more benefit. When residual stenosis is <30%, lower residual stenosis may indicate more vascular endothelial damage during the procedure; that could lead to a higher risk of symptomatic ISR.

We also identified another counterintuitive factor, namely younger age, that led to higher ISR rates post-stent implantation. Turk et al[58] also reported that ISR is more common in younger patients after treatment with the Wingspan system. One reason the authors hypothesized was that lesions in younger patients represented more of inflammatory arteriopathy than primary atherosclerosis. Previous research has shown that inflammatory connective tissue disease is associated with cardiovascular risk and there was a negative interaction between connective tissue disease and age.[61] We suspect that the inflammatory response may be more active in younger patients with atherosclerotic disease facing a greater risk of ISR, but more proof and evidence are needed.

Our study showed no association between the ISR rate and different stent types, including balloon-mounted stents and self-expandable stents (SESs). Previous studies and a systematic review suggested that lesions with SESs were more prone to ISR than those with balloon-mounted stents due to the higher residual stenosis degree, higher flexibility, and the lower radial force of SESs.[36,62,63] Our study presented higher degrees of residual stenosis after SES implantation as well ($P = .033$). The negative correlation between residual stenosis and the ISR rate found in this study may conceal positive correlations of SES. Further studies are needed to identify whether the lesions with SES have higher restenosis rates and the physiopathologic mechanism.

Several limitations of our meta-analysis need to be discussed. First, most studies were retrospective, and the sample size in 72% of series was <100 patients. The target population of studies varied within the inclusion criteria, resulting in limited generalization of population characteristics such as distribution of lesion location, proportion of stent types used, and preprocedural stenosis degree. Second, the variables extracted from studies were limited because of the meta-analysis design. Age and residual stenosis are important risk factors for ISR. However, we could only analyze the relationship between mean age and mean residual stenosis of each study and ISR. The platelet inhibition ratio, indicators of inflammatory response, serum lipid levels, and blood glucose levels during the follow-up period that may lead to ISR were rarely mentioned in the studies. Third, the patients' enrollment in these studies spanned 2 decades (1996–2018), during which time the technique of intracranial stent implantation and the standardization and compliance of medications have improved. These factors may also have an effect on ISR. In addition, there was considerable heterogeneity in the effect estimates of some risk factors we studied.

Our study has some implications for clinical practice. The risk factors discussed in the meta-analysis could help neurointerventionists develop more cautious operation and image follow-up plans when patients have a high risk for ISR.

CONCLUSIONS

Our study showed promising results of in-stent restenosis for symptomatic atherosclerotic stenosis. Studies are needed to further expatiate on the mechanisms by which younger patient age, vertebrobasilar junction location, and low residual stenosis could increase ISR and symptomatic ISR, respectively.

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