Predictors of In-Stent Stenosis Following the Implantation of Pipeline Embolization Devices for the Treatment of Aneurysms Located at or beyond the Circle of Willis in the Anterior Circulation

Yajing Ma, Xin Deng, Junfan Chen, Feng Fan, Kaihao Han, Sheng Guan and Xinbin Guo

AJNR Am J Neuroradiol 2024, 45 (4) 412-417
doi: https://doi.org/10.3174/ajnr.A8144
http://www.ajnr.org/content/45/4/412

Predictors of In-Stent Stenosis Following the Implantation of Pipeline Embolization Devices for the Treatment of Aneurysms Located at or beyond the Circle of Willis in the Anterior Circulation

Yajing Ma, Xin Deng, Junfan Chen, Feng Fan, Kaihao Han, Sheng Guan, and Xinbin Guo

ABSTRACT

BACKGROUND AND PURPOSE: In-stent stenosis is commonly observed after stent implantation. There is no consensus on the contributing factors for in-stent stenosis, especially for aneurysms located at or beyond the circle of Willis in the anterior circulation. This study aimed to investigate the morbidity and determinants of in-stent stenosis in distal anterior circulation aneurysms following the implantation of Pipeline Embolization Devices.

MATERIALS AND METHODS: Patients who underwent Pipeline Embolization Device treatment at our center between January 1, 2018, and June 15, 2023, were enrolled. Distal anterior circulation aneurysms were defined as those occurring at or beyond the circle of Willis, including anterior communicating artery aneurysms, anterior cerebral artery aneurysms, and MCA aneurysms. Baseline information, aneurysm characteristics, and follow-up data of patients were analyzed. Patients were divided into 2 groups: the in-stent stenosis group (patients with a loss of >25% of the lumen diameter of the parent artery) and the non-in-stent stenosis group. Binary logistic regression and restricted cubic spline curves were used to explore risk factors.

RESULTS: We included 85 cases of 1213 patients treated with flow-diverter devices at our hospital. During an average follow-up period of 9.07 months, the complete occlusion rate was 77.64%. The overall incidence of in-stent stenosis was 36.47% (31/85), of which moderate stenosis accounted for 9.41% (8/85), and severe stenosis, 5.88% (5/85) (triglyceride-glucose index ≥ 8.95; OR = 6.883, P = .006). The difference in diameters between the stent and parent artery of ≥0.09 mm (OR = 6.534, P = .015) and 55 years of age or older (OR = 3.507, P = .036) were risk factors for in-stent stenosis. The restricted cubic spline curves indicated that the risk of in-stent stenosis increased as the difference in diameter between stent and parent artery and the triglyceride-glucose index increased.

CONCLUSIONS: Compared with the on-label use of Pipeline Embolization Devices, the rate of in-stent stenosis did not obviously increase when treating distal anterior circulation aneurysms with these devices. The incidence of in-stent stenosis was 36.47% when defined as a lumen diameter loss of >25%, and 15.2% when defined as a lumen diameter loss of >50%. Stent-size selection and biochemical indicators can potentially impact the incidence of in-stent stenosis.

ABBREVIATIONS: d = parent artery diameter; Dd = difference in diameter between stent and parent artery; ISS = in-stent stenosis; PED = Pipeline Embolization Device; TyG = triglyceride-glucose

Positive outcomes have been reported for Pipeline Embolization Device (PED; Medtronic) treatment for appropriately selected patients with intracranial aneurysms.[1,2] Recently, there have also been several studies investigating the safety and efficacy of the off-label uses of the PED, one of which is in the treatment of distal circulation aneurysms,[3-7] referring to aneurysms occurring at the circle of Willis or beyond.

Distal circulating aneurysms are difficult to treat due to several factors, such as the small diameter of the parent artery (d), increased vascular curvature, and the presence of perforating arteries, which also increase the risk of clinical complications. The use of small devices (≤3 mm in diameter) in the treatment of these aneurysms is safe and does not increase the incidence of in-stent stenosis (ISS) or other clinical complications.[8] However, Liou and Li[9] suggested that ISS may be more noteworthy in smaller PEDs because there is less room for stenosis to occur. Although most ISS stenoses are reported to be asymptomatic, studies have shown an increased incidence of long-term complications in patients with

Received October 26, 2023; accepted after revision December 11.

From the Department of Interventional Neuroradiology (Y.M., X.D., J.C., F.F., K.H., S.G., X.G.), The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan Province, China; and Neurointerventional Engineering Research Center of Henan Province (S.G.), Henan Province, China.

Please address correspondence to Xinbin Guo, PhD, The First Affiliated Hospital of Zhengzhou University; e-mail: gxb3906080@sina.com

Indicates article with online supplemental data.

http://dx.doi.org/10.3174/ajnr.A8144

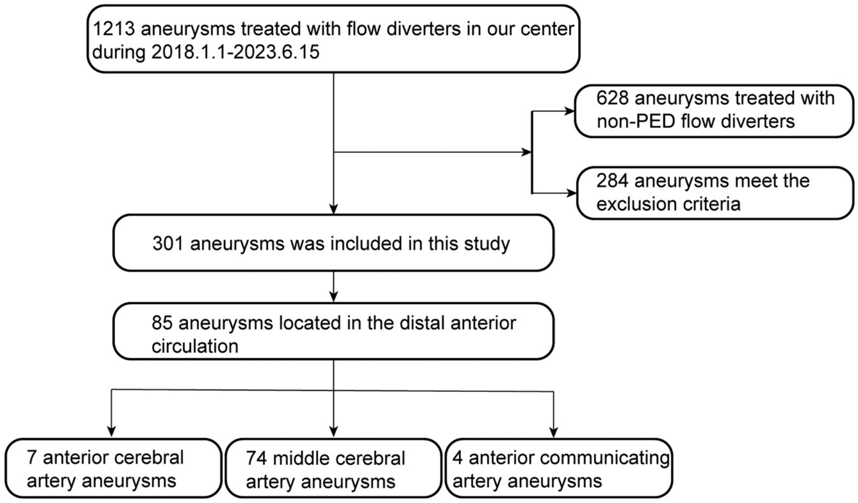

FIG 1. Flow chart of the study.

ISS,[10,11] which can be fatal. Therefore, we aimed to perform a retrospective study to investigate the incidence of and factors associated with ISS following the treatment of distal anterior circulation aneurysms with PEDs to accurately identify high-risk patients and ensure timely interventions. This article follows the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) reporting guidelines.

MATERIALS AND METHODS

Study Design

This retrospective study included 85 aneurysms treated with a Pipeline Flex (Medtronic) at our center from January 1, 2018, to June 15, 2023. The exclusion criteria were as follows: 1) younger than 18 years of age; 2) acutely ruptured aneurysms; 3) inadequate information for analysis because of incomplete clinical or imaging data; and 4) patients who were noncompliant and did not adhere to medication instructions. More details are summarized in Fig 1. The study was approved by the Ethics Committee of Scientific Research and Clinical Trial of The First Affiliated Hospital of Zhengzhou University. All study participants provided informed consent.

Data Collection and Definitions

The following information was collected for each participant: 1) baseline information (sex, age, body mass index, alcohol use, smoking status, blood pressure, major comorbidities, preoperative and postoperative mRS score, laboratory index, and so forth); 2) aneurysm-related information (location, neck, maximum diameter, proximal and distal parent artery diameters, the presence of multiple aneurysms, incorporation with a branch, and history of stent placement at the target site); and 3) surgical method, stent size, and follow-up imaging data, evaluated according to the O'Kelly-Marotta grading system.[12]

Distal anterior circulation aneurysms refer to aneurysms that occur at or beyond the circle of Willis, including aneurysms in the anterior communicating artery, anterior cerebral artery, and MCA. Venous blood samples were collected from participants after overnight fasting. The triglyceride-glucose (TyG) index was calculated as follows: [fasting triglyceride (mg/dL) × fasting glucose (mg/dL) /2)].[13] The parent artery diameter (d) was defined as the average diameter of the arteries on both sides of the aneurysm neck. The difference in diameter between the stent and parent artery (Dd) is the diameter of the stent. The maximum diameter was defined as the maximum distance from the midpoint of the neck to the dome of the aneurysm.

All measurements were performed independently by 2 neurointerventionalists with >5 years of experience on 3D DSA. If the difference between the 2 measurements was ≤0.5 mm, the average was used as the final data; in the case of measurement discrepancies of >0.5 mm, a third neurointerventionalist with >10 years of endovascular treatment experience evaluated the case. A consensus was then reached by a panel of 3 physicians.

Perioperative Management and Follow-Up

Patients with unruptured aneurysms routinely received 5–7 days of conventional dual antiplatelet therapy (aspirin, 100 mg once daily, + clopidogrel, 75 mg once daily) preoperatively. The effectiveness of the treatment was determined by thromboelastographic monitoring. For those who did not meet the standard of antiplatelet therapy, the dosage, adjusted according to the results of the genetic assessment; or aspirin, 100 mg once daily, + ticagrelor, 90 mg twice daily, was administered. Patients were monitored for ischemic/hemorrhagic complications, and the drug dosage was promptly adjusted as needed. They were also evaluated by thromboelastography before discharge, and if arachidonic acid and adenosine phosphate levels did not reach standard values (arachidonic acid >50% and adenosine phosphate >30%), clopidogrel was replaced with ticagrelor (90 mg/day, twice daily). Dual antiplatelet therapy was postoperatively administered for 6 months. Then, all patients were re-admitted to the hospital for a DSA examination; on the basis of these findings, a decision was made to transition to monotherapy.

Neurointerventionalists with >10 years of experience in treating aneurysms determined the stent selection. All patients were treated with Pipeline Flex stents. For achieving good apposition, the stent diameter was usually similar to the proximal d of the aneurysm. Balloon angioplasty was commonly used to correct severe stent malapposition and/or incomplete apposition.

Outcomes

As the primary outcome, ISS was defined as >25% loss of vessel diameter at the stent deployment site or vessel occlusion within 5 mm on either side of the stent. Shrinkage was defined as mild if it was >25%, moderate if >50%, and severe if >75%. Regarding the secondary outcome, complete occlusion of the aneurysm was defined as grade D on the O'Kelly-Marotta scale.[12] Clinical outcomes were evaluated using mRS scores, and complications

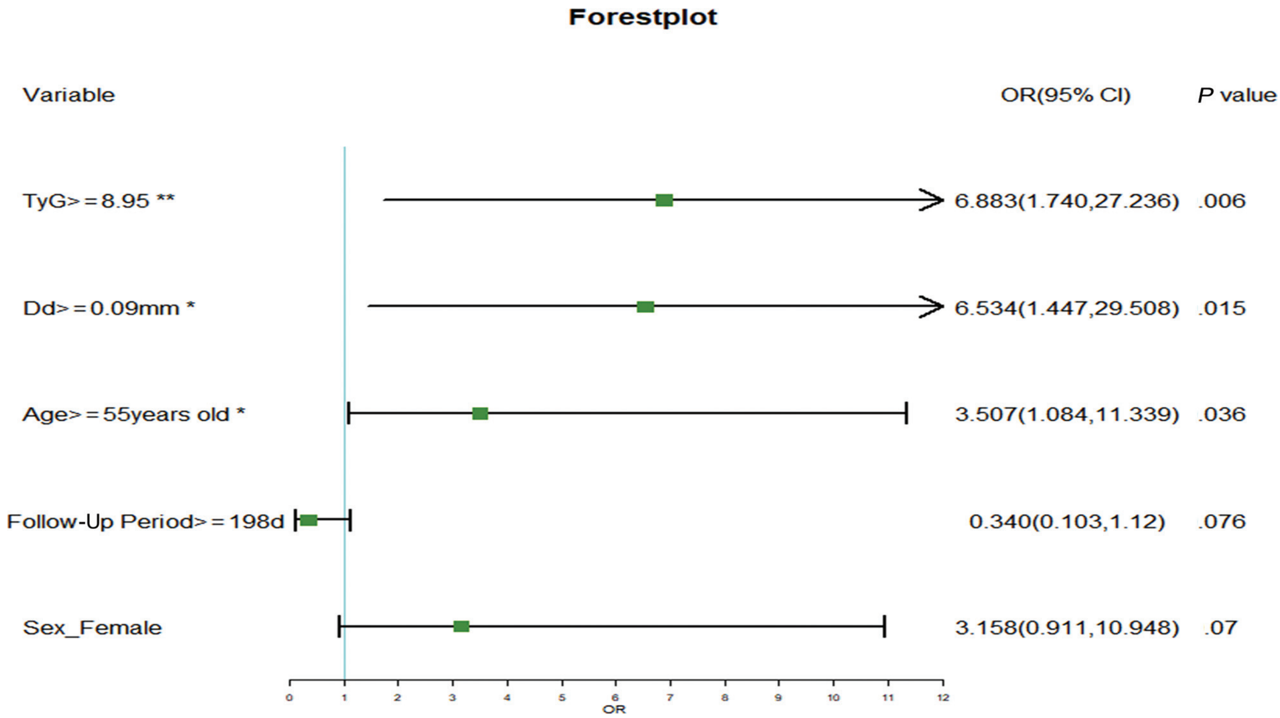

FIG 2. Results of the multivariable logistic regression analysis shown by a forest plot. * indicates $P < .05$; **, $P < .01$.

included hemorrhage, thrombosis, SAH, stroke, TIA, and access site–related complications.

Statistical Analysis

Statistical analyses were performed using SPSS, Version 25 (IBM) and R statistical and computing software (Version 4.2.2; http://www.r-project.org). Continuous variables with normal distribution are presented as mean (SD), and non-normally distributed data, as median (interquartile range). Differences were compared using the χ^2 test for categoric variables and the Mann–Whitney *U* test for continuous variables.

According to the principle of the maximal Youden index, age, the TyG index, and Dd were converted into binary data. In addition, the d was divided into <2.5 mm and ≥2.5 mm according to the definition of a small artery, and the body mass index was divided into <28 and ≥28 kg/m^2 (Online Supplemental Data). The confounders included in the multivariable model were selected using a cutoff *P* value of <.1 in univariate analysis. A multivariable logistic regression model (backward-stepwise) was used to analyze the association between confounders and ISS. Additionally, restricted cubic spline curves were performed to examine the associations among the TyG index, Dd, and ISS. The reference points for the TyG index and Dd were their corresponding medians. To balance the best fit and overfitting in restricted cubic spline, we used the Akaike information criterion to select the optimal number of knots. Two-tailed tests were performed, and a *P* value < .05 was considered statistically significant.

RESULTS

Baseline Information

A total of 85 patients were enrolled, of whom 53 patients (62.3%) were female. The overall incidence of ISS was 36.47% (31/85), of which moderate stenosis was 9.41% (8/85) and severe stenosis was 5.88% (5/85). Compared with the non-ISS group, the ISS group had a higher mean age (58.90 [SD, 2.06] years versus 54.59 [SD, 1.65] years, $P = .111$), TyG index (8.65 [SD, 0.09] versus 8.41 [SD, .07], $P = .052$), proportion of female patients (77.4% versus 53.7%, $P = .03$), rate of stent malapposition (16.1% versus 1.9%, $P = .042$), and a smaller parent artery diameter (2.37 mm [SD, 0.07] versus 2.58 mm [SD, 0.07], $P = .049$) (Online Supplemental Data). The results of multivariable logistic regression analysis can be found in the Online Supplemental Data and Fig 2 (forest plot).

Factors Associated with ISS

TyG Index. The risk of ISS in the group with a TyG index of ≥8.95 was 6.883 times higher than that in the group with a TyG index of <8.95 ($P = .006$). When the TyG index was treated as a continuous variable in a restricted cubic spline after adjusting for age, Dd, sex, and the follow-up period, the risk of ISS increased with the increase in TyG index (Fig 3*A*).

Dd. The risk of ISS in the Dd ≥ 0.09 mm group was 6.534 times higher than that in the Dd <0.09 mm group. After we adjusted for age, TyG index, sex, and follow-up period, the risk of ISS increased as Dd increased (Fig 3*B*).

Diameter of the Parent Artery. The rate of ISS in the d ≥ 2.5-mm group was 21.05%, with 1 case (2.63%) presenting with moderate stenosis and no cases of severe stenosis. Meanwhile, the rate of ISS in the d < 2.5-mm group was 48.94%, with 7 cases (14.89%) of moderate stenosis and 5 (10.64%) of severe stenosis. According to the restricted cubic spline curve, the risk of ISS decreased as the d increased (Fig 3*C*).

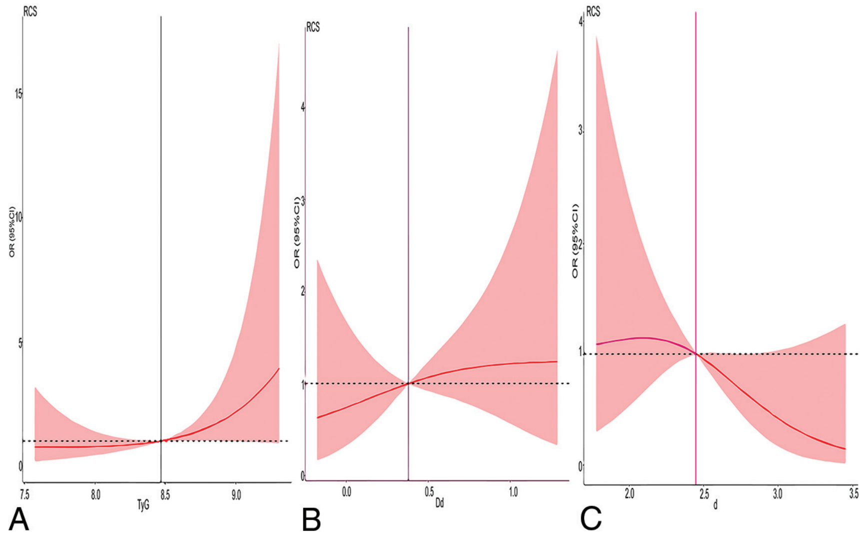

FIG 3. *A*, Restricted cubic splines for the adjusted dose-response association of the TyG index for ISS. Data were fitted with a regression model using restricted cubic spines with 3 knots at the 10th, 50th, and 90th percentiles of the TyG index. The y-axis represents the OR, and the *shadow regions* are 95% confidence intervals. *P* nonlinear = .346, *P* overall = .0265; TyG = 8.47, OR = 1. *B*, Restricted cubic splines for the adjusted dose-response association of the Dd for ISS. Data were fitted with a logistic regression model using restricted cubic spines with 3 knots at the 10th, 50th, and 90th percentiles of the Dd. The y-axis represents the OR, and the *shadow regions* are 95% confidence intervals. *P* nonlinear = .697, *P* overall = .034; Dd = 0.38 mm, OR = 1. *C*, Restricted cubic splines for the dose-response association of the d for ISS. Data were fitted with a logistic regression model using restricted cubic spines with 3 knots at the 10th, 50th, and 90th percentiles of the d. The y-axis represents the OR, and the *shadow regions* are 95% confidence intervals. *P* nonlinear = .298, *P* overall = .149; d = 2.45 mm, OR = 1. The restricted cubic splines indicate that the risk of ISS increases with increasing TyG index and Dd, and decreases with increasing parent artery diameter.

Age. The risk of ISS was 3.507 times higher in patients 55 years of age or older than in those younger than 55 years of age (46.67% versus 25%, *P* = .036). The rates of coexisting parent artery stenosis, hypertension, diabetes, and cardiovascular disease in the 55 years of age or older group were 13.3%, 77.78%, 17.78%, and 11.1%, respectively, whereas the rates in the younger than 55 years of age group were 7.5%, 40%, 2.5%, and 0%, respectively. The rates of balloon use were 4.44% and 2.5% in the 55 years of age and older and the younger than 55 years of age groups, respectively.

Follow-Up Period. The median follow-up period was shorter in the ISS group than in the non-ISS group (197 days versus 238.5 days, *P* = .208). The percentage of patients with a follow-up period of ≥198 days was 48.4% in the ISS group and 68.5% in the non-ISS group (*P* = .067). In multivariate logistic regression, there was no significant difference in the follow-up period between the 2 groups (*P* = .076).

Others. Female patients accounted for 62.35% (53/85) of the cohort and had a higher incidence of ISS (45.28% versus 21.88%); however, there was no significant difference in multivariate logistic regression analysis (*P* = .070). We also analyzed variables such as balloon use, stent length, difference in length between the stent and aneurysm neck size, aneurysm morphology, d, parent artery stenosis (>50%), and smoking status, but no significant differences were found.

DISCUSSION

We included 85 cases of 1213 patients treated in our hospital, with an average follow-up of 9.07 months and a complete occlusion rate of 77.64%. The overall incidence of ISS was 36.47%. The TyG index of ≥8.95, a Dd of ≥0.09 mm, and 55 years of age or older were risk factors for ISS. The restricted cubic spline curves indicated that the risk of ISS increased as the Dd and TyG index increased.

As the indications for PEDs continue to expand, neurointerventionalists worldwide are attempting to use these stents in the treatment of distal anterior circulation aneurysms. Compared with ICA aneurysms, distal anterior circulation aneurysms are usually irregularly shaped, often at bifurcations, and may be incorporated with important branch arteries. The parent arteries are tortuous and relatively small in diameter, making treatment difficult and complications more likely. There is significant heterogeneity in the reported incidence of ISS due to the differences in factors such as grading criteria, aneurysm location and size, and patient baseline information across studies. The Pipeline for Uncoilable or Failed Aneurysms (PUFS) study considered any degree of lumen diameter loss within the stent as stenosis and found an ISS rate of 100%;[2] the corresponding probability was 6.6% when defining >25% lumen diameter loss as ISS. However, all included aneurysms were in the ICA. John et al[14] reported an incidence of ISS of 9.8% with a mean follow-up of 12.5 months, with only 3 cases of distal aneurysms. In a large study conducted in China, the rate of ISS was found to be 10.03%,[10] with a mean d of >3.5 mm. In anterior circulation aneurysms, distal aneurysms accounted for only 3.5%. According to a recent study by Wei et al,[11] the incidence of moderate and severe ISS was 15.2%, the same as ours, whereas distal arterial aneurysms accounted for only 2.3%.

To date, no study has investigated the incidence rate and associated factors of ISS after PED placement for distal anterior circulation aneurysms. Given the critical function of the distal anterior circulation, identifying patients at high risk of ISS and providing appropriate medical prophylaxis are critical. The associated factors included the TyG index, arterial and stent diameters, age, sex, and other factors.

The TyG index is a composite indicator calculated from fasting blood glucose and triglycerides, each of which represents the degree of insulin resistance in the liver and fat cells.[15] Cardiovascular studies have shown that a higher TyG index is associated with an increased incidence of coronary artery disease and an unfavorable prognosis.[16-18] Individuals with a higher TyG index may also have a higher risk of stroke.[19] As a marker of insulin resistance, the influence of TyG on blood vessels can be explained by the mechanisms associated with insulin resistance. Hyperglycemia increases the production of reactive oxygen species, resulting in insulin resistance with impaired insulin-stimulated translocation of glucose transporter type 4 and glucose uptake.[20] In addition, reactive oxygen species activate proinflammatory signaling.[21] Moreover, increased free fatty acid levels directly inhibit glucose transport by causing mitochondrial dysfunction,[22,23] which enhances glucotoxicity. Insulin can stimulate the production of nitric oxide in endothelial cells[24]; an elevated TyG index may interfere with insulin signaling, reduce insulin sensitivity, and thereby affect the local microenvironment of the blood vessels and alter hemodynamics. Insulin can additionally inhibit cell migration and neointimal growth following arterial damage,[25] and the mechanism of ISS is caused by excessive growth of the intima. These factors may be the mechanisms behind the higher incidence of ISS in patients with higher TyG index.

Regarding the d and the difference between the diameters of the stent and parent artery, typically, the small diameter and tortuosity of the parent arteries increases the difficulty of intraoperative procedures and may cause vascular injury. Endothelial damage leads to platelet adhesion, activation, aggregation, and even thrombus formation, causing local hemodynamic disturbance. Additionally, the increased reactive oxygen species induced by hyperglycemia can promote nitrous oxide clearance, thereby restricting vasodilation.[26] The increased expression of proinflammatory genes caused by reactive oxygen species, combined with the weakened anti-inflammatory effect of nitrous oxide, activates the inflammation mechanism. In clinical practice, neurointerventionists tend to select stents slightly larger than the parent artery diameter to avoid ischemic events in the presence of important perforating arteries such as the lenticulostriate and Huebner recurrent arteries. Our restricted cubic spline curve shows an increased risk of ISS as Dd increases: when Dd = 0.38 mm, the OR = 1. Therefore, we suggest that when a stent covers the perforating arteries in A1 and M1, a stent slightly larger (preferably not more than 0.5 mm) than the diameter of the parent arteries should be selected to prevent the development of ISS.

Studies of age and sex show that younger patients are more likely to develop ISS due to a stronger repair mechanism.[27] However, we showed that patients aged older than 55 years of age are more prone to developing ISS, which may be due to the higher incidence of comorbidities and increased vascular tortuosity associated with aging, as well as a relatively higher prevalence of concomitant stenosis of the parent arteries and a weaker anti-inflammatory mechanism.

Estrogen can activate endothelial nitric oxide synthase in endothelial cells via the phosphatidylinositol-3-kinase–dependent signaling pathway, thereby increasing nitrous oxide levels and regulating local blood flow, while exerting anti-inflammatory effects.[28] However, as estrogen levels decline with aging and menopause, the regulating effect disappears. Additionally, estrogen can stimulate the retention of water and sodium. Decreased levels of estrogen increase the viscosity of the blood to a certain extent.

Additionally, ISS peaks at 12 months postprocedure with minimal progression thereafter.[29] However, ISS can be reversed within 24 months, implying that intraluminal hyperplasia may undergo remodeling, leading to a decrease in lost luminal diameter. Recent studies on animals have suggested that ISS may be associated with endothelial thrombosis.[30] Incomplete stent apposition may result in greater wall shear stress in the corresponding area, leading to increased intimal hyperplasia and ultimately resulting in ISS.[31] We included a follow-up period, stent malapposition, and parent arteries with >50% stenosis in a multivariable logistic regression analysis, but none showed statistical significance. Studies have reported the association between smoking status, balloon angioplasty, fusiform aneurysm, non-aspirin use, and ISS after PED implantation, which may be related to endothelial damage, inflammatory mechanisms, and other factors. We found no significant differences between the 2 groups in these factors.

This study has certain limitations. First, it is a retrospective study, which could result in some selection bias. Second, it may have overestimated stent restenosis rates because of a median follow-up of 9.07 months and the lack of long-term follow-up. Third, strict dual antiplatelet management at our center may have limited the investigation of drug-related effects. Finally, treatment of distal anterior circulation aneurysms with the PED is an off-label use and has been used in only a few clinical cases. Large prospective studies may be required to validate the results of this study.

CONCLUSIONS

A major difference in diameter between the stent and the parent artery, a higher TyG index, and 55 years of age or older are associated with an increased rate of ISS. Selecting a stent of similar or slightly larger diameter than the parent artery to avoid ISS is recommended. Managing comorbidities should also be emphasized in clinical practice.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

REFERENCES

1. Hanel RA, Kallmes DF, Lopes DK, et al. **Prospective study on embolization of intracranial aneurysms with the Pipeline device: the PREMIER study 1 year results.** *J Neurointerv Surg* 2020;12:62–66 CrossRef Medline
2. Becske T, Kallmes DF, Saatci I, et al. **Pipeline for uncoilable or failed aneurysms: results from a multicenter clinical trial.** *Radiology* 2013;267:858–68 CrossRef Medline
3. Yavuz K, Geyik S, Saatci I, et al. **Endovascular treatment of middle cerebral artery aneurysms with flow modification with the use of the Pipeline Embolization Device.** *AJNR Am J Neuroradiol* 2014;35:529–35 CrossRef Medline
4. Primiani CT, Ren Z, Kan P, et al. **A2, M2, P2 aneurysms and beyond: results of treatment with Pipeline Embolization Device in 65 patients.** *J Neurointerv Surg* 2019;11:903–07 CrossRef Medline
5. Pistocchi S, Blanc R, Bartolini B, et al. **Flow diverters at and beyond the level of the circle of Willis for the treatment of intracranial aneurysms.** *Stroke* 2012;43:1032–38 CrossRef Medline
6. Martínez-Galdámez M, Romance A, Vega P, et al. **Pipeline Endovascular Device for the treatment of intracranial aneurysms at the level of the circle of Willis and beyond: multicenter experience**. *J Neurointerv Surg* 2015;7:816–23 CrossRef Medline
7. Lin N, Lanzino G, Lopes DK, et al. **Treatment of distal anterior circulation aneurysms with the Pipeline Embolization Device: a US multicenter experience.** *Neurosurgery* 2016;79:14–22 CrossRef Medline

8. Martin AR, Cruz JP, O'Kelly C, et al. **Small pipes: preliminary experience with 3-mm or smaller Pipeline flow-diverting stents for aneurysm repair prior to regulatory approval**. *AJNR Am J Neuroradiol* 2015;36:557–61 CrossRef Medline
9. Liou TM, Li YC. **Effects of stent porosity on hemodynamics in a sidewall aneurysm model.** *J Biomech* 2008;41:1174–83 CrossRef Medline
10. Turhon M, Kang H, Liu J, et al. **In-stent stenosis after Pipeline Embolization Device in intracranial aneurysms: incidence, predictors, and clinical outcomes.** *Neurosurgery* 2022;91:943–51 CrossRef Medline
11. Wei D, Deng D, Gui S, et al. **Machine learning to predict in-stent stenosis after Pipeline Embolization Device placement.** *Front Neurol* 2022;13:92984 CrossRef Medline
12. O'Kelly CJ, Krings T, Fiorella D, et al. **A novel grading scale for the angiographic assessment of intracranial aneurysms treated using flow diverting stents**. *Interv Neuroradiol* 2010;16:133–37 CrossRef Medline
13. Park K, Ahn CW, Lee SB, et al. **Elevated TyG index predicts progression of coronary artery calcification.** *Diabetes Care* 2019;42:1569–73 CrossRef Medline
14. John S, Bain MD, Hui FK, et al. **Long-term follow-up of in-stent stenosis after Pipeline flow diversion treatment of intracranial aneurysms.** *Neurosurgery* 2016;78:862–67 CrossRef Medline
15. Tian X, Chen S, Zhang Y, et al. **Time course of the triglyceride glucose index accumulation with the risk of cardiovascular disease and all-cause mortality.** *Cardiovasc Diabetol* 2022;21:183 CrossRef Medline
16. Luo E, Wang D, Yan G, et al. **High triglyceride-glucose index is associated with poor prognosis in patients with acute ST-elevation myocardial infarction after percutaneous coronary intervention.** *Cardiovasc Diabetol* 2019;18:150 CrossRef Medline
17. Guo X, Shen R, Yan S, et al. **Triglyceride-glucose index for predicting repeat revascularization and in-stent restenosis in patients with chronic coronary syndrome undergoing percutaneous coronary intervention.** *Cardiovasc Diabetol* 2023;22:43 CrossRef Medline
18. Ding X, Wang X, Wu J, et al. **Triglyceride-glucose index and the incidence of atherosclerotic cardiovascular diseases: a meta-analysis of cohort studies.** *Cardiovasc Diabetol* 2021;20:76 CrossRef Medline
19. Wang A, Wang G, Liu Q, et al. **Triglyceride-glucose index and the risk of stroke and its subtypes in the general population: an 11-year follow-up.** *Cardiovasc Diabetol* 2021;20:46 CrossRef Medline
20. Kim J, Montagnani M, Koh KK, et al. **Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms.** *Circulation* 2006;113:1888–904 CrossRef Medline
21. Kamata H, Honda SI, Maeda S, et al. **Reactive oxygen species promote TNFalpha-induced death and sustained JNK activation by inhibiting MAP kinase phosphatases.** *Cell* 2005;120:649–61 CrossRef Medline
22. Savage DB, Petersen KF, Shulman GI. **Mechanisms of insulin resistance in humans and possible links with inflammation.** *Hypertension* 2005;45:828–33 CrossRef Medline
23. Lowell BB, Shulman GI. **Mitochondrial dysfunction and type 2 diabetes.** *Science* 2005;307:384–87 CrossRef Medline
24. Zeng G, Nystrom FH, Ravichandran LV, et al. **Roles for insulin receptor, PI3-kinase, and Akt in insulin-signaling pathways related to production of nitric oxide in human vascular endothelial cells.** *Circulation* 2000;101:1539–45 CrossRef Medline
25. Breen DM, Chan KK, Dhaliwall JK, et al. **Insulin increases reendothelialization and inhibits cell migration and neointimal growth after arterial injury.** *Arterioscler Thromb Vasc Biol* 2009;29:1060–66 CrossRef Medline
26. Salt IP, Morrow VA, Brandie FM, et al. **High glucose inhibits insulin-stimulated nitric oxide production without reducing endothelial nitric-oxide synthase Ser1177 phosphorylation in human aortic endothelial cells.** *J Biol Chem* 2003;278:18791–97 CrossRef Medline
27. Sweid A, Starke RM, Herial N, et al. **Predictors of complications, functional outcome, and morbidity in a large cohort treated with flow diversion.** *Neurosurgery* 2020;87:730–43 CrossRef Medline
28. Simoncini T, Hafezi-Moghadam A, Brazil DP, et al. **Interaction of oestrogen receptor with the regulatory subunit of phosphatidylinositol-3-OH kinase.** *Nature* 2000;407:538–41 CrossRef Medline
29. Gui S, Chen X, Wei D, et al. **Long-term outcomes and dynamic changes of in-stent stenosis after Pipeline embolization device treatment of intracranial aneurysms.** *J Neurointerv Surg* 2023;15:1187–93 CrossRef Medline
30. Monteiro A, Lopes DK, Aghaebrahim A, et al. **Optical coherence tomography for elucidation of flow-diversion phenomena: the concept of endothelized mural thrombus behind reversible in-stent stenosis in flow-diverters.** *Interv Neuroradiol* 2021;27:774–80 CrossRef Medline
31. Sindeev S, Prothmann S, Frolov S, et al. **Intimal hyperplasia after aneurysm treatment by flow diversion.** *World Neurosurg* 2019;122:e577–83 CrossRef Medline