PREVENTIVE AND ACUTE INTERVENTION FOR INTRACRANIAL ATHEROSCLEROTIC DISEASE

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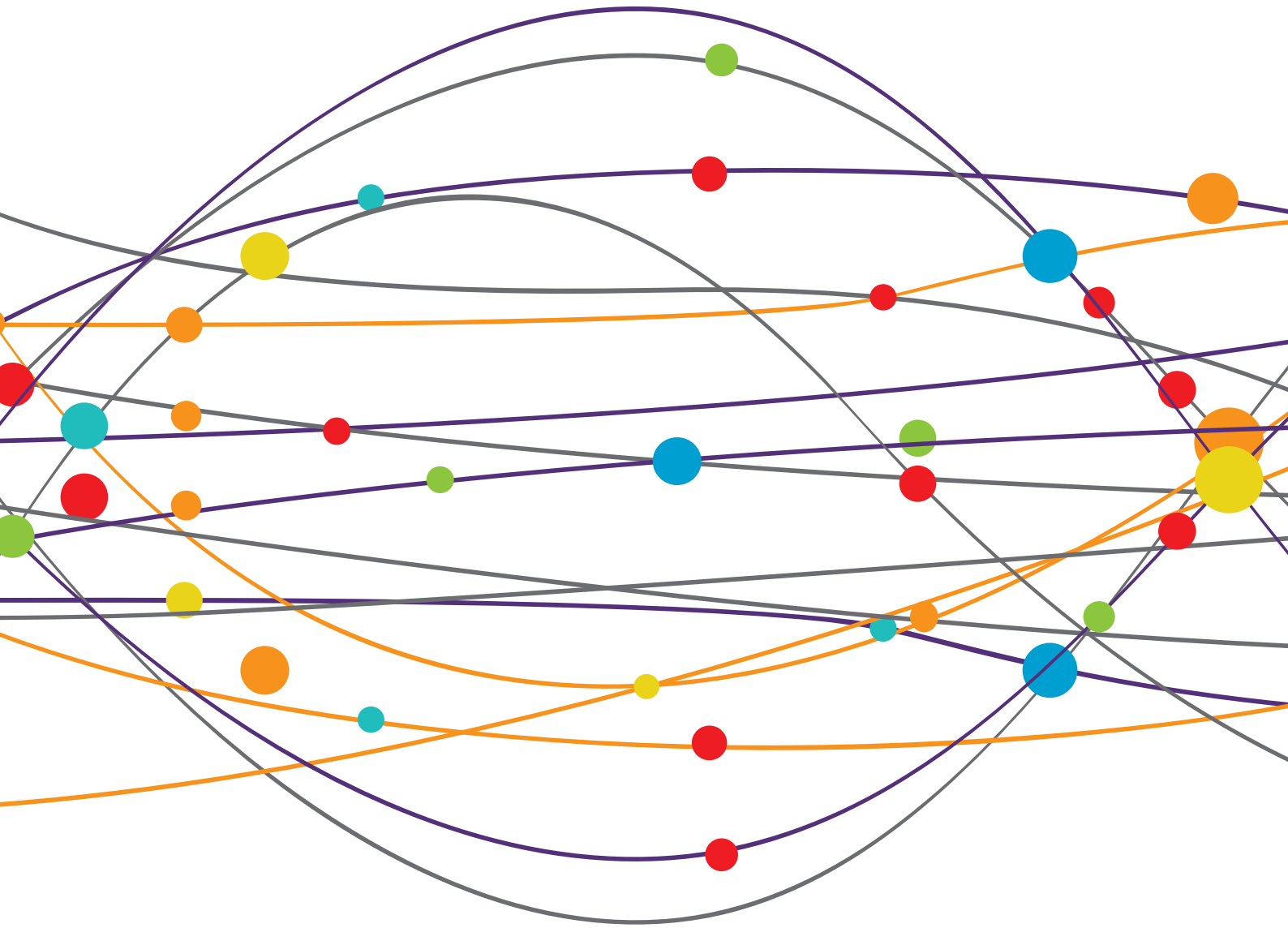

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PREVENTIVE AND ACUTE INTERVENTION FOR INTRACRANIAL ATHEROSCLEROTIC DISEASE

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Table of Contents

04 ***Editorial: Preventive and Acute Intervention for Intracranial Atherosclerotic Disease***
Jang-Hyun Baek, Byung Moon Kim, Simon Chun-Ho Yu and Oh Young Bang

07 ***Angioplasty and Stenting of Intracranial Arterial Stenosis in Perforator-Bearing Segments: A Comparison Between the Anterior and the Posterior Circulation***
Hannes Nordmeyer, René Chapot, Ayhan Aycil, Christian P. Stracke, Marta Wallocha, M. Jeffrie Hadisurya, Markus Heddier, Patrick Haage and Ralph Weber

15 ***Endovascular Treatment of Intracranial Atherosclerotic Stenosis: Current Debates and Future Prospects***
Jichang Luo, Tao Wang, Peng Gao, Timo Krings and Liqun Jiao

25 ***Weighing in on the Off-Label Use: Initial Experience of Neuroform EZ Stenting for Intracranial Arterial Stenosis in 45 Patients***
Zhihua Du, Jing Mang, Shengyuan Yu, Chenglin Tian, Xiangyu Cao, Xinfeng Liu, Renzheng Ma, Rongju Zhang, Bin Lv and Jun Wang

34 ***Optical Coherence Tomography of Spontaneous Basilar Artery Dissection in a Patient With Acute Ischemic Stroke***
Peng Gao, Liqiang Gui, Bin Yang, Timo Krings and Liqun Jiao

41 ***Vessel-Wall Magnetic Resonance Imaging of Intracranial Atherosclerotic Plaque and Ischemic Stroke: A Systematic Review and Meta-Analysis***
Han Na Lee, Chang-Woo Ryu and Seong Jong Yun

54 ***Solitaire Thrombectomy for Acute Stroke Due to Intracranial Atherosclerosis-Related Occlusion: ROSE ASSIST Study***
Jin Soo Lee, Seong-Joon Lee, Ji Man Hong, Jin Wook Choi, Joonsang Yoo, Jeong-Ho Hong, Chang-Hyun Kim, Yong-Won Kim, Dong-Hun Kang, Yong-Sun Kim, Yang-Ha Hwang and Sung-Il Sohn

63 ***CTA-Based Truncal-Type Occlusion is Best Matched With Postprocedural Fixed Focal Stenosis in Vertebrobasilar Occlusions***
Seong-Joon Lee, Ji Man Hong, Jin Wook Choi, Dong-Hun Kang, Yong-Won Kim, Yong-Sun Kim, Jeong-Ho Hong, Joonsang Yoo, Chang-Hyun Kim, Sung-Il Sohn, Yang-Ha Hwang and Jin Soo Lee

74 ***Endovascular and Clinical Outcomes of Vertebrobasilar Intracranial Atherosclerosis-Related Large Vessel Occlusion***
Jang-Hyun Baek, Byung Moon Kim, Ji Hoe Heo, Dong Joon Kim, Hyo Suk Nam and Young Dae Kim

83 ***Endovascular Therapy for Acute Ischemic Stroke of Intracranial Atherosclerotic Origin—Neuroimaging Perspectives***
Oh Young Bang, Byung Moon Kim, Woo-Keun Seo and Pyoung Jeon

93 ***Endovascular Treatment of Acute Stroke Due to Intracranial Atherosclerotic Stenosis–Related Large Vessel Occlusion***
Hyungjong Park, Jang-Hyun Baek and Byung Moon Kim

100 ***Angiographical Identification of Intracranial, Atherosclerosis-Related, Large Vessel Occlusion in Endovascular Treatment***
Jang-Hyun Baek and Byung Moon Kim

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EDITORIAL
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Editorial: Preventive and Acute Intervention for Intracranial Atherosclerotic Disease

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Keywords: intracranial atherosclerosis, endovascular treatment, large vessel occlusion, preventive treatment, ischemic stroke

Editorial on the Research Topic

Preventive and Acute Intervention for Intracranial Atherosclerotic Disease

Intracranial atherosclerotic disease (ICAD) is one of the most important etiologies for acute stroke. Although ICAD has its own distinct characteristics, acute and preventive endovascular treatment (EVT) for ICAD has not been well-studied. Recently, several important ICAD endovascular issues have been developed. First, in the modern era when mechanical thrombectomy has prevailed, ICAD is regarded as a relevant reason for the ineffectiveness of mechanical thrombectomy treatment (1–3). For an acute occlusion by ICAD, different EVT strategies should be elaborated (4). Second, after the SAMMPRIS trial, preventive EVT for ICAD has been discouraged (5). Instead, most patients with ICAD have been treated by intensive medical treatment. To advance preventive EVT for ICAD, it seems to need a breakthrough. This Research Topic discussed the issues for endovascular management of ICAD.

As the first issue, this Research Topic included (1) the method to identify an acute ICAD-related large vessel occlusion (ICAD-LVO) and (2) the EVT strategy for ICAD-LVO. Baek et al. described a unique angiographical way to identify ICAD-LVO before or during EVT—an "occlusion type." Among the occlusion types, truncal-type occlusion was considered an ICAD-LVO. Truncal-type occlusion was significantly associated with non-embolic occlusion (6, 7). Furthermore, stent retriever thrombectomy was ineffective for the truncal-type occlusion, which needed different types of endovascular modalities other than mechanical thrombectomy devices. In this Research Topic, detailed methodology to assess occlusion type was explained. This review also discussed a few concerns with regard to determining occlusion type. Considering that we do not have reliable information about the etiology of acute LVO before or in the early EVT period, this review might be helpful to set up an optimal EVT strategy. Lee et al. compared occlusion type with the classical definition of ICAD-LVO. The truncal-type occlusion determined by computed tomography angiography was best correlated with fixed focal stenosis in the posterior circulation. This finding is well-understood by the fact that occlusion type in the posterior circulation was less influenced by the degree of pial collateral flow or embolus size, as described in the review by Baek et al. Based on reports by Baek et al. and Lee et al., it seems that those two angiographical surrogate markers for ICAD-LVO should be complementary for a better definition of ICAD-LVO. Besides the angiographical method to identify ICAD-LVO, Bang et al. focused on neuro-imaging features that can aid identification of ICAD-LVO and that should be considered when performing EVT for ICAD-LVO. ICAD-LVO may have different anatomic, hemodynamic, and pathophysiologic

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features on neuroimaging compared to embolic occlusion. In neuroimaging, ICAD-LVO is associated with intracranial plaques, erythrocyte-poor thrombi, more severe arterial tortuosity with calcification, perforator-bearing segments, and preexisting collaterals, which should be considered when treating ICAD-LVO endovascularly. Even for ICAD-LVO, a stent retriever is still commonly used as the first-line modality. However, we do not exactly know how the stent retriever acts in ICAD-LVO. Lee et al. retrospectively compared outcomes of stent retriever thrombectomy between ICAD-LVO and embolic occlusion. The first-line stent retriever thrombectomy in ICAD-LVO could give a similar immediate successful reperfusion rate to embolic occlusion, although ICAD-LVO finally needed more ICAD-specific modalities such as balloon angioplasty, stenting, or intra-arterial tirofiban infusion. From previous studies, we already know that ICAD-LVO commonly needs the ICAD-specific modalities to achieve a successful recanalization (8–10). This can be also observed in the report by Baek et al.. They compared procedural and clinical outcomes between ICAD-LVO and embolic occlusion in the posterior circulation. Conventional mechanical thrombectomy was less effective in ICAD-LVO. With the use of ICAD-specific modalities, they could get a comparable successful recanalization rate, procedural time, and favorable outcomes for those with embolic occlusions. Such an endovascular strategy based on ICAD-specific modalities was well-summarized in the review by Park et al.. They proposed ways to identify ICAD-LVO, optimal choice of the front-line mechanical thrombectomy modality, and rescue strategy with ICAD-specific modalities after mechanical thrombectomy failure. With all these articles, in ICAD-LVO, successful recanalization could be achieved and time to recanalization could be shorter, which eventually led to better patient clinical outcomes.

As the second issue, this Research Topic included several subtopics on preventive EVT for ICAD. Luo et al. described EVT for ICAD. As we already know, intracranial stenting for secondary prevention of stroke associated with ICAD was not favorable in most clinical situations. However, authors expected that EVT with improved devices and techniques for carefully selected ICAD patients might be beneficial. In fact, Du et al. reported a case series of medically intractable ICAD patients who underwent stenting with Neuroform EZ, a self-expandable stent more easily handled than Wingspan. According to their report, stenting with Neuroform EZ was completely feasible in all patients. Luo et al. also pointed out that perforators around an atherosclerotic lesion is an important factor affecting outcomes of EVT for ICAD. In this Research Topic, Nordmeyer et al. reported that balloon angioplasty with/without stenting was harmful in perforator-bearing atherosclerotic lesions. In particular, periprocedural and follow-up strokes were significantly more frequent in ICAD in the posterior circulation, of which all periprocedural events were perforator strokes.

Differentiation of ICAD from other etiologies (such as arterial dissection, etc.) is also an important issue. Interestingly, Gao et al. reported the case of an acute stroke with an arterial lesion that was evaluated by optical coherence tomography. For their case with basilar artery stenosis, optical coherence tomography gave definite information about arterial dissection and this might be helpful to diagnose ICAD when angiography is ambiguous. In ICAD, vessel wall magnetic resonance imaging can be also helpful. Lee et al. systemically reviewed previous studies of vessel wall magnetic resonance imaging for ICAD. Some imaging findings, such as plaque enhancement, positive remodeling, and plaque surface irregularity were associated with stroke events in patients with ICAD. This finding could be helpful for estimating plaque vulnerability in decision making for ICAD management.

In conclusion, ICAD is obviously a big hurdle in EVT for LVO. For preventive EVT for ICAD, it is a situation that needs successful clinical trials. However, EVT for ICAD will be most likely developed by optimal endovascular strategy and more advanced endovascular devices and techniques. This Research Topic provides an insight into the future prospects of EVT for ICAD.

AUTHOR CONTRIBUTIONS

J-HB and BK conceived the manuscript. J-HB drafted the manuscript. BK, SY, and OB critically revised the manuscript. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Lee JS, Hong JM, Lee KS, Suh HI, Choi JW, Kim SY. Primary stent retrieval for acute intracranial large artery occlusion due to atherosclerotic disease. *J Stroke*. (2016) 18:96–101. doi: 10.5853/jos.2015.01347
2. Matias-Guiu JA, Serna-Candel C, Matias-Guiu J. Stroke etiology determines effectiveness of retrievable stents. *J Neurointerv Surg*. (2014) 6:e11. doi: 10.1136/neurintsurg-2012-010395
3. Al Kasab S, Almadidy Z, Spiotta AM, Turk AS, Chaudry MI, Hungerford JP, et al. Endovascular treatment for AIS with underlying ICAD. *J Neurointerv Surg*. (2017) 9:948–51. doi: 10.1136/neurintsurg-2016-012529
4. Kim BM. Causes and solutions of endovascular treatment failure. *J Stroke*. (2017) 19:131–42. doi: 10.5853/jos.2017.00283
5. Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med*. (2011) 365:993–1003. doi: 10.1056/NEJMoa1105335
6. Baek JH, Kim BM, Kim DJ, Heo JH, Nam HS, Song D, et al. Importance of truncal-type occlusion in stentriever-based thrombectomy for acute stroke. *Neurology*. (2016) 87:1542–50. doi: 10.1212/WNL.0000000000003202
7. Baek JH, Kim BM, Heo JH, Kim DJ, Nam HS, Kim YD. Outcomes of endovascular treatment for acute intracranial atherosclerosisrelated large vessel occlusion. *Stroke*. (2018) 49:2699–705. doi: 10.1161/STROKEAHA.118.022327
8. Yi TY, Chen WH, Wu YM, Zhang MF, Chen YH, Wu ZZ, et al. Special endovascular treatment for acute large artery occlusion resulting from atherosclerotic disease. *World Neurosurg*. (2017) 103:65–72. doi: 10.1016/j.wneu.2017.03.108
9. Kang DH, Kim YW, Hwang YH, Park SP, Kim YS, Baik SK. Instant reocclusion following mechanical thrombectomy of *in situ* thromboocclusion and the role of low-dose intra-arterial tirofiban. *Cerebrovasc Dis*. (2014) 37:350–5. doi: 10.1159/000362435
10. Kang DH, Yoon W, Kim SK, Baek BH, Lee YY, Kim YW, et al. Endovascular treatment for emergent large vessel occlusion due to

severe intracranial atherosclerotic stenosis. *J Neurosurg.* (2018) 22:1–8. doi: 10.3171/2018.1.JNS172350

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ORIGINAL RESEARCH
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Angioplasty and Stenting of Intracranial Arterial Stenosis in Perforator-Bearing Segments: A Comparison Between the Anterior and the Posterior Circulation

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Background and Purpose: Subgroup analysis of the SAMMPRIS trial showed a higher rate of periprocedural perforator strokes with the Wingspan stent in the basilar artery in patients with symptomatic intracranial atherosclerotic stenosis (ICAS). It remains unclear whether angioplasty (PTA) alone or in combination with other stent types (PTAS) will yield similar results in perforator-bearing segments of the anterior and posterior circulation.

Methods: We retrospectively analyzed the periprocedural complication rate, long term outcome and stroke etiology in 59 consecutive patients with ICAS of the middle cerebral artery (79 treatments) and 67 patients with ICAS of the intracranial vertebral and basilar artery (76 treatments) treated with PTA or PTAS from 2007 to 2015 in a high-volume neuro-interventional center.

Results: Periprocedural symptomatic ischemic strokes occurred significantly more often in patients with posterior vs. anterior ICAS treatment (14.5 vs. 5.1%, $p = 0.048$). During a mean follow-up period of 19 (±23.7) months, 5 recurrent ischemic and 2 hemorrhagic strokes (10.4%) occurred in the territory of the treated artery in posterior circulation compared to 2 ischemic strokes in the anterior circulation (3.4%, $p = 0.549$). Overall, significantly more patients treated for a posterior ICAS suffered a periprocedural or follow-up stroke [25% vs. 11.4%, $p = 0.024$]. Periprocedural ischemic strokes were predominantly perforator strokes (73.3%), while all ischemic strokes during follow-up were caused by distal embolization (57.1%) or delayed stent occlusion (42.9%). There was no difference between PTA alone and PTAS.

Conclusion: The periprocedural and long-term symptomatic stroke rate was significantly higher in the treatment of perforator-bearing arteries in the posterior circulation. There was no difference between PTA alone or PTAS.

Keywords: intracranial stenosis, atherosclerosis, intracranial embolism and thrombosis, perforators, ischemic stroke, stenting, angioplasty, PTA

INTRODUCTION

Symptomatic intracranial atherosclerotic stenosis (ICAS) is thought to be one of the leading causes of ischemic stroke worldwide due to a much higher prevalence in Asians compared to Caucasians (1) and bears a high risk of stroke recurrence (2). Recent randomized studies have shown a significantly higher risk of endovascular treatment of ICAS with percutaneous transluminal angioplasty and stenting (PTAS) compared to aggressive medical treatment [SAMMPRIS (3), VISSIT (4)]. A pooled analysis of the randomized SAMMPRIS and VISSIT trials (5) and an older meta-analysis of case studies found a higher risk of periprocedural stroke in treatment of ICAS in the posterior circulation (6). What is more, a detailed analysis in the SAMMPRIS trial using the Wingspan stent showed that the majority of periprocedural ischemic strokes (within 30 days after randomization) were caused by occlusion of perforator arteries (7). It was therefore hypothesized that a potential approach to reduce the risk of perforator artery occlusion by displacement of an atheroma into the artery ostium during stenting might be PTA alone (8). However, only a small randomized trial with 18 patients has compared PTA alone to PTAS in symptomatic ICAS so far (9). Furthermore, no detailed data on stroke mechanisms during long term follow-up after ICAS treatment has been published so far. In November 2016 the European Stroke Organization stated in their Karolinska Stroke Update (ESO-KSU) (10) that PTA or PTAS carried out by experienced personnel may be considered in a few special situations in patients with symptomatic ICAS (Grade C evidence) only and claimed further studies.

In order to understand interventional treatment risks of perforator-bearing brain arteries, we compared frequency and pathophysiology of periprocedural and long-term strokes and asymptomatic DWI lesions between the anterior and the posterior circulation in Caucasian patients with ICAS treated by PTA alone or PTAS with other stent types than Wingspan.

METHODS

Patients

We retrospectively reviewed all neurointerventional angioplasty and stenting procedures from January 2007 to February 2015 and identified all interventional procedures performed in perforator-bearing segments of symptomatic ICAS (M1-segment of the MCA, V4-segment of the VA and/or BA) with documented preceding transient ischemic attack or ischemic stroke in a tertiary high-volume center. Patients with non-atherosclerotic lesions such as arterial dissection or Moyamoya angiopathy were excluded from the study.

Patient charts were then evaluated regarding age at intervention, sex, cardiovascular risk factors (hypertension, hyperlipidemia, diabetes mellitus, current smoking), atrial fibrillation, previous stroke or TIA, and time point of intervention in relation to the last TIA/stroke. Furthermore medical secondary stroke prevention (antiplatelet therapy, oral anticoagulation, statins, antihypertensives) before intervention and at discharge was recorded.

The study was approved by the local ethics committee of the University Duisburg-Essen.

Imaging Analysis

The degree of the symptomatic ICAS was analyzed on digital subtraction angiography (DSA) using the method proposed in the WASID trial (11). A brain MRI with T1-weighted, T2-weighted and diffusion-weighted sequences was performed after PTA/PTAS to investigate for new ischemic or hemorrhagic brain lesions. New diffusion-weighted brain lesions were classified as clinical overt or silent. In cases where brain MRI was not feasible (i.e., cardiac pacemaker), a post-interventional brain CT was performed.

Periprocedural or long term ischemic strokes were classified as perforator stroke due to an occlusion of a perforator-bearing artery, as embolic stroke in the distal territory of the treated artery, or as stroke caused by a local (stent) thrombotic occlusion of the treated artery. Hemorrhagic strokes were classified as subarachnoid or intracerebral hemorrhage.

Periprocedural Management and PTA/PTAS Procedure

All patients received antiplatelet therapy with 100 mg aspirin and 75 mg clopidogrel daily. A clopidogrel loading dose at the day prior to the intervention was given in all patients being on a monotherapy with aspirin. Dual antiplatelet therapy was then administered for 3 months. Thereafter monotherapy with one platelet inhibitor was continued. Patients showing a non-response to clopidogrel on Multiplate® Analyzer testing (Roche Diagnostics, available from 2012) were given prasugrel or ticagrelor in addition to aspirin.

All patients were treated under general anesthesia by an experienced neuroradiologist with intra-arterial blood pressure monitoring. During the procedure 5.000 IU heparin were given intravenously right after groin puncture. The standard approach of ICAS treatment in our department is primary PTA with monorail balloons. The parent artery diameter was measured on 2D and 3D DSA images proximal and distal to the stenosis. In case of a post-stenotic dilatation, the vessel diameters proximal to the stenosis and distal to the dilatation were considered the normal diameter. In case of technical success (normalized or clearly improved hemodynamics and no vessel dissection) after PTA alone, the procedure was terminated. In cases of recoil of the stenosis or vessel dissection, the PTA was followed by stenting. Depending on the length of the stenosis and the angulation of the affected vessel, either balloon mounted coronary stents (mainly Coroflex® blue, B.Braun) or self-expanding intracranial stents (mainly Neuroform®, Stryker, and Acclino®, Acandis) were used. When self-expanding stents were used, the predominant technical approach for placement of the delivery catheter was parallel navigation along the remaining microwire that had been used for the PTA to minimize the risk of vessel perforation by exchange maneuvers.

Abbreviations: MCA, middle cerebral artery; BA, basilar artery; V4, V4-segment of the vertebral artery; SD, standard deviation; TIA, transitory ischemic attack; PTA, percutaneous transluminal angioplasty.

A restenosis with recurrent symptoms or proven hemodynamic significance on control DSA or perfusion imaging (CT-Perfusion or MR-Perfusion) was treated by PTAS in case of primary treatment without stenting and by PTA with drug eluting balloons in cases of primary PTAS.

Periprocedural Complications and Long-Term Outcome

Endovascular procedures were assessed regarding technical angiographic complication such as distal wire perforations, vessel rupture, dissection, thromboembolism, and parent or side branch artery occlusion. Neurological function was examined within 24 h after the procedure and at hospital discharge. All patients were scheduled for follow-up conventional angiography and neurological examination 6–12 months after the procedure. Patients not eligible for conventional angiography were controlled with MR or CT angiography. When no clinical long term follow-up examination had been performed, a questionnaire was sent to the patient or a telephone interview was performed to assess functional outcome (modified Rankin scale, mRS) and recurrent strokes.

Statistical Analysis

Baseline characteristics, periprocedural complications and long-term outcome parameters were compared using either the Mann-Whitney-*U* test for ordinal variables or the Chi-square test for categorical variables, when appropriate.

Uni- and multivariate logistic regression analyses were performed to identify predictors of peri-interventional and long-term stroke in the territory of the treated ICAS. Cox regression analysis was performed to estimate the crude and adjusted (for age and sex) hazard ratio (HR) with 95% confidence intervals (CI). The Kaplan-Meier method and log-rank test were used to detect differences for the cumulative probability of periprocedural and recurrent (ischemic and hemorrhagic) stroke in the territory of the treated artery.

All statistical analyses were performed with SPSS (Version 21.0. IBM Corp., Armonk, NY).

RESULTS

A total of 126 patients with symptomatic ICAS of the perforator-bearing segments of the MCA M1-segment (59 patients, 1 patient with bilateral M1-stenosis, with a total of 79 treatments) and V4-segment of the VA and/or BA (67 patients with a total of 76 treatments) were treated with PTA alone or Stent-PTA during 01/2007 and 02/2015.

In the posterior circulation group 61 treatments were performed in the BA, 12 in the VA and 3 combined in the VA and BA in one session.

Baseline characteristics are shown in **Table 1**. Mean age of treated patients was 67 ± 12.1 years. Compared to ICAS in the MCA, patients with a posterior circulation stenosis were significantly more often male (76.3 vs. 49.4%, $p = 0.001$), older (70 ± 8 vs. 61 ± 13.8, $p < 0.001$) and had more often concomitant atrial fibrillation (19.4 vs. 7.8%, $p = 0.037$) treated with oral anticoagulation (22.2 vs. 6.4%, $p = 0.005$). Furthermore, patients with posterior circulation ICAS had significantly more often a stenosis ≥70% (89.5 vs. 72.7%, $p = 0.008$). The symptomatic ICAS was treated within 7 days after the last TIA/stroke in almost one third of all patients with no significant difference between BA/V4 and MCA stenosis (Table 2 in Supplementary Material).

Nineteen of the 59 (32.2%) patients with MCA M1-stenosis and 9 of the 67 (13.4%) patients with V4 and/or BA stenosis were treated for restenosis during a mean follow-up of 19 (±23.5) months. PTA alone was performed in 61 and PTAS in 94 of all interventions. There was no significant difference in overall use of stenting between patients with MCA and BA/V4 stenosis (62.0 vs. 59.2%, $p = 0.72$). Self-expanding stents were significantly more often used in the treatment of MCA stenosis (46.8 vs. 25.0%, $p < 0.001$), while balloon-mounted stents were significantly more often used in the straight BA/V4 segments (35.5 vs. 13.9, $p = 001$). Treatment for symptomatic restenosis was performed by PTA alone in 11 cases and PTAS in 15 cases. In two patients treatment of restenosis failed for technical reasons.

Periprocedural Complications and Silent DWI Lesions

Patients treated for BA/V4 stenosis experienced significantly more often a periprocedural symptomatic infarction compared with patients treated for MCA stenosis [11 (14.5%) vs. 4 (5.1%), $p = 0.048$], while there was no significant difference in periprocedural intracranial hemorrhage [1 (1.3%) vs. 3 (3.8%), $p = 0.33$] or vessel dissection of the treated artery [4 (5.3%) vs. 1 (1.3%), $p = 0.159$]. There were no distal wire perforations observed and the only intraprocedural SAH to occur resulted from a balloon-ruptured vessel with no clinical sequelae. This patient died 3 months after endovascular treatment from a BA thrombosis due to cessation of antiplatelet treatment.

The hazard ratio for a new periprocedural symptomatic infarction adjusted for age and sex in the posterior circulation was 9.53 (95%CI 0.96 to 94.31, $p = 0.054$) compared to the anterior circulation. Periprocedural infarction rate was also significantly higher in patients treated for posterior circulation stenosis when only first interventional treatments were analyzed (14.7 vs. 1.7%, $p = 0.009$). Three out of 4 (75%) periprocedural ischemic strokes in the anterior circulation (one embolic stroke), and 8 out of 11 (72.7%) periprocedural ischemic strokes in the posterior circulation were classified as perforator occlusions, while the remaining 3 periprocedural ischemic strokes in the posterior circulation were classified as mixed perforator and embolic.

Early MRI controls within 3 days post-procedural were available in 76 out of 79 patients in the anterior circulation group and 68 out of 76 patients in the posterior circulation group. New clinically silent DWI lesions were frequently found in both groups with no significant difference between anterior and posterior circulation (23.5% in BA/V4 stenosis vs. 23.6% in M1 stenosis). There were 18 silent DWI lesions in the anterior circulation, thereof 6 in a lenticulostriate perforator territory and 12 cortical embolic in the corresponding MCA territory. In the posterior circulation 3 silent DWI lesions occurred in a medullary or pontine perforator territory and 13 were cortical lesions in a

cerebellar or posterior cerebral artery territory. Illustrative cases are shown in **Figures 1**, **2**.

Long-Term Follow-Up

During a mean follow-up period of 19 (±23.7) months, non-significantly more patients treated for BA/V4 stenosis suffered a recurrent ischemic or hemorrhagic stroke in the corresponding vessel territory than patients treated for a MCA M1-stenosis [7 (10.4%) vs. 2 (3.4%), adjusted HR 1.68, 95% CI 0.31–9.10, $p = 0.549$]. Five of the 7 recurrent events in the territory of the BA/V4 stenosis were ischemic strokes, 3 of them classified as delayed stent occlusion and 2 as embolic strokes (see illustrative case in **Figure 3**). None of the two ischemic strokes occurring during follow-up in the territory of the treated MCA M1-stenosis was classified as perforator occlusion (one delayed stent occlusion and one embolic stroke). Stent occlusion was caused in one patient by cessation of antiplatelet therapy leading to a lethal basilar artery thrombosis. Ischemic strokes in other territories during follow-up occurred in 1 and 2 patients in the anterior and the posterior circulation group, respectively. One patient with a BA stenosis treated by PTA suffered a SAH from a post-stenotic aneurysm 2 months after the procedure and completely recovered after coiling of the aneurysm. Another patient with a BA stenosis treated by PTA experienced an intraparenchymal

TABLE 1 | Baseline patient characteristics and procedural specifications.

	All treatments	MCA	BA/V4	*p*-value*
Patients, n	126	59	67	
Total no. of treatments, n	155	79	76	
Treatment for restenosis, n	28	19	9	
Age at time of primary treatment, years, mean (SD; min-max)	67 (12.1; 26–85)	61 (13.8; 26–85)	70 (8.0; 47–83)	**<0.001**
Sex, male, n (%)	97 (62.6)	39 (49.4)	58 (76.3)	**0.001**
Arterial hypertension, n (%)	131 (88.5)	66 (86.8)	65 (90.3)	0.512
Hyperlipidaemia, n (%)	128 (85.9)	64 (83.1)	64 (88.9)	0.312
Diabetes mellitus, n (%)	56 (37.6)	31 (40.3)	25 (34.7)	0.486
Atrial fibrillation, n (%)	20 (13.4)	6 (7.8)	14 (19.4)	**0.037**
Current smoker, n (%)	21 (14.1)	15 (19.5)	6 (8.3)	0.051
Statin before treatment, n (%)	124 (83.8)	64 (84.2)	60 (83.3)	0.885
Oral anticoagulation before treatment, n (%)	21 (14.0)	5 (6.4)	16 (22.2)	**0.005**
Antihypertensive medication before treatment, n (%)	132 (88.6)	66 (85.7)	66 (91.7)	0.253
Degree of stenosis ≥ 70%, n (%)	124 (81.0)	56 (72.7)	68 (89.5)	**0.008**
Procedure ≤ 7 days after last TIA or stroke, n (%)	36 (30)	16 (26.7)	20 (33.3)	0.426
Stent-PTA, n (%)	94 (60.6)	49 (62.0)	45 (59.2)	0.720
Self-expanding stent, n (%)	56 (36.1)	38 (48.1)	18 (23.7)	**<0.001**
Balloon mounted stent, n (%)	38 (24.5)	11 (13.9)	27 (35.5)	**0.001**
Follow-up interval, months, mean (SD, min-max)	19 (23.7; 0–111)	18.5 (24.3; 0–111)	19 (23.5; 0–96)	0.875

**p-values refer to comparison between MCA and BA/V4 treatment. Bold values indicate statistical significance with a p-value < 0.05*

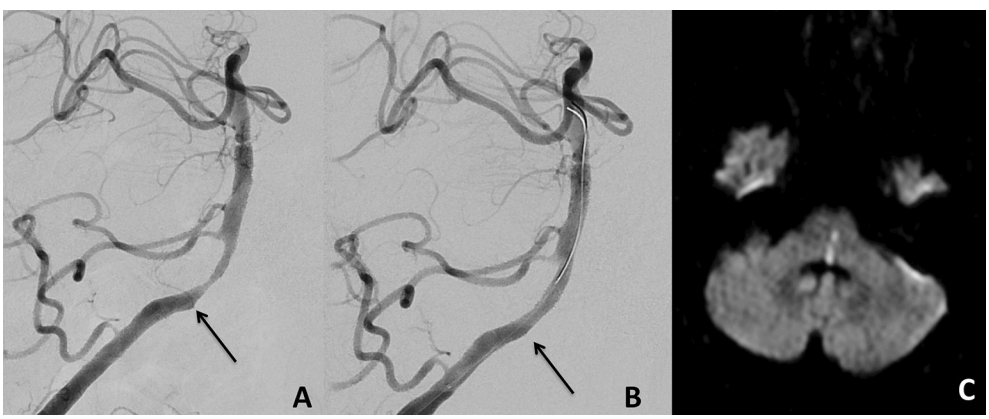

FIGURE 1 | Proximal basilar artery stenosis before treatment **(A)** with the arrow indicating a perforating artery arising at the proximal part of the stenosis. Stent-PTA led to an occlusion of this perforating artery **(B)**. MRI at day 1 after the procedure showed a left paramedian pontomedullary DWI lesion leading to a mRS score of 4 on follow-up examination after 6 months **(C)**.

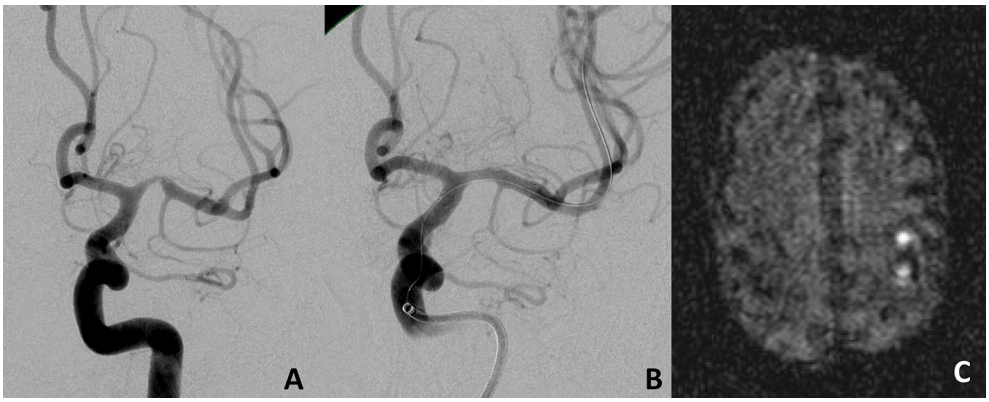

FIGURE 2 | Proximal left middle cerebral artery M1 stenosis before **(A)** and after **(B)** Stent-PTA treatment. MRI at day 1 after the procedure showed asymptomatic cortical embolic infarctions in the left middle cerebral artery territory **(C)**.

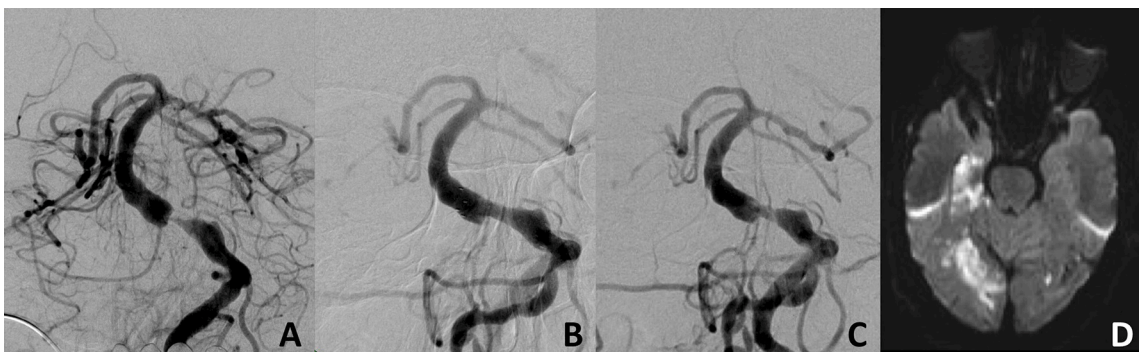

FIGURE 3 | Basilar artery stenosis at the level of the origin of the anterior inferior cerebellar artery before **(A)** and after **(B)** Stent-PTA treatment. In-stent thrombosis after discontinuation of double antiplatelet therapy 4 months after treatment **(C)** with multiple embolic infarcts in the territories of both posterior cerebral arteries **(D)**.

hemorrhage in the posterior lobe. In three more patients ischemic strokes occurred in other vascular territories due to other aetiologies (i.e., atrial fibrillation). No hemorrhagic stroke occurred during long-term follow-up in patients treated for a MCA M1-stenosis.

Combined Periprocedural and Long-Term Outcome

Significantly more patients treated for a BA/V4 stenosis suffered a treatment-related periprocedural or long term ischemic or hemorrhagic stroke than patients treated for a MCA M1-stenosis [19 (25%) vs. 9 (11.4%); adjusted HR 3.78, 95% CI 1.19–12.0, $p = 0.024$]. The Kaplan-Meier curve for the cumulative probability of stroke in the territory of the treated artery is shown in **Figure 4**.

Multivariate logistic regression analysis showed that a posterior circulation stenosis was the only significant variable of symptomatic brain infarction or hemorrhage in the treated vessel territory during intervention or long-term follow-up ($p = 0.044$). Mortality during follow-up was non-significantly higher in patients with BA/V4 stenosis [6 (11.8%) vs. 1 (1.3%), adjusted HR 3.85, 95% CI 0.41–36.55, $p = 0.24$]. Four of the 7 deaths were clearly related to the PTA/PTAS procedure.

A favorable outcome defined as mRS 0-2 at follow-up was achieved by 88.3% in the anterior and 78.4% in the posterior circulation (adjusted HR 0.74; 95% CI 0.45–1.20, $p = 0.215$).

Subgroup Analysis

There were no significant differences in any periprocedural or long-term outcome parameter between patients treated with PTA alone ($n = 61$) or PTAS ($n = 94$): periprocedural symptomatic infarction 6.6 vs. 11.7% (HR 0.97, 95% CI 0.28–3.34, $p = 0.957$), periprocedural hemorrhage 1.6 vs. 3.2% ($p = 0.437$), dissection 4.9 vs. 2.1% (HR 0.35, 95% CI 0.06–2.13, $p = 0.256$), recurrent stroke in the corresponding vessel territory 9.3 vs. 4.5% (HR 0.47, 95% CI 0.13–1.76, $p = 0.265$), mortality 3.3 vs. 5.3% (HR 1.47, 95% CI 0.29–7.61, $p = 0.644$).

When patients were dichotomized for early ($\leq$7 days, $n = 36$) vs. late (>7 days, $n = 84$; 7 patients with missing information) intervention after the most recent cerebrovascular event, there were also no significant differences in any outcome parameter (periprocedural symptomatic infarction 5.6 vs. 10.8%, HR 2.03, 95% CI 0.42–9.90, $p = 0.379$; periprocedural hemorrhage 2.8 vs.

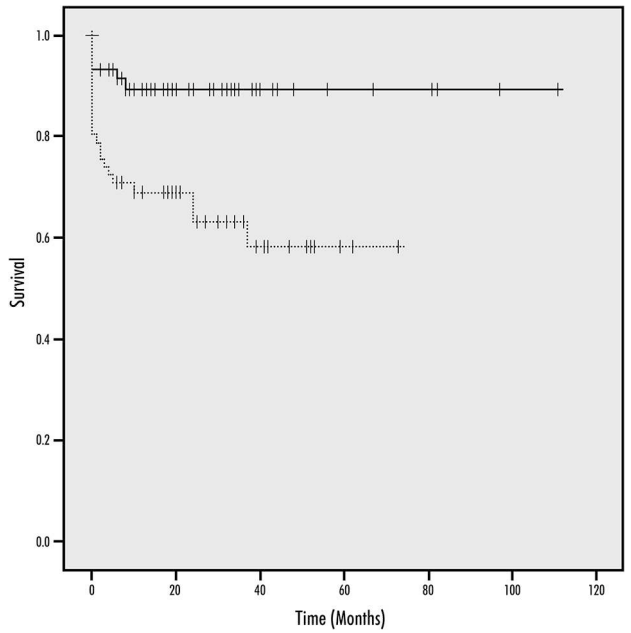

FIGURE 4 | Kaplan-Meier Curves for the cumulative probability of periprocedural ischemic or hemorrhagic stroke and during follow-up (continuous line, anterior circulation; dotted line, posterior circulation; y-axis, survival; x-axis, time in months).

2.4%, HR 1.28, 95% CI 0.11–14.51, $p = 0.841$; dissection 5.6 vs. 2.4%, $p = 0.957$; recurrent stroke in the corresponding vessel territory 11.8 vs. 4.0%, HR 0.35, 95% CI 0.07–1.63, $p = 0.179$; mortality 8.3 vs. 4.8%, HR 0.69, 95% CI 0.15–3.21, $p = 0.640$).

DISCUSSION

Given the negative results of the randomized trials on endovascular treatment of symptomatic ICAS [SAMMPRIS (3), VISSIT (4)] and the following decisions of the American Food and Drug Agency (12) and the European Agencies [i.e., the German (13)] to narrow the indications for the use of (the Wingspan) stents for ICAS, we retrospectively examined a large cohort of Caucasian patients with symptomatic ICAS involving intracranial perforator-bearing arterial segments treated with PTA alone or combined PTA and stenting with other stent types. Similar to the randomized trials SAMMPRIS and VISSIT, we observed an overall high rate (22.2%) of ischemic or hemorrhagic symptomatic strokes in the territory of the treated artery, with a significantly higher rate in the posterior circulation. The primary endpoint in SAMMPRIS which included death within 30 days after enrolment occurred in 23% of the patients in the PTAS group during a mean follow-up period of 32.4 months (14). The rate of stroke in the territory of the treated artery in VISSIT was even higher with 34.5% within 1 year of randomization (4). One has to take into account that our stroke rate included 28 recurrent interventional procedures for restenosis of the initially treated ICAS for a total of 155 treatments in our 126 patients, and that our patient cohort was older compared with both SAMMPRIS and VISSIT. The rate of periprocedural infarction was also significantly higher in patients treated for a posterior circulation ICAS when only initial interventional treatments were analyzed in our study. This finding was in line with the detailed analysis of periprocedural strokes in SAMMPRIS (7), a pooled analysis of SAMMPRIS, and VISSIT (5), and an older meta-analysis of case studies (6). In contrast, periprocedural complication rate was not higher in the posterior circulation in the German INTRASTENT multicentric registry (15). However the comparison is limited because recurrence of stroke during long term follow-up was not assessed in INTRASTENT nor in the meta-analysis performed by Gröschel et al. (6, 15).

Three quarters of the periprocedural ischemic strokes in both the anterior and posterior circulation were perforator strokes due to the occlusion of one or more perforating arteries by the atheromatous debris during PTA or stenting (the so called "snow plowing effect") (16). In contrast, ischemic strokes during long-term follow-up were caused by delayed stent thrombosis of the treated ICAS (partly due to discontinuation of antiplatelet treatment), or embolic strokes in the territory of the treated artery, and not by perforator occlusion. Thus, the mechanism of periprocedural and long-term ischemic stroke is different in patients with ICAS involving perforator segments treated with PTA(S). To our knowledge, there is no published detailed analysis from SAMMPRIS, VISSIT or large case series available which has investigated the etiology of ischemic strokes during long-term follow-up in detail. A possible explanation of the higher rate of periprocedural perforator strokes in the posterior brain circulation is the smaller mean diameter of the perforating arteries (17). Whether high-resolution MRI with visualization of the vessel wall and the atherosclerotic plaque characteristics might result in lower periprocedural ischemic stroke rates in ICAS treatment is questionable since spatial resolution of routinely available 3 Tesla MRI is not able to depict small perforator arteries but only plaque location and contrast enhancement (18, 19). Thus, plaque visualization can be used for image guided treatment planning when it comes to assess an eccentric lesion that is presumably located at the origin of perforating arteries (e.g., the dorsal or dorso-lateral part of the basilar artery).

In contrast to SAMMPRIS, no wire vessel perforation occurred in our study. Distal wire perforations may be associated with difficult exchanges of PTA balloon and stent delivery catheters as shown in the SAMMPRIS analysis with impact of operator and center experience. High enrolling centers had lower rates of hemorrhagic stroke (9.8% at sites enrolling <12 patients vs. 2.7% at sites enrolling ≥ 12 patients) (8).

A strong point of our study was the rigorous assessment of peri-interventional clinical silent ischemic lesions on DWI MRI after PTA(S), which has only been published in two retrospective Asian case series so far (20, 21). The observed high rate of asymptomatic DWI lesions in one third of our Caucasian patients was in line with the reported 31.7% in 123 Korean patients (20), and lower compared to 46% in 50 Chinese patients (21). Other interventional procedures such as carotid stenting and transcatheter aortic valve implantations have also found such

high rates of new embolic brain DWI lesions (22, 23). The clinical impact of these silent ischemic lesions in "non-eloquent" brain areas is still under debate (24), but there is increasing evidence that these embolic MRI lesions might result in subtle neuropsychological sequelae (25). These asymptomatic DWI lesions might have even a higher harmful impact in patients with previous TIA or ischemic stroke and result in future vascular dementia.

The SAMMPRIS investigators hypothesized that PTA alone might substantially lower the risk of periprocedural strokes despite inconsistent study results (14). To date, only a very small randomized trial with 18 included patients compared PTA alone vs. PTAS and did not find a difference in stroke and death rate within 1 month (9). A single-center registry of consecutively treated ICAS patients found a lower stroke rate with PTA alone after 1 year (26), while an older meta-analysis of case series reported a lower 1-year stroke-and/or-death rate with PTAS (27). We did not observe a significant difference in symptomatic stroke rate or asymptomatic DWI lesions between PTA alone or PTAS nor did we detect any complications due to the antiplatelet regimen. However, treatment with PTA and PTAS was not randomized and different stent systems were used in our retrospective study. Balloon-mounted stents were significantly more often used for treatment of posterior ICAS in our study, raising the question, whether this stent type led to the higher complication rate. Only an adequately powered randomized trial against best medical treatment will be able to answer the hypothesis whether PTA alone might substantially lower the risk of periprocedural strokes. Another major limitation of our study is the different long term follow-up periods in our patient cohort.

In conclusion, we have found that PTA alone or PTAS is especially harmful in perforator-bearing segments of the posterior brain circulation due to periprocedural perforator occlusions and delayed stent occlusion or embolic strokes during long term-follow-up. No difference in stroke rate between PTA and PTAS was observed. Silent DWI lesions occurred in almost one third of all treated patients with no difference between the anterior and posterior circulation.

AUTHOR CONTRIBUTIONS

HN initiated and designed the study, acquired patient data, analyzed and interpreted the data, drafted and revised the paper. He is guarantor. RC initiated the study, analyzed and interpreted data, and revised the draft paper. AA and MW were involved in patient data acquisition, analyzed and interpreted data, and revised the draft paper. MJH, CS, MH, and PH analyzed and interpreted data, and revised the draft paper. RW wrote the statistical analysis plan, acquired, analyzed and interpreted data, and revised the draft paper.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2018.00533/full#supplementary-material

REFERENCES

1. Wang Y, Zhao X, Liu L, Soo YOY, Pu Y, Pan Y, et al. Prevalence and outcomes of symptomatic intracranial large artery stenoses and occlusions in China: the Chinese Intracranial Atherosclerosis (CICAS) Study. *Stroke* (2014) 45:663–9. doi: 10.1161/STROKEAHA.113.003508
2. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med.* (2005) 352:1305–16. doi: 10.1056/NEJMoa043033
3. Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med.* (2011) 365:993–1003. doi: 10.1056/NEJMoa1105335
4. Zaidat OO, Fitzsimmons B-F, Woodward BK, Wang Z, Killer-Oberpfalzer M, Wakhloo A, et al. Effect of a balloon-expandable intracranial stent vs medical therapy on risk of stroke in patients with symptomatic intracranial stenosis: the VISSIT randomized clinical trial. *JAMA* (2015) 313:1240–8. doi: 10.1001/jama.2015.1693
5. Tsivgoulis G, Katsanos AH, Magoufis G, Kargiotis O, Papadimitropoulos G, Vadikolias K, et al. Percutaneous transluminal angioplasty and stenting for symptomatic intracranial arterial stenosis: a systematic review and meta-analysis. *Ther Adv Neurol Disord.* (2016) 9:351–8. doi: 10.1177/1756285616650357
6. Groschel K, Schnaudigel S, Pilgram SM, Wasser K, Kastrup A. A systematic review on outcome after stenting for intracranial atherosclerosis. *Stroke* (2009) 40:e340–7. doi: 10.1161/STROKEAHA.108.532713
7. Fiorella D, Derdeyn CP, Lynn MJ, Barnwell SL, Hoh BL, Levy EI, et al. Detailed analysis of periprocedural strokes in patients undergoing intracranial stenting in Stenting and Aggressive medical management for preventing recurrent stroke in intracranial stenosis (SAMMPRIS). *Stroke* (2012) 43:2682–8. doi: 10.1161/STROKEAHA.112.661173
8. Derdeyn CP, Fiorella D, Lynn MJ, Rumboldt Z, Cloft HJ, Gibson D, et al. Mechanisms of Stroke After Intracranial Angioplasty and Stenting in the SAMMPRIS Trial. *Neurosurgery* (2013) 72:777–95. doi: 10.1227/NEU.0b013e318286fdc8
9. Qureshi AI, Chaudhry SA, Siddiq F, Majidi S, Rodriguez GJ, Suri MFK. A randomized trial comparing primary angioplasty versus stent placement for symptomatic intracranial stenosis. *J Vasc Interv Neurol.* (2013) 6:34–41.
10. Ahmed N, Steiner T, Caso V, Wahlgren N, for the ESO-KSU session participants. Recommendations from the ESO-Karolinska stroke update conference, stockholm 13–15 November 2016. *Eur Stroke J.* (2017) 2:95–102. doi: 10.1177/2396987317699144
11. Samuels OB, Joseph GJ, Lynn MJ, Smith HA, Chimowitz MI. A standardized method for measuring intracranial arterial stenosis. *AJNR Am J Neuroradiol.* (2000) 21:643–646.
12. FDA. *Food and Drug Administration. FDA safety communication: narrowed indications for use for the Wingspan Stent System.* (2012).
13. GBA. *2016-09-15_KHMe-RL_Einsatz-Stents-intrakran-Stenosen_ZD.pdf [Internet]. [cited 2017 Nov 2].* Available online at: https://www.g-ba.de/downloads/40-268-3999/2016-09-15_KHMe-RL_Einsatz-Stents-intrakran-Stenosen_ZD.pdf
14. Derdeyn CP, Chimowitz MI, Lynn MJ, Fiorella D, Turan TN, Janis LS, et al. Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. *Lancet* (2014) 383:333–41. doi: 10.1016/S0140-6736(13)62038-3
15. Kurre W, Berkefeld J, Brassel F, Bruning R, Eckert B, Kamek S, et al. In-hospital complication rates after stent treatment of 388 symptomatic

intracranial stenoses: results from the INTRASTENT multicentric registry. *Stroke* (2010) 41:494–8. doi: 10.1161/STROKEAHA.109.568063
16. Leung TW, Yu SCH, Lam WWM, Chan AYY, Lau AYL, Wong LKS. Would self-expanding stent occlude middle cerebral artery perforators? *Stroke* (2009) 40:1910–2. doi: 10.1161/STROKEAHA.108.532416
17. Djulejić V, Marinković S, Milić V, Georgievski B, Rašić M, Aksić M, et al. Common features of the cerebral perforating arteries and their clinical significance. *Acta Neurochir.* (2015) 157:743–54. doi: 10.1007/s00701-015-2378-8
18. Jiang W-J, Yu W, Ma N, Du B, Lou X, Rasmussen PA. High resolution MRI guided endovascular intervention of basilar artery disease. *J Neurointerventional Surg.* (2011) 3:375–8. doi: 10.1136/jnis.2010.004291
19. Chung J-W, Kim BJ, Sohn CH, Yoon B-W, Lee S-H. Branch atheromatous plaque: a major cause of lacunar infarction (High-Resolution MRI Study). *Cerebrovasc Dis Extra*. (2012) 2:36–44. doi: 10.1159/000341399
20. Park KY, Kim BM, Kim DJ, Kim DI, Heo JH, Nam HS, et al. Incidence and risk factors for diffusion-weighted imaging (+) lesions after intracranial stenting and its relationship with symptomatic ischemic complications. *Stroke* (2014) 45:3298–303. doi: 10.1161/STROKEAHA.114.006182
21. Yeo LLL, Wu YM, Chen YL, Yeh CH, Lee TH, Wong HF. MRI audit of complications in intracranial stenosis treated with Wingspan device. *J NeuroInterventional Surg.* (2017) 9:466–70. doi: 10.1136/neurintsurg-2016-012799
22. Bonati LH, Jongen LM, Haller S, Flach HZ, Dobson J, Nederkoorn PJ, et al. New ischaemic brain lesions on MRI after stenting or endarterectomy for symptomatic carotid stenosis: a substudy of the International Carotid Stenting Study (ICSS). *Lancet Neurol.* (2010) 9:353–62. doi: 10.1016/S1474-4422(10)70057-0
23. Kahlert P, Knipp SC, Schlamann M, Thielmann M, Al-Rashid F, Weber M, et al. Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation. *Circulation* (2010) 121:870–8. doi: 10.1161/CIRCULATIONAHA.109.855866
24. Bendszus M, Stoll G. Silent cerebral ischaemia: hidden fingerprints of invasive medical procedures. *Lancet Neurol.* (2006) 5:364–72. doi: 10.1016/S1474-4422(06)70412-4
25. Herm J, Fiebach JB, Koch L, Kopp UA, Kunze C, Wollboldt C, et al. Neuropsychological effects of MRI-detected brain lesions after left atrial catheter ablation for atrial fibrillationclinical perspective: long-term results of the MACPAF Study. *Circ Arrhythm Electrophysiol.* (2013) 6:843–50. doi: 10.1161/CIRCEP.113.000174
26. Al-Ali F, Cree T, Hall S, Louis S, Major K, Smoker S, et al. Predictors of unfavorable outcome in intracranial angioplasty and stenting in a single-center comparison: results from the borgess medical center-intracranial revascularization registry. *Am J Neuroradiol.* (2011) 32:1221–26. doi: 10.3174/ajnr.A2530
27. Siddiq F, Memon MZ, Vazquez G, Safdar A, Qureshi AI. Comparison between primary angioplasty and stent placement for symptomatic intracranial atherosclerotic disease: meta-analysis of case series. *Neurosurgery* (2009) 65:1024–33; discussion 1033–4. doi: 10.1227/01.NEU.0000360138.54474.52

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Endovascular Treatment of Intracranial Atherosclerotic Stenosis: Current Debates and Future Prospects

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Intracranial atherosclerotic stenosis (ICAS) is a common cause of transient ischemic attack (TIA) and ischemic stroke. Endovascular treatment, including balloon angioplasty alone, balloon-mounted stents, and self-expandable stent placement with or without prior angioplasty, is an alternative to medical treatment for the prevention of recurrent TIA or ischemic stroke in patients with ICAS. Although the SAMMPRIS and VISSIT trials supported medical management alone against endovascular treatments, both randomized controlled trials (RCT) were criticized due to flaws relating to patient-, intervention-, and operator-related factors. In this review, we discuss the current debate regarding these aspects and suggest approaches to solve current controversies in the future. In our opinion, endovascular treatment in carefully selected patients, individualized choice of endovascular treatment subtypes, and an experienced multidisciplinary team managing the patient in the pre-, peri- and post-procedural period have the potential to provide safe and efficious treatment of patients with symptomatic ICAS.

Keywords: intracranial atherosclerotic stenosis, endovascular treatment, patient selection, angioplasty, stent, operator experience

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INTRODUCTION

Stroke is the second leading cause of death worldwide, after ischemic heart disease (1, 2), and 87% of cases are ischemic stroke (3). Intracranial atherosclerotic stenosis (ICAS) is one of the most common causes of ischemic stroke, accounting for up to 30 to 50% of ischemic stroke in Asia (4). According to the report titled "Global Burden of Stroke," the incidence and prevalence of stroke has increased gradually in developing countries, which bear most of the burden caused by stroke across the world (5).

To date, medical management, including antiplatelet therapy, intensive cardiovascular risk factor control, as well as lifestyle management, is still recommended as the first-line therapy for ICAS to prevent recurrent transient ischemic attack (TIA) and ischemic stroke. However, despite intensive medical management, a high risk of recurrent TIA and stroke was still observed in patients with high-grade (70–99%) symptomatic ICAS. This group of patients was considered to be refractory to aggressive medical therapy. Data from the SAMMPRIS trial (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis trial) showed that the rate of 1 year stroke or death in symptomatic ICAS patients with more than a 70% degree of stenosis was as high as 12.6% in the medical arm (6). In addition, a lifestyle coach was assigned to

every patient in the medical arm, which is unlikely to be available within general healthcare systems, especially in low- or middle-income countries (7). Therefore, endovascular treatment, including balloon angioplasty alone, balloon-mounted stent placement, or self-expandable stent placement, was considered as an alternative option for the prevention of recurrent TIA or ischemic stroke in patients with a high degree of ICAS.

Although the results of both the SAMMPRIS and VISSIT (the Vitesse Intracranial Stent Study for Ischemic Stroke Therapy) trials supported the use of aggressive medical management as being superior to stent therapy (6, 8), some prospective and retrospective studies from both Europe and Asia reported encouraging results for endovascular treatment (9–14). In this article, we will review the current literature related to angioplasty or stent placement for ICAS and discuss the current debate regarding three aspects: patient-, intervention-, and operator-related factors. We will also discuss future research directions for dealing with current controversies and how to solve them.

THREE ASPECTS OF FACTORS AFFECT OUTCOMES OF ENDOVASCULAR TREATMENT

Endovascular treatment of symptomatic ICAS has been facing controversy since the publication of the SAMMPRIS trial, which was the only multicenter, prospective, randomized controlled trial (RCT) of intracranial stenting for ICAS in America, enrolling symptomatic patients with recent (i.e., within 30 days) TIA or non-disabling stroke and who were identified as having 70–99% stenosis of a major intracranial artery. The aim of the trial was to compare the efficiency of recurrent stroke prevention between percutaneous transluminal angioplasty and stenting (PTAS) with aggressive medical management vs. aggressive medical management alone. The initial design was to recruit 764 patients randomly divided into the PTAS group or medical management group. However, the trial was halted early because of the unexpected result of a 30 days death or stroke rate of 14.7% (10.2% ischemic and 4.5% hemorrhagic) in the PTAS group, compared with 5.8% in the medical management group. This result indicated that the short-term safety of medical management was superior to PTAS in the patients treated in this trial. Moreover, the long-term efficacy of medical management in the SAMMPRIS trial was also superior to PTAS, with 1, 2, and 3 years rates of mortality or stroke of 12.6, 14.1, and 14.9% in the medical management group compared to 19.7, 20.6, and 23.9% in the PTAS group, respectively (7). Similar to the SAMMPRIS trial, the results of the VISSIT trial, published in 2015, which was the first randomized clinical trial comparing balloon-mounted stent treatment with medical therapy in patients with severe stenosis (70–99%) of symptomatic ICAS, also indicated that aggressive medical management was superior to angioplasty or stenting. The 30 days and 1 year TIA or stroke rates were 24.1 and 36.2% in the stent group vs. 9.4 and 15.1% in medical group, respectively. Because of the negative results of stenting from both RCTs, the attitude toward angioplasty or stenting to prevent recurrent TIA or stroke caused by intracranial atherosclerosis has diminished the enthusiasm for angioplasty or stenting for treatment of intracranial atherosclerosis in most centers (15, 16). However, controversies have been raised for both trials including patient-, intervention-, and operator-related factors. These may influence the outcomes of PTAS for the treatment of ICAS. Therefore, there are still ongoing debates focusing on the best treatment of ICAS.

Patient Selection

The method of patient selection is one of the major criticisms of the SAMMPRIS trial. There are three primary points to follow when enrolling patients in a trial, which were ignored in SAMMPRIS.

First, more than one-third (35.3%) of the patients in the PTAS group were not refractory to medical therapy when qualifying events were evaluated for enrollment in SAMMPRIS. However, Wingspan stent, a self-expanding nitinol intracranial stent and the only type of stent used in SAMMPRIS, was approved for Humanitarian Device Exemption in 2005 and recommended for use by the Food and Drug Administration (FDA) only in symptomatic patients with more than 50% intracranial stenosis after failure of antithrombotic therapy (17). Patients who failed antithrombotic therapy may benefit more from endovascular treatment than those who did not. A study that included symptomatic ICAS patients, with 95.5% (43/45) failing at least one kind of antithrombotic therapy, showed a 30 days stroke or vascular death rate of 6.6% after endovascular treatment, which was significantly better than SAMMPRIS (18).

Second, the median time from the qualifying event to randomization in SAMMPRIS was 7 days (interquartile range: 4–16 days) in the PTAS group, which indicated that most patients were treated in the acute or subacute stage. The detailed analysis of SAMMPRIS results demonstrated no relationship between the time from the qualifying event to PTAS and the risk of ischemic events (19). Early recanalization of intracranial stenosis with PTAS may rescue the ischemic penumbra by increasing the downstream flow of the territory at the stenosis artery, which may improve symptoms of neurologic deficits (20). However, the problems of stability of plaque and reperfusion hemorrhage in the acute or subacute stage must be considered. A high risk of recurrent TIA or stroke due to the "snow-plowing" of unstable plaque was regarded as the major cause of perforator infarction in patients treated with endovascular therapy (21). A *post-hoc* analysis of periprocedural strokes in patients who underwent angioplasty or stent placement in the SAMMPRIS trial found that perforator occlusion was the most common cause of periprocedural stroke (19). Another risk of emergency endovascular treatment is reperfusion hemorrhage. The intracranial microcirculation in the territory of acute cerebral infarction is considered to be unstable, which may result in a higher risk of reperfusion hemorrhage after the procedure for symptomatic ICAS patients treated in the acute or subacute stage. In a surveillance study, the Japanese Registry of Neuroendovascular Therapy, 1,133 ICAS patients underwent intracranial percutaneous transluminal angioplasty or stenting. The results showed that the number of hemorrhagic complications was significantly greater in patients who received

endovascular treatment between 24 h and 14 days after the onset of symptoms as compared to those who received treatment later (22). Hence, PTSA implemented at the proper time may decrease the risk of perioperative complications.

Third, the mechanism of ischemic stroke was not reported upon and may dramatically effect upon the complication and efficacy rate of intracranial stenosis. Intracranial atherosclerotic disease may become symptomatic due to (a) local perforator ischemia, (b) artery to artery embolism, (c) hemodynamic hypoperfusion, or, (d) a combination of the aforementioned mechanisms (23–25) (see **Figure 1**). Efficacy and risks of treatment will naturally differ between each different pathological mechanism. Studies found that symptomatic ICAS patients with hypoperfusion or poor collateral circulation in the downstream area of stenotic arteries could benefit more from endovascular treatment than those with other mechanisms of ischemic stroke (26). A study found that a combination of dual antithrombotic medicine, high-dose statins, and rigorous lifestyle management may be effective for lowering the risk of artery-to-artery embolism in patients with ICAS (25). Moreover, perforator ischemia possibly causes an excessive risk of periprocedural stroke due to occlusion of (additional) perforators through "snow-plowing" plaque toward their origins (27). Abou-Chebl et al. found that the exclusion of symptomatic patients with perforator infarction before PTAS in SAMMPRIS could decrease the rate of 30 days ischemic stroke from 14.7 to 9.4% (28). Therefore, identification of the mechanism underlying the recent ischemic stroke event may be a way to reduce the risk of perioperative complications of PTAS treatment. However, no further classification based on the specific mechanisms of stroke was made at the enrolment of the SAMMPRIS trial. Patients were simply grouped as TIA or stroke, which could not differentiate patients with hypoperfusion or poor collateral circulation downstream of the stenotic arteries.

The VISSIT trial had similar flaws. It was impossible to tell whether the participants failed antithrombotic therapy or not. The median time from qualifying events to stenting was 12.3 days, also within the acute or subacute stage. Hemodynamic symptomatology was not used to select participants (8).

In summary, the aforementioned flaws of study design in both the SAMMPRIS and VISSIT trials have a non-negligible impact on the credibility of previous studies to deny the potential positive effect in carefully selected patients with symptomatic ICAS for PTAS.

Contrary to SAMMPRIS and VISSIT, results from several prospective trials in Asia demonstrated promising outcomes concerning endovascular treatment for ICAS: A multicenter prospective study in China included 354 symptomatic high-grade ICAS patients with hypoperfusion symptoms and poor collaterals. These patients received balloon-mounted stent, self-expandable stent placement, or balloon angioplasty alone based on technical considerations regarding access and lesion morphology in the subacute phase after the onset of symptoms; patients with embolic thrombosis, lacunar infarcts, severe vascular tortuosity, non-atherosclerotic lesions, or a baseline modified Rankin Scale (mRS) score of >3 were excluded. The 30 days stroke, TIA, or death rate was 4.3%, which was significantly lower than that in the SAMMPRIS and VISSIT trials (12). Prior to this study, a single-center prospective study with 158 symptomatic ICAS patients and the same inclusion criteria and endovascular treatment demonstrated a 30 days composite stroke, myocardial infarction, or death rate of 4.4% (11). Similarly, another investigator-initiated, government-funded, prospective, multicenter registration trial with 100 symptomatic ICAS patients 3 weeks after the index ischemic event and without perforator stroke and/or disabling stroke (mRS >3) who were treated with angioplasty and self-expandable stent demonstrated an overall 30 days stroke and/or death rate of 2% (95% confidence interval, 0.2–7.0%) (13). Hence, the selection of patients and the timing of treatment appears to be of importance for ICAS.

The Type of Treatment

Treatment type may also affect outcomes. In SAMMPRIS, there were 224 lesions of ICAS, among which 61.2% were in the anterior circulation and the remaining were in the posterior circulation. The sole endovascular stent was the Wingspan stent. However, data showed that complication rates were different between the anterior and posterior circulation. Data from a systematic review including 31 studies and 1,177 symptomatic, high-grade ICAS patients receiving stent treatment demonstrated a significantly lower rate of periprocedural complications in the anterior circulation than that in the posterior circulation (6.6 vs. 12.1%, $P < 0.01$) (29). There are many types of endovascular techniques available for ICAS treatment, including balloon angioplasty alone, balloon-mounted stent (Pharos Vitesse), and self-expandable stents (Wingspan), each of which has its own features and specific advantages relating to different intracranial artery lesions. The characteristics and location of these lesions can be used to choose the type of angioplasty or stenting to treat symptomatic ICAS patients:

Balloon Angioplasty Alone

Balloon angioplasty alone is the first and simplest endovascular therapy used for the treatment of intracranial stenosis, which increases perfusion of the downstream territory of the stenotic artery by dilating the caliber of the stenotic segment, decreasing or eliminating ongoing or recurrent neurologic symptoms, and potentially delaying or preventing secondary occlusion and stroke. The enthusiasm of balloon angioplasty alone for intracranial stenosis can be traced to the 1980s, when the prognosis of high-grade intracranial stenosis was poor with medical treatment (30, 31). Sundt et al. reported the first successful cases of transluminal balloon angioplasty for patient with high-grade, atherosclerotic, stenotic basilar artery who were refractory to anticoagulant therapy, of which the angiographic and short-term clinical results were excellent (32). Unfortunately, with more cases of intracranial stenosis with balloon angioplasty reported, more periprocedural complications were also reported, such as arterial dissection with consecutive thrombosis or rupture, residual stenosis due to sequestration or vessel recoiling, and acute or subacute vascular occlusion due to the formation of a wall hematoma (33). The high risk of complications induced the development of new technologies of balloon angioplasty. Submaximal balloon angioplasty with slow inflation was developed and recommended as a proper option for intracranial stenosis (33). In a study of 41 consecutive,

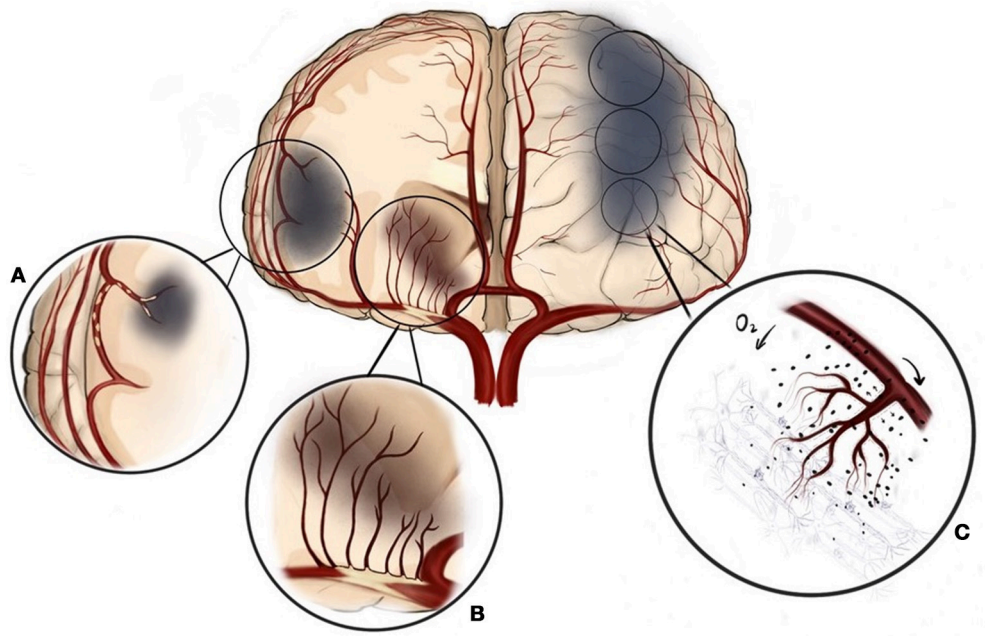

FIGURE 1 | Three different mechanisms of ischemic stroke can be present in intracranial atherosclerosis. **(A)** Artery to artery embolism, **(B)** Local perforator ischemia, **(C)** Hemodynamic hypoperfusion.

symptomatic, high-grade (≥70%) ICAS patients, treatment was submaximal balloon angioplasty alone. The 30 days event rate and 1 year perioperative and ischemic event-free survival rate were 4.9 and 91%, respectively, both of which were better than those of the medical and PTAS group in the SAMMPRIS trial (34). Recently, a prospective phase I trial of 24 patients with significant intracranial stenosis treated with submaximal balloon angioplasty alone also reported better safety outcomes, with no 30 days ischemic stroke in the territory of the treated stenotic vessel and good efficacy outcomes, including a 1 year recurrent stroke rate of 5.55% and no mortality or hemorrhage event (35). Therefore, using current techniques and equipments, intracranial balloon angioplasty alone can be performed safely and efficiently in patients with symptomatic ICAS.

Balloon-Mounted Stent

In the early stages of intracranial stent deployment, most balloon-mounted stents used to treat symptomatic ICAS patients were coronary stents, which were not designed for intracranial vasculature and thus were difficult to deliver through the tortuous cervical and intracranial vasculature (36). Therefore, the deployment of a balloon-mounted stent often resulted in distortion of the regional anatomy and sometimes led to traumatic injury to the tortuous vascular segments because of the stiffness and the lack of conformability of the high-pressure double-lumen balloon catheter. Meanwhile, a balloon-mounted stent demands a greater expansion to inflate the lumen but lacks intrinsic expansion forces, which may increase the risk of perforator damage due to plaque shifting when the lesion is near or in the location of perforating arteries (37). With the advancement of intracranial stents, various types of intracranial balloon-mounted stents have been developed for the treatment of symptomatic ICAS (38). Although some inherited flaws of intracranial balloon-mounted stents still exist, they have advantages in some aspects. First, the stenosis can be inflated in a single step by a single operator. Second, the radial force of current used is strong enough to withhold the recoil phenomenon generated by the plaque or the vessel wall. Third, the likelihood of exact stent placement is improved, which keeps the stent length short and avoids covering the normal vessel segment (39). The INTRASTENT registry study comparing balloon-mounted stents to self-expandable stents in 409 symptomatic ICAS patients reported no statistically significant difference in complication rates, but the balloon-mounted stent was prone to a higher risk of perforator strokes, while the self-expandable stent tended to result in more thromboembolic events (40). A recent study comparing the short-term outcomes of stenting in 97 patients with symptomatic intracranial vertebrobasilar artery stenosis showed that balloon-mounted stents have a lower rate of residual stenosis and are more suitable for the patient with smooth arterial access and a short and concentric stenosis (Mori A lesion) than the self-expandable stent (41). Given that the residual stenosis rate was one of the major factors affecting restenosis, less residual stenosis is thus more beneficial for the prevention of restenosis (42). In summary, these advantages of the balloon-mounted stent show its potential for the treatment of symptomatic ICAS.

Self-Expandable Stent

The only currently available self-expandable stent (Wingspan) has been the most widely used intracranial stent for the

treatment of ICAS ever since its FDA's approval. In clinical practice, submaximal balloon angioplasty is performed prior to deployment of the stent (38). Because the Wingspan stent system is more flexible and passes the tortuous intracranial vasculature more easily than balloon-mounted systems, it has a higher technical success rate (39). Moreover, the Wingspan stent system has a lower risk of perforator infarctions (40), because the angioplasty can be undersized thus, minimizing the risk to the adjacent normal parent vessel. In addition, the small outward radial force of the self-expandable stent decreases the compression force delivered to the plaque near the perforating arteries (17). These advantages of the self-expandable stent have made its use more prevalent in the treatment of ICAS. However, the design of the self-expandable stent still has considerable flaws. On one hand, its two-step maneuver may lengthen procedure duration, which potentially increases the risk of embolic stroke. On the other hand, the exchange wire maneuver may increase the risk of subarachnoid hemorrhage due to inadvertent and uncontrolled movement of guide-wire tip (36). Regarding the restenosis rate, the self-expandable stent is inferior to the balloon-mounted stent. A study of 46 lesions in 45 symptomatic ICAS patients who had failed antithrombotic therapy were treated with the Wingspan stent. Results showed that the restenosis rate (defined as more than 50% of the initial lumen) was 42.8, 9.5% of which was symptomatic (18).

To our best knowledge, contemporary angioplasty and stenting used to treat symptomatic ICAS patients has some specific advantages for different lesions of ICAS. The individualized selection of different subtypes of PTAS for patients may influence the outcome of the treatment.

Operator Experience

Operator experience was shown to be a factor related to the outcome of endovascular therapy for ICAS: greater operator experience was associated with a lower rate of perioperative complications (43, 44). However, a *post-hoc* analysis of the SAMMPRIS trial showed that operators with more credentialing case numbers (>10) were associated with higher 30 days complication rates compared to those with fewer cases (19.0 vs. 9.9%, $P = 0.11$), whereas high-volume centers with enrollment $\geq$12 had lower rates of hemorrhagic stroke compared with low-volume centers (2.7 vs. 9.8%, $P = 0.043$) (45). This controversial result showed no correlation between operator experience and the volume of centers, and more experienced operators were prone to having more periprocedural complications. Data from the National Institutes of Health Multicenter Wingspan Registry showed that operators in high-volume centers were more proficient and had lower complication rates than those in low-volume centers (46). Hence, the credibility of using 10 cases (as used in SAMMPRIS) to assess the experience of operators is questionable. Ten cases could have been underestimated for assessing the adequacy of experience with the Wingspan procedure (47). In addition, operators enrolled in SAMMPRIS were required to submit 20 cases of intracranial angioplasty, but only three cases had to be with the Wingspan system (48). Therefore, different designs of the Wingspan stent and other types of stents, as well as the tortuous vasculature in atherosclerotic lesions, may account for the insufficient credentialing criteria of three cases of Wingspan stent system (28).

PROSPECT IN FUTURE

Endovascular therapy with careful selection of patients, proper types of PTAS, and experienced operators may reduce the risks of perioperative complications and provide greater benefit for symptomatic ICAS patients. Therefore, we should pay more attention to these aspects in the future.

Careful Selection of Patient

It is important to carefully select applicable patients with symptomatic intracranial stenosis, which is the first step in reducing the rate of perioperative complications.

ICAS patients who fail under medical management may require endovascular treatment. In 2012, the FDA modified the indication of the Wingspan stent, highlighting that patients identified as refractory to medical management must meet the criteria of having at least two strokes while receiving aggressive medical management (49). Patients who are refractory to medical management, defined as a recurrent ischemic event despite the combination of maximal-dose dual antiplatelet therapy, intensive cardiovascular risk factor control, and rigorous lifestyle management, may benefit more from endovascular treatment.

In addition, identification of the mechanism for the recent stroke is also important. Patients with hypoperfusion or poor collateral circulation of the downstream territory at the stenotic arteries may benefit more from endovascular treatment, while patients with perforator occlusion will have no benefit (or may even be harmed) from angioplasty. Patients with artery-artery embolism may benefit from aggressive medical management. In clinical practice, advanced neuroimaging technologies could be used to identify stroke mechanisms. For instance, brain imaging of infarct patterns on diffusion-weighted imaging could infer the underlying stroke mechanisms (50). The perforator pattern is characterized by infarct lesions in the subcortical or perforator territory, i.e., in the territory perfused by perforating vessels that originate at the site of stenosis. An arterial embolic pattern is characterized by infarct lesions located in the downstream territory of the stenotic vessel (cortical, subcortical, or both) and is limited to the territory supplied by a single intracranial culprit artery. The border-zone or hemodynamic pattern is characterized by one or more infarct lesions located in the internal border-zone region in the corona radiata or centrum semiovale and/or in the cortical border-zone region, between the middle cerebral artery and anterior cerebral artery or between the middle cerebral artery and posterior cerebral artery (see **Figure 2** for examples). The mixed pattern presents a combination of any of the previous infarct patterns described above (51–53). Hypoperfusion may also be estimated by reduced blood flow on computed tomography perfusion, perfusion-weighted imaging on magnetic resonance or single-photon emission computed tomography (see **Figure 3**) (54). Collaterals may be assessed on digital subtraction angiography

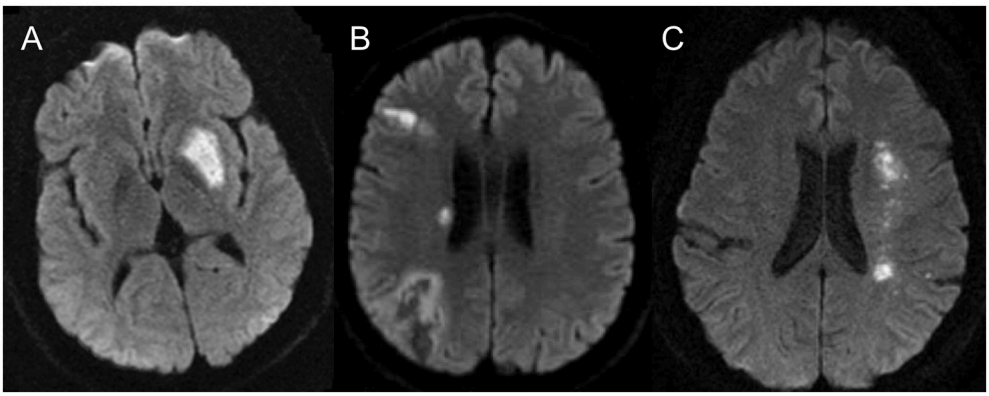

FIGURE 2 | Ischemia pattern for the different pathological mechanisms seen in intracranial atherosclerosis: **(A)** demonstrates the typical perforator type infarct, **(B)** demonstrates the artery to artery embolic infarct and **(C)** demonstrates the classical deep watershed zone for the hemodynamic infarcts.

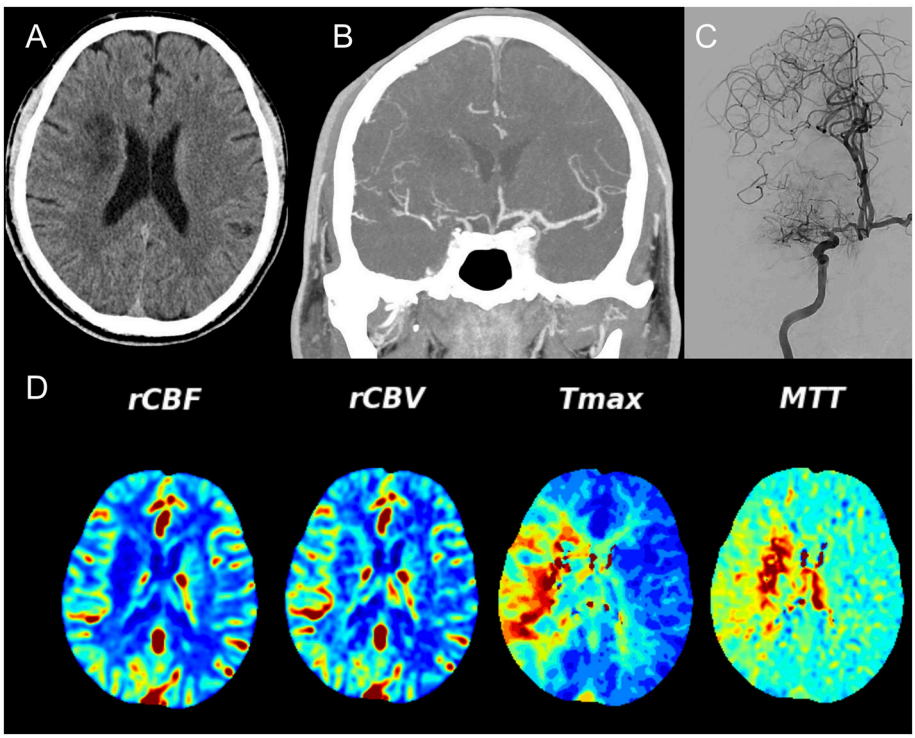

FIGURE 3 | Unenhanced CT **(A)** demonstrates recent ischemia in a deep watershed pattern, CTA **(B)** in a coronal view shows a high degree MCA stenosis that is confirmed on conventional angiography **(C)**. Note the excellent collateral network from the leptomeningeal collaterals from the ACA territory toward the MCA territory. **(D)** Demonstrates the CT Perfusion parameters – relative cerebral blood flow (rCBF) and — volume (rCBV) that are both still normal whereas the Time to maximum contrast (Tmax) and the mean transit time (MTT) are significantly delayed over the right hemisphere indicating hypoperfusion.

with the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology Collateral Flow Grading System, which could be categorized as none (grade 0), poor (grades 1 or 2), or good (grades 3 or 4) (55).

Moreover, optimizing the time of endovascular treatment from qualifying events is also important to reduce procedural-related complications, including plaque detachment and reperfusion hemorrhage. Several studies demonstrated that the early time period after index ischemic event is the period of highest risk of recurrent ischemic events in patients with ICAS (56–59). A consensus conference regarding ICAS held that the risk of recurrent TIA or stroke is highest within 2 weeks after index ischemic event in patients with symptomatic ICAS (60). The WASID (the Warfarin vs. Aspirin for Symptomatic Intracranial Disease) trial showed that patients treated within

2.5 weeks after the first ischemic event had a 1.7-times higher risk of recurrent stroke than those treated later (61). It is seemingly that early endovascular treatment after the index ischemic event is more significant to reduce the risk of recurrent ischemic events in patients with symptomatic ICAS than deferred endovascular treatment. However, angioplasty or stenting itself is a risk factor that may increase the rate of recurrent TIA or stroke due to plaque vulnerability and disorder of blood-brain barrier in initial time period after the index ischemic event. Delaying the procedure for symptomatic patients with recent TIA or stroke may allow stabilization of plaque and cerebrovascular self-regulation, which would offset the adverse aspects of endovascular treatment. The National Institutes of Health Multicenter Wingspan Intracranial Stent Registry Study of 160 symptomatic ICAS patients treated by Gateway balloon and Wingspan stent system demonstrated that stent placement performed 10 days after a qualifying ischemic event was associated with a lower rate of 30 days stroke and/or death compared with stent placement performed within 10 days of the event (8 vs. 17%, $P = 0.082$) (46). Several Asian intracranial stenting trials excluding patients of acute stroke within 3 weeks concluded a low risk of recurrent stoke or death in patients treated with angioplasty or/and stenting (e.g., Miao 4.3%; Gao 2%) (12, 13). Giving in positive data from Asian trials and our anecdotal experience, a time interval of 3 weeks from the qualifying event to endovascular treatment may be a proper cutoff that has a greater benefit for symptomatic ICAS patients, certainly, which requires further studies.

Type of Angioplasty and Stenting

Endovascular technologies are constantly evolving with the development of new technologies of stent deployment and delivery. Next generation stents are likely to be more flexible, easier to deliver, and capable of preventing long-term restenosis. However, the contemporary design of endovascular treatment for ICAS, such as balloon angioplasty alone, self-expandable stents, and balloon-mounted stents, has inherent advantages as well as disadvantages. Based on the characteristics of the plaque, procedural arterial access, length of lesions, and diameter of culprit arteries, different types of endovascular treatment may be chosen individually to obtain the best possible clinical outcomes. According to the Mori classification, three different types of stenoses can be subclassified: Mori A, a short and concentric lesion with a short length (<5 mm); Mori B, a tubular or extreme eccentric lesion with intermediate length (between 5 and 10 mm); Mori C, a diffuse lesion with a long length (>10 mm) (62). These authors argues, that balloon-mounted stents are suitable for patients with smooth arterial access and Mori A lesions, midbasilar artery, and distal M1 segment lesions; self-expanding stents may be suitable for patients with tortuous arterial access and Mori B or C lesions; and balloon angioplasty alone is suitable for patients with tortuous arterial access with Mori A lesions and a small target-vessel diameter of <2.5 mm (11). In addition, characteristics of plaque can now be identified using high-resolution vessel wall magnetic resonance imaging (HR-MRI) for detailed visualization of the vessel wall before endovascular treatment (see **Figure 4** for an example) (63–65). For example, ulcerous plaques, fibrous cap ruptured plaques,

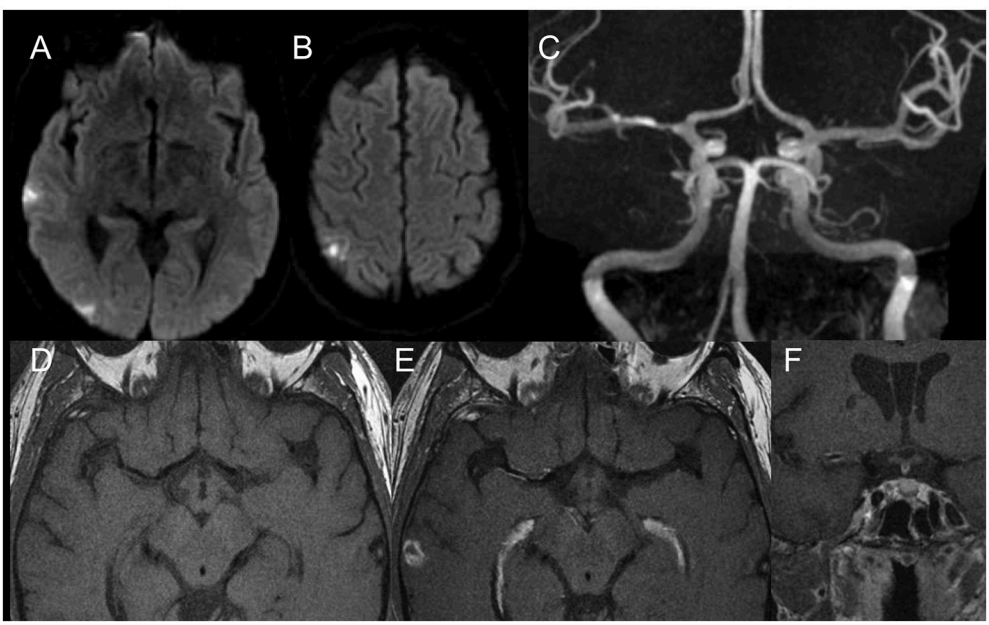

FIGURE 4 | Diffusion weighted scans **(A,B)** demonstrate multiple distal (embolic) foci of ischemia in the right MCA territory. MR Angiography **(C)** shows a moderate degree MCA stenosis in the proximal M1. High resolution vessel wall imaging in axial cuts before **(D)** and after **(E)** contrast enhancement as well as coronal T1 weighted vessel wall imaging sequences after contrast enhancement **(F)** demonstrate a hot plaque with dense eccentric enhancement. Given the embolic nature, the "hot plaque" characteristics and the relatively low degree of stenosis in a patient who was not on optimal therapy, it was decided to not perform an endovascular therapy.

or plaques adjacent to perforator-rich vessel segments can be identified by HR-MRI to help clinicians make better clinical decisions and risk assessments regarding ICAS treatment (66).

Learning Curve of Intracranial Angioplasty or Stenting

Because endovascular treatment requires operators to undergo a learning process, perioperative complications may be reduced by improving operator experience (67). A prospective study of 95 consecutive patients at a single center, splitting data into quarters for learning curve analysis, demonstrated that procedural problems, technical failures, and guidewire- or angioplasty-related hemorrhage were almost the same in the first three quarters but significantly declined in the fourth quarter, indicating a learning curve and a trend of technical maturation in the fourth quarter (47). As there is a learning curve to achieve technical maturity, operators are required to learn from their own mistakes in previous practice and meanwhile to absorb experience from other operators and the literature (41). In addition, alternative training techniques, such as simulation models and virtual reality training, have become valid approaches for training interventionalists (68). Using these techniques, the operator's experience for endovascular treatment could be enhanced in order to maximally guarantee the safety of patients and the efficacy of the endovascular therapy.

As literatures reported, the measures to assess experience of operator for endovascular treatment include: (a) individual accumulative cases of intracranial angioplasty or/and stenting for ICAS in total; (b) individual mean cases of intracranial angioplasty or/and stenting for ICAS per year; (c) the morbidity or mortality rates of angioplasty or/and stenting for ICAS submitted by individual; and d) the center volume of angioplasty or/and stenting cases for ICAS per year (48, 69, 70). Unfortunately, there is a lack of consensus to evaluate technical maturity for operator due to the diversity of interventional discipline and medical condition around the world. We suggest a combination of four measures mentioned above be used to assess the technical maturity for endovascular treatment. For instance, a pilot study of China Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS) trial was performed to test the credentialing of the operators and participating centers from three aspects of stenting experience, perioperative complications, and the volume of stenting cases. The study demonstrated an excellent result of endovascular treatment for ICAS that only two ischemic strokes within 30 days (13, 70).

CONCLUSIONS

Endovascular treatments, such as balloon angioplasty alone, balloon-mounted stents, and self-expandable stents, may be of benefit for carefully selected ICAS patients. Two prospective, multicenter, RCT are presently underway to re-evaluate the benefits of endovascular treatments in carefully selected patients (CASSISS trial, and the Wingspan Stent System Post-Market Surveillance Study (WEAVE) trial) (70, 71). These trials' strict selection criteria, identification of stroke mechanisms of intracranial atherosclerosis, as well as use of experienced neurointerventionists in high-volume centers are what makes them of interest for the re-evaluation of invasive ICAS treatment.

AUTHOR CONTRIBUTIONS

LJ and PG provided ideas of the review. JL conducted the review and drafted the initial manuscript. TK and TW critically reviewed and revised the review. All the authors reviewed and approved final version of the manuscript.

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REFERENCES

1. Feigin VL. Stroke in developing countries: can the epidemic be stopped and outcomes improved? *Lancet Neurol.* (2007) 6:94–7. doi: 10.1016/s1474-4422(07)70007-8
2. Strong K, Mathers C, Bonita R. Preventing stroke: saving lives around the world. *Lancet Neurol.* (2007) 6:182–7. doi: 10.1016/s1474-4422(07)70031-5
3. Koton S, Schneider AL, Rosamond WD, Shahar E, Sang Y, Gottesman RF, et al. Stroke incidence and mortality trends in US communities, 1987 to 2011. *JAMA* (2014) 312:259–68. doi: 10.1001/jama.2014.7692
4. Gorelick PB, Wong KS, Bae HJ, Pandey DK. Large artery intracranial occlusive disease: a large worldwide burden but a relatively neglected frontier. *Stroke* (2008) 39:2396–9. doi: 10.1161/STROKEAHA.107.505776
5. Feigin VL, Norrving B, Mensah GA. Global burden of stroke. *Circ Res.* (2017) 120:439–48. doi: 10.1161/CIRCRESAHA.116.308413
6. Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med.* (2011) 365:993–1003. doi: 10.1056/NEJMoa1105335
7. Derdeyn CP, Chimowitz MI, Lynn MJ, Fiorella D, Turan TN, Janis LS, et al. Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. *Lancet* (2014) 383:333–41. doi: 10.1016/S0140-6736(13)62038-3
8. Zaidat OO, Fitzsimmons BF, Woodward BK, Wang Z, Killer-Oberpfalzer M, Wakhloo A, et al. Effect of a balloon-expandable intracranial stent vs. medical therapy on risk of stroke in patients with symptomatic intracranial stenosis: the VISSIT randomized clinical trial. *JAMA* (2015) 313:1240–8. doi: 10.1001/jama.2015.1693
9. Yu SC, Leung TW, Hung EH, Lee KT, Wong LK. Angioplasty and stenting for intracranial atherosclerotic stenosis with nitinol stent: factors affecting technical success and patient safety. *Neurosurgery* (2012) 70:104–13. doi: 10.1227/NEU.0b013e3182320bb0
10. Park S, Kim JH, Kwak JK, Baek HJ, Kim BH, Lee DG, et al. Intracranial stenting for severe symptomatic stenosis: self-expandable versus balloon-expandable stents. *Interv Neuroradiol.* (2013) 19:276–82. doi: 10.1177/159101991301900303

11. Miao Z, Song L, Liebeskind DS, Liu L, Ma N, Wang Y, et al. Outcomes of tailored angioplasty and/or stenting for symptomatic intracranial atherosclerosis: a prospective cohort study after SAMMPRIS. *J Neurointerv Surg.* (2015) 7:331–5. doi: 10.1136/neurintsurg-2014-011109
12. Miao Z, Zhang Y, Shuai J, Jiang C, Zhu Q, Chen K, et al. Thirty-day outcome of a multicenter registry study of stenting for symptomatic intracranial artery stenosis in China. *Stroke* (2015) 46:2822–9. doi: 10.1161/STROKEAHA.115.010549
13. Gao P, Wang D, Zhao Z, Cai Y, Li T, Shi H, et al. Multicenter prospective trial of stent placement in patients with symptomatic high-grade intracranial stenosis. *AJNR Am J Neuroradiol.* (2016) 37:1275–80. doi: 10.3174/ajnr.A4698
14. Maier IL, Karch A, Lipke C, Behme D, Mpotsaris A, Kabbasch C, et al. Transluminal angioplasty and stenting versus conservative treatment in patients with symptomatic basilar artery stenosis: perspective for future clinical trials. *Clin Neuroradiol.* (2016) 28:33–38. doi: 10.1007/s00062-016-0528-x
15. Turan TN, Cotsonis G, Lynn MJ, Wooley RH, Swanson S, Williams JE, et al. Intracranial stenosis: impact of randomized trials on treatment preferences of US neurologists and neurointerventionists. *Cerebrovasc Dis.* (2014) 37:203–11. doi: 10.1159/000358120
16. Zaidat OO, Castonguay AC, Nguyen TN, Becker KJ, Derdeyn CP, Nelson PK, et al. Impact of SAMMPRIS on the future of intracranial atherosclerotic disease management: polling results from the ICAD symposium at the International Stroke Conference. *J Neurointerv Surg.* (2014) 6:225–30. doi: 10.1136/neurintsurg-2013-010667
17. Bose A, Hartmann M, Henkes H, Liu HM, Teng MM, Szikora I, et al. A novel, self-expanding, nitinol stent in medically refractory intracranial atherosclerotic stenoses: the Wingspan study. *Stroke* (2007) 38:1531–7. doi: 10.1161/STROKEAHA.106.477711
18. Samaniego EA, Tari-Capone F, Linfante I, Silva CF, Spilberg G, Gounis M, et al. Wingspan experience in the treatment of symptomatic intracranial atherosclerotic disease after antithrombotic failure. *J Neurointerv Surg.* (2013) 5:302–5. doi: 10.1136/neurintsurg-2012-010321
19. Fiorella D, Derdeyn CP, Lynn MJ, Barnwell SL, Hoh BL, Levy EI, et al. Detailed analysis of periprocedural strokes in patients undergoing intracranial stenting in stenting and aggressive medical management for preventing recurrent stroke in intracranial stenosis (SAMMPRIS). *Stroke* (2012) 43:2682–8. doi: 10.1161/STROKEAHA.112.661173
20. Naess H, Kurtz M, Thomassen L, Waje-Andreassen U. Serial NIHSS scores in patients with acute cerebral infarction. *Acta Neurol Scand.* (2016) 133:415–20. doi: 10.1111/ane.12477
21. Derdeyn CP, Fiorella D, Lynn MJ, Rumboldt Z, Cloft HJ, Gibson D, et al. Mechanisms of stroke after intracranial angioplasty and stenting in the SAMMPRIS trial. *Neurosurgery* (2013) 72:777–95; discussion 795. doi: 10.1227/NEU.0b013e318286fdc8
22. Izumi T, Imamura H, Sakai N, Miyachi S. Angioplasty and stenting for intracranial stenosis. *Neurol Med Chir.* (2014) 54:46–53. doi: 10.2176/nmc.oa.2013-0319
23. Wong KS, Shan GM, Yu LCF, Tjark Hansberg MD, Frcr WWML, Droste DW, et al. Mechanisms of acute cerebral infarctions in patients with middle cerebral artery stenosis: a diffusion-weighted imaging and microemboli monitoring study. *Ann Neurol.* (2006) 52:74–81. doi: 10.1002/ana.10250
24. Kim JS, Nah HW, Park SM, Kim SK, Cho KH, Lee J, et al. Risk factors and stroke mechanisms in atherosclerotic stroke: intracranial compared with extracranial and anterior compared with posterior circulation disease. *Stroke* (2012) 43:3313–8. doi: 10.1161/STROKEAHA.112.658500
25. Lopez-Cancio E, Matheus MG, Romano JG, Liebeskind DS, Prabhakaran S, Turan TN, et al. Infarct patterns, collaterals and likely causative mechanisms of stroke in symptomatic intracranial atherosclerosis. *Cerebrovasc Dis.* (2014) 37:417–22. doi: 10.1159/000362922
26. Banerjee C, Chimowitz MI. Stroke caused by atherosclerosis of the major intracranial arteries. *Circ Res.* (2017) 120:502–13. doi: 10.1161/CIRCRESAHA.116.308441
27. van den Wijngaard IR, Holswilder G, van Walderveen MA, Algra A, Wermer MJ, Zaidat OO, et al. Treatment and imaging of intracranial atherosclerotic stenosis: current perspectives and future directions. *Brain Behav.* (2016) 6:e00536. doi: 10.1002/brb3.536
28. Abou-Chebl A, Steinmetz H. Critique of "stenting versus aggressive medical therapy for intracranial arterial stenosis" by Chimowitz et al in the New England Journal of Medicine. *Stroke* (2012) 43:616–20. doi: 10.1161/STROKEAHA.111.641563
29. Groschel K, Schnaudigel S, Pilgram SM, Wasser K, Kastrup A. A systematic review on outcome after stenting for intracranial atherosclerosis. *Stroke* (2009) 40:e340–7. doi: 10.1161/STROKEAHA.108.532713
30. O'Leary DH, Clouse ME. Percutaneous transluminal angioplasty of the cavernous carotid artery for recurrent ischemia. *AJNR Am J Neuroradiol.* (1984) 5:644.
31. Purdy PD, Devous MD Sr., Unwin DH, Giller CA, Batjer HH. Angioplasty of an atherosclerotic middle cerebral artery associated with improvement in regional cerebral blood flow. *AJNR Am J Neuroradiol.* (1990) 11:878–80.
32. Jr ST, Smith HC, Campbell JK, Vlietstra RE, Cucchiara RF, Stanson AW. Transluminal angioplasty for basilar artery stenosis. *Mayo Clin Proc.* (1980) 55:673.
33. Connors JJ, III, Wojak JC. Percutaneous transluminal angioplasty for intracranial atherosclerotic lesions: evolution of technique and short-term results. *J Neurosurg.* (1999) 91:415–23. doi: 10.3171/jns.1999.91.3.0415
34. Dumont TM, Kan P, Snyder KV, Hopkins LN, Siddiqui AH, Levy EI. Revisiting angioplasty without stenting for symptomatic intracranial atherosclerotic stenosis after the stenting and aggressive medical management for preventing recurrent stroke in intracranial stenosis (SAMMPRIS) study. *Neurosurgery* (2012) 71:1103–10. doi: 10.1227/NEU.0b013e318271bcb8
35. Dumont TM, Sonig A, Mokin M, Eller JL, Sorkin GC, Snyder KV, et al. Submaximal angioplasty for symptomatic intracranial atherosclerosis: a prospective phase I study. *J Neurosurg.* (2016) 125:964–71. doi: 10.3171/2015.8.jns15791
36. Chatterjee AR, Derdeyn CP. Stenting in intracranial stenosis: current controversies and future directions. *Curr Atheroscler Rep.* (2015) 17:48. doi: 10.1007/s11883-015-0527-4
37. Investigators SS. Stenting of symptomatic atherosclerotic lesions in the vertebral or intracranial arteries (SSYLVIA): study results. *Stroke* (2004) 35:1388–92. doi: 10.1161/01.STR.0000128708.86762.d6
38. Ding D, Liu KC. Applications of stenting for intracranial atherosclerosis. *Neurosurg Focus* (2011) 30:E15. doi: 10.3171/2011.3.FOCUS1149
39. Berkefeld J, Zanella FE. Intracranial stenting of atherosclerotic stenoses: current status and perspectives. *Clin Neuroradiol.* (2009) 19:38–44. doi: 10.1007/s00062-009-8039-7
40. Kurre W, Brassel F, Bruning R, Buhk J, Eckert B, Horner S, et al. Complication rates using balloon-expandable and self-expanding stents for the treatment of intracranial atherosclerotic stenoses: analysis of the INTRASTENT multicentric registry. *Neuroradiology* (2012) 54:43–50. doi: 10.1007/s00234-010-0826-y
41. Liu L, Zhao X, Mo D, Ma N, Gao F, Miao Z. Stenting for symptomatic intracranial vertebrobasilar artery stenosis: 30-day results in a high-volume stroke center. *Clin Neurol Neurosurg.* (2016) 143:132–8. doi: 10.1016/j.clineuro.2016.02.029
42. Yue X, Yin Q, Xi G, Zhu W, Xu G, Zhang R, et al. Comparison of BMSs with SES for symptomatic intracranial disease of the middle cerebral artery stenosis. *Cardiovasc Intervent Radiol.* (2011) 34:54–60. doi: 10.1007/s00270-010-9885-z
43. Jiang WJ, Du B, Leung TW, Xu XT, Jin M, Dong KH. Symptomatic intracranial stenosis: cerebrovascular complications from elective stent placement. *Radiology* (2007) 243:188–97. doi: 10.1148/radiol.2431060139
44. Jiang WJ, Yu W, Du B, Gao F, Cui LY. Outcome of patients with ≥70% symptomatic intracranial stenosis after Wingspan stenting. *Stroke* (2011) 42:1971–5. doi: 10.1161/STROKEAHA.110.595926
45. Derdeyn CP, Fiorella D, Lynn MJ, Barnwell SL, Zaidat OO, Meyers PM, et al. Impact of operator and site experience on outcomes after angioplasty and stenting in the SAMMPRIS trial. *J Neurointerv Surg.* (2013) 5:528–33. doi: 10.1136/neurintsurg-2012-010504
46. Nahab F, Lynn MJ, Kasner SE, Alexander MJ, Klucznik R, Zaidat OO, et al. Risk factors associated with major cerebrovascular complications after intracranial stenting. *Neurology* (2009) 72:2014–9. doi: 10.1212/01.wnl.0b013e3181a1863c
47. Yu SC, Leung TW, Lee KT, Wong LK. Learning curve of Wingspan stenting for intracranial atherosclerosis: single-center experience

of 95 consecutive patients. *J Neurointerv Surg.* (2014) 6:212–8. doi: 10.1136/neurintsurg-2012-010593
48. Chimowitz MI, Lynn MJ, Turan TN, Fiorella D, Lane BF, Janis S, et al. Design of the stenting and aggressive medical management for preventing recurrent stroke in intracranial stenosis trial. *J Stroke Cerebrovasc Dis.* (2011) 20:357–68. doi: 10.1016/j.jstrokecerebrovasdis.2011.05.001
49. US Food and Drug Administration. *Narrowed Indications for Use for the Stryker Wingspan Stent System: FDA Safety Communication* (2012). Available online at: https://wayback.archive-it.org/7993/20170722215747/https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm314600.htm
50. Wong KS, Caplan LR, Kim JS. Stroke mechanisms. *Front Neurol Neurosci.* (2016) 40:58–71. doi: 10.1159/000448302
51. Levy EI, Hanel RA, Boulos AS, Bendok BR, Kim SH, Gibbons KJ, et al. Comparison of periprocedure complications resulting from direct stent placement compared with those due to conventional and staged stent placement in the basilar artery. *J Neurosurg.* (2003) 99:653–60. doi: 10.3171/jns.2003.99.4.0653
52. Holmstedt CA, Turan TN, Chimowitz MI. Atherosclerotic intracranial arterial stenosis: risk factors, diagnosis, and treatment. *Lancet Neurol.* (2013) 12:1106–14. doi: 10.1016/S1474-4422(13)70195-9
53. Wang Y, Lu Z, Sun S, Yang Y, Zhang B, Kang Z, et al. Risk factors, topographic patterns and mechanism analysis of intracranial atherosclerotic stenosis ischemic stroke. *Int J Neurosci.* (2017) 127:267–75. doi: 10.1080/00207454.2016.1188298
54. Wang Y, Zhao X, Liu L, Soo YO, Pu Y, Pan Y, et al. Prevalence and outcomes of symptomatic intracranial large artery stenoses and occlusions in China: the Chinese Intracranial Atherosclerosis (CICAS) Study. *Stroke* (2014) 45:663–9. doi: 10.1161/STROKEAHA.113.003508
55. Higashida RT, Furlan AJ, Roberts H, Tomsick T, Connors B, Barr J, et al. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. *Stroke* (2003) 34:e109–37. doi: 10.1161/01.str.0000082721.62796.09
56. Lovett JK, Dennis MS, Sandercock PA, Bamford J, Warlow CP, Rothwell PM. Very early risk of stroke after a first transient ischemic attack. *Stroke* (2003) 34:e138–40. doi: 10.1161/01.str.0000080935.01264.91
57. Hill MD, Yiannakoulias N, Jeerakathil T, Tu JV, Svenson LW, Schopflocher DP. The high risk of stroke immediately after transient ischemic attack: a population-based study. *Neurology* (2004) 62:2015–20. doi: 10.1212/01.WNL.0000129482.70315.2F
58. Lovett JK, Coull AJ, Rothwell PM. Early risk of recurrence by subtype of ischemic stroke in population-based incidence studies. *Neurology* (2004) 62:569–73. doi: 10.1212/01.WNL.0000110311.09970.83
59. Rothwell PM, Warlow CP. Timing of TIAs preceding stroke: time window for prevention is very short. *Neurology* (2005) 64:817–20. doi: 10.1212/01.wnl.0000152985.32732.ee
60. Qureshi AI, Feldmann E, Gomez CR, Johnston SC, Kasner SE, Quick DC, et al. Consensus conference on intracranial atherosclerotic disease: rationale, methodology, and results. *J Neuroimaging* (2009) 19:1S—10S. doi: 10.1111/j.1552-6569.2009.00414.x
61. Kasner SE, Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, et al. Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis. *Circulation* (2006) 113:555–63. doi: 10.1161/CIRCULATIONAHA.105.578229
62. Mori T, Fukuoka M, Kazita K, Mori K. Follow-up study after intracranial percutaneous transluminal cerebral balloon angioplasty. *AJNR Am J Neuroradiol.* (1998) 19:1525–33.
63. Xu WH, Li ML, Gao S, Ni J, Zhou LX, Yao M, et al. *In vivo* high-resolution MR imaging of symptomatic and asymptomatic middle cerebral artery atherosclerotic stenosis. *Atherosclerosis* (2010) 212:507–11. doi: 10.1016/j.atherosclerosis.2010.06.035
64. Mossa-Basha M, Alexander M, Gaddikeri S, Yuan C, Gandhi D. Vessel wall imaging for intracranial vascular disease evaluation. *J Neurointerv Surg.* (2016) 8:1154–9. doi: 10.1136/neurintsurg-2015-012127
65. Zhu XJ, Wang W, Liu ZJ. High-resolution magnetic resonance vessel wall imaging for intracranial arterial stenosis. *Chin Med J (Engl).* (2016) 129:1363–70. doi: 10.4103/0366-6999.182826
66. Shi M, Wang S, Zhou H, Cheng Y, Feng J, Wu J. Wingspan stenting of symptomatic middle cerebral artery stenosis and perioperative evaluation using high-resolution 3 Tesla MRI. *J Clin Neurosci.* (2012) 19:912–4. doi: 10.1016/j.jocn.2011.08.027
67. Cai Q, Li Y, Xu G, Sun W, Xiong Y, Sun W, et al. Learning curve for intracranial angioplasty and stenting in single center. *Catheter Cardiovasc Interv.* (2014) 83:E94–100. doi: 10.1002/ccd.25038
68. Neequaye SK, Aggarwal R, Van Herzeele I, Darzi A, Cheshire NJ. Endovascular skills training and assessment. *J Vasc Surg.* (2007) 46:1055–64. doi: 10.1016/j.jvs.2007.05.041
69. Zaidat OO, Castonguay AC, Fitzsimmons BF, Woodward BK, Wang Z, Killer-Oberpfalzer M, et al. Design of the vitesse intracranial stent study for ischemic therapy (VISSIT) trial in symptomatic intracranial stenosis. *J Stroke Cerebrovasc Dis.* (2013) 22:1131–9. doi: 10.1016/j.jstrokecerebrovasdis.2012.10.021
70. Gao P, Zhao Z, Wang D, Wu J, Cai Y, Li T, et al. China Angioplasty and stenting for symptomatic intracranial severe stenosis (CASSISS): A new, prospective, multicenter, randomized controlled trial in China. *Interv Neuroradiol.* (2015) 21:196–204. doi: 10.1177/1591019915581778
71. Stryker Neurovascular. *Post Market Surveillance Study of the Wingspan Stent System (WEAVE).* ClinicalTrials.gov ID: NCT02034058. (2014). Available online at: https://www.clinicaltrials.gov/ct2/show/NCT02034058?cond

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Weighing in on the Off-Label Use: Initial Experience of Neuroform EZ Stenting for Intracranial Arterial Stenosis in 45 Patients

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Background: The role of stenting for intracranial arterial stenosis (ICAS) has been increasingly debated due to negative results of randomized trials. Thus, exploration of more appropriate devices may hopefully shed light on the endovascular approach, especially for patients with recalcitrant ICAS related to a high risk of stroke. We sought to present and analyze the data of Neuroform EZ stenting for medically refractory ICAS in a single-center series.

Materials and methods: Between November 2016 and January 2018, 45 consecutive patients treated with the Neuroform EZ stent were included in our retrospective study. Outcomes evaluation included successful procedure rate, vascular event within 30 days and recurrent stenosis for at least 6 months after the procedure.

Results: The technical success rate was 100% for all 46 stenotic lesions. Mean pre-stent stenosis was 86.5 ± 8.7%, improving to 23.7 ± 18.1% after stenting. Combined procedure related vascular event rate was 2.2% (n = 1) within 30 days after the procedure. No in-stent restenosis was observed during an average follow-up period of 7.3 months.

Conclusion: The Neuroform EZ stent system could serve as an off-label but promising optional device for ICAS stenting in a carefully selected subgroup of patients. Further longer-term clinical follow-up is mandatory to validate our initial results.

Keywords: intracranial arterial stenosis, endovascular treatment, stent, Neuroform EZ, efficacy

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INTRODUCTION

Intracranial arterial stenosis (ICAS) attributable to atherosclerosis is one of the most common causes of stroke worldwide (1). Therapeutic strategies for this high-risk disease include intensive management of risk factors, combination antiplatelet treatment, and endovascular therapy (1). As an optional treatment for symptomatic ICAS, elective percutaneous transluminal angioplasty and stenting (PTAS) had been introduced with the advent of the Gateway balloon/Wingspan stent system (2, 3). However, subsequent data from the randomized trial (SAMMPRIS) indicated that aggressive medical management was superior to PTAS with the use of the Wingspan stent system, because of the poor outcomes and high rates of perioperative complications of PTAS (4).

Nevertheless, there are still a considerable number of patients with ICAS who remain at high risk of stroke in the real-world despite aggressive medical therapy (5–7). Taking the complications associated with device selection into careful consideration, the exploration for more safe and effective endovascular procedure with the new option of devices for this subgroup of patients challenges both neurologists and neurointerventionists (8–10). Recently, the Neuroform stent had been used for ICAS in several case series (11–13). Thus, for the relatively small sample size, beyond the scope of the indicated uses outlined in the device manual, the experience of the Neuroform EZ stenting for ICAS was still limited. The purpose of the present study was to respectively evaluate the feasibility and safety of this alternative procedure, and preliminarily provide the indications of the Neuroform EZ stent use for medically refractory ICAS in a single-center series.

PATIENTS AND METHODS

Patients

We retrospectively reviewed our patient database to identify individuals with ICAS which had been treated using the Neuroform EZ stent. Clinical and procedural data of included patients were examined by a stroke neurologist (RM) and a neurointerventionist (RZ) independently. The following data were recorded: demographic data, clinical presentation, lesion characteristics, procedural feasibility, complications and follow-up angiographic results. Before data extraction, the inclusion, and exclusion criteria had been defined as follows. Inclusion criteria: (1) Symptomatic ICAS (70–99% stenosis) with hypoperfusion of the stenotic arterial territory. (2) Aggressive medical management (dual antiplatelet medication for at least 3 months) failed to prevent recurrent low-flow TIAs, nondisabling ischemic stroke, or progressive stenosis. (3) The stenotic arterial territory had no sufficient collaterals. Exclusion criteria: (1) Non-atherosclerotic intracranial arterial stenosis, e.g., identified or suspected vasculitis or vessel dissection. (2) Acute cerebral infarction within two weeks. (3) Patients with a baseline modified Rankin score (mRS) of >3 points before the procedure. The demographic characteristics of patients were obtained from the hospital records, including age, gender and ethnicity. Lesion morphology was described as location, Mori classification and whether there was perforator involvement.

Procedure

Angiography and interventional procedures were performed in the interventional suite with a biplane angiography system (Allura Xper FD20/20, Phillips, the Netherlands). Patients were pretreated with aspirin 100 mg/day and clopidogrel 75 mg/day for at least 5 days prior to the procedure, until an adequate response to both aspirin (AA inhibition >70%) and clopidogrel (ADP inhibition >30%) was detected by thromboelastography (TEG). Heparin was given as an intravenous bolus dose of 50 U/kg before the procedure, and a continuous flushing sodium solution (2.5 U/ml) was administered in arterial lines during the procedure(activated clotting time [ACT] maintained around 150-250 s). After general anesthesia and femoral artery cannulation, a 6 F Envoy guiding catheter (Cordis Neurovascular, USA) was placed into the artery proximal to the target lesion. Over a 200-cm Synchro-14 guidewire (Stryker Neurovascular, USA), an Echelon 10 microcatheter (ev3 Neurovascular, USA) was navigated to the distal part of the stenosis. The Synchro guidewire was then retrieved, and through the microcatheter, a 300-cm Transcend exchange wire (Boston Scientific, USA) was advanced into the artery distal to the stenosis. Pre-stent angioplasty was performed with the Gateway balloon (Stryker Neurovascular, USA), balloon sizes were selected to be similar to at least 80% of the diameter of the vessel either proximally or distally to the stenosis, balloons were slowly inflated (1 atm per 10–15 s) up to the nominal pressure. For consecutive stenting, an XT-27 microcatheter (Stryker Neurovascular, USA) was advanced bypass the stenosis over the exchange wire, the Neuroform EZ stent (Stryker Neurovascular, USA) was advanced through the XT-27 microcatheter and positioned until the stenosis was centered between the ends of the stent, and then deployed. After the procedure, intravenous heparin was maintained for the first 24 h, followed by aspirin 100 mg/day and clopidogrel 75 mg/day for at least 6 months, then one (with more optimal platelet inhibition) of the dual antiplatelet agents was administered daily thereafter.

Follow-Up

Follow-up information on clinical and angiographic outcomes was reviewed and collected by a trained neurointerventionist (BL). Clinical follow-up information was obtained from hospital records, in-person visit or telephone interview at 1, 3, 6, and 12 months, and yearly thereafter. Angiographic follow-up was

TABLE 1 | Baseline characteristics of the patients.

Baseline characteristic	Result
Number of patients	45
Age	65 ± 10.8
GENDER	
Male	29 (64.4%)
Female	16 (35.6%)
LESION LOCATION	
Distal ICA	1 (2.2%)
MCA	24 (52.2%)
Distal VA	5 (10.9%)
BA	16 (34.8%)
LESION MORPHOLOGY	
Mori Type A	11 (23.9%)
Mori Type B	28 (60.9%)
Mori Type C	7 (15.2%)
Perforators involvement	27 (58.7%)
No perforators involvement	19 (41.3%)
PREPROCEDURAL PRESENTATIONS	
Hypoperfusion without stroke	16 (35.6%)
Hypoperfusion stroke	23 (51.1%)
Hypoperfusion with perforator strokes	25 (55.6%)

scheduled at ∼6 and 12 months. DSA was routinely used to access the vascular outcomes unless patients refused invasive assessment, in which CTA was used.

Outcomes Assessment

The preoperative and postoperative residual stenosis rate was calculated according to the WASID method (14). The pre- and postoperative neurological status was assessed using mRS and Institutes of Health Stroke Scale (NIHSS). The following data were collected consecutively:

- Technical feasibility: Defined as accurate delivery and deployment of the stent at the site of the target lesion, and improvement of the stenosis to less than 30%.
- Early complications: Defined as the 30-day rate of any procedure-related vascular event (TIA or stroke attributable to the territory of the target artery). A TIA was defined as any ischemic event resulting in a transient neurological deficit but resolved within 24 h. A stroke was defined as any hemorrhagic or ischemic event resulting in a new neurological deficit (scaled by the NIHSS and mRS score) lasting −24 h.
- Late complications: Defined as combined procedure-related permanent neurologic morbidity (scaled by the mRS score) and mortality rate beyond 30 days after PTAS.
- In-stent restenosis (ISR): Defined as luminal diameter stenosis over 50% for at least 6 months after the procedure.

RESULTS

Patients

Between November 2016 and January 2018, 45 consecutive patients underwent Neuroform EZ stenting for symptomatic ICAS, a total of 46 intracranial atherosclerotic lesions were included. Intracranial stenting was performed only when (1) dual antiplatelet medication (aspirin and clopidogrel for at least 3 months) failed to prevent further ischemic events, (2) at least 2 weeks after the new-onset stroke and (3) non-atherosclerotic etiology were excluded. Our Preliminary indications of the Neuroform EZ stent use included (1) lesions involved perforator-bearing segments, (2) lesions in small vessels, (3) lesions with tortuous access vessel, which rendered potential access failure of other stents, and (4) lesions at bifurcations, e.g., top of the basilar artery, distal M1 segments.

Among all the lesions, 2.2% ($n = 1$) located in the distal internal carotid artery (ICA) in, 52.2% ($n = 24$) in the middle cerebral artery (MCA), 10.9% ($n = 5$) in the distal vertebral artery (VA) and 34.8% ($n = 16$) in the basilar artery (BA); Mori type A lesions were 23.9% ($n = 11$), type B were 60.9% ($n = 28$) and type C were 15.2% ($n = 7$); perforator branches involved in 58.7% ($n = 27$) of the lesions. The lesion-related presentations prior to procedure were classified as (1) hypoperfusion without stroke in 35.6% ($n = 16$), (2) hypoperfusion stroke 51.1% ($n = 23$), and (3) hypoperfusion with perforator strokes in 55.6% ($n = 25$). The baseline characteristics of the patients are shown in **Table 1**.

Technical Feasibility and Vascular Outcome

The technical success rate was 100%. After treatment, the degree of stenosis was reduced to less than 30% (mean 23.7 ± 18.1%). Catheter angiography or computed tomography angiography (CTA) follow-up were obtained in 33 patients (73.3%). No recurrent stenosis was noted in all these patients with a mean follow-up period of 7.3 month. In total, 12 patients (26.7%) refused to undergo repeated DSA or CTA examination during the follow-up period. Of these, the preoperative and postoperative stenosis rate was (80.7 ± 7.3%) and (20.7 ± 13.7%), respectively. No deterioration of neurological function was noted in the clinical follow-up (mean 8.8 month) records of all these patients. Between different subgroups (Anterior circulation vs. Posterior circulation, Perforator-bearing vs. Non-perforator-bearing), no significant different was found in the outcomes. For the primary outcomes of different lesion types, differences between the subgroups were not statistically significant. The clinical variables of the patients in the different subgroups are shown in **Table 2**. Examples of Neuroform EZ stenting for ICAS are provided in **Figures 1–3**.

Complications

- Early complications: The combined procedure related any vascular event rate within 30 days was 2.2% ($n = 1$). The patient was a 28-year-old male, he presented with recurrent episodes of right-sided hemianesthesia and aphasia over the prior year. He had a medical history of hypertension (first diagnosed 3 years ago), smoking (15 years, 10 cigarettes per day), alcohol consumption (10 years, 500 ml of white liquor per day) and a right anterior cerebral artery stroke (3 years previously, with no obvious sequelae, mRS = 0). A preprocedural angiogram revealed high-grade stenosis of the

TABLE 2 | The clinical variables of the patients.

	All lesions	Anterior circulation	Posterior circulation	Perforator-bearing	Non-perforator-bearing
No. of lesions	46	25	21	26	20
Preoperative stenosis rate (%)	86.5 ± 8.7	84.1 ± 7.1	89.6 ± 9.6[a]	82.7 ± 7.5	92.1 ± 7.1[b]
Postoperative stenosis rate (%)	23.7 ± 18.1	22.1 ± 12.8	24.6 ± 19.4[a]	20.4 ± 14.5	27.5 ± 15.7[b]
Average follow-up time (months)	8.6	8.9	8.2	8.5	8.8
Procedure-related complication at 30 days *n* (%)	1(2.2)	1(4)	0	1(3.8)	0
In-stent restenosis rate	0	0	0	0	0

[a]*compared with the anterior circulation group ($p > 0.05$),* [b]*compared with the perforator-bearing group ($p > 0.05$).*

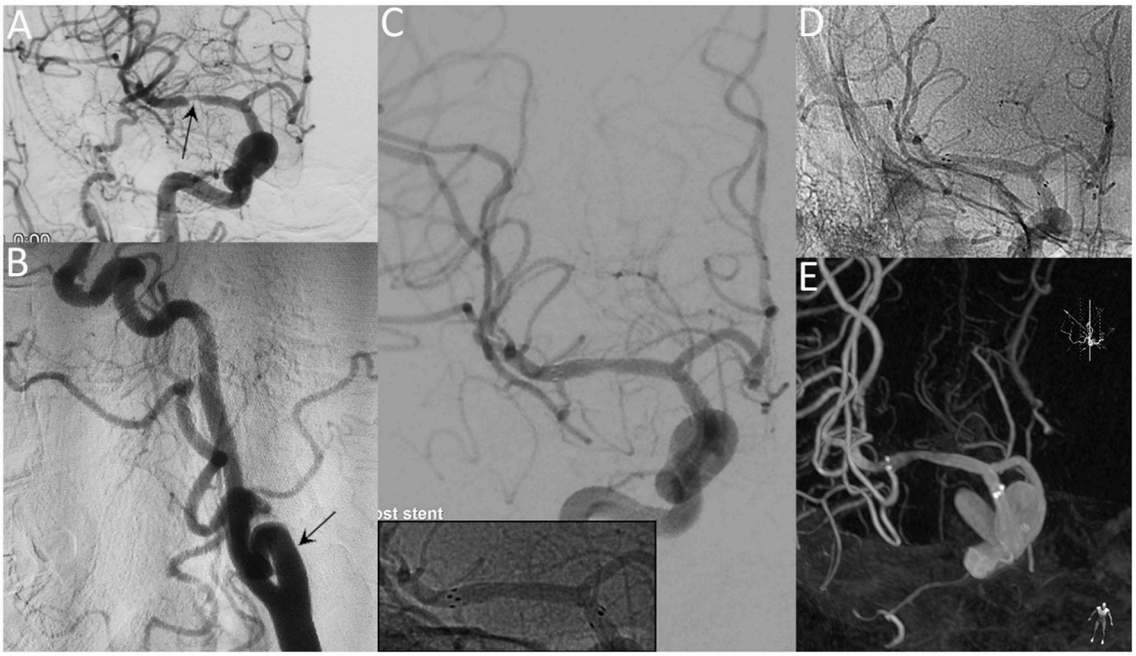

FIGURE 1 | A 65-year-old female with a significant symptomatic stenosis of the right MCA. Preprocedural DSA images demonstrate high-grade stenosis (arrow) **(A)** and the tortuous right ICA (arrow) **(B)**. Postprocedural DSA images **(C)** reveal a residual stenosis of 10% (Insert: radiopaque markers of the stent). Unsubtracted angiogram **(D)** and XperCT **(E)** reveal patent stent with good apposition at the 8-month follow-up.

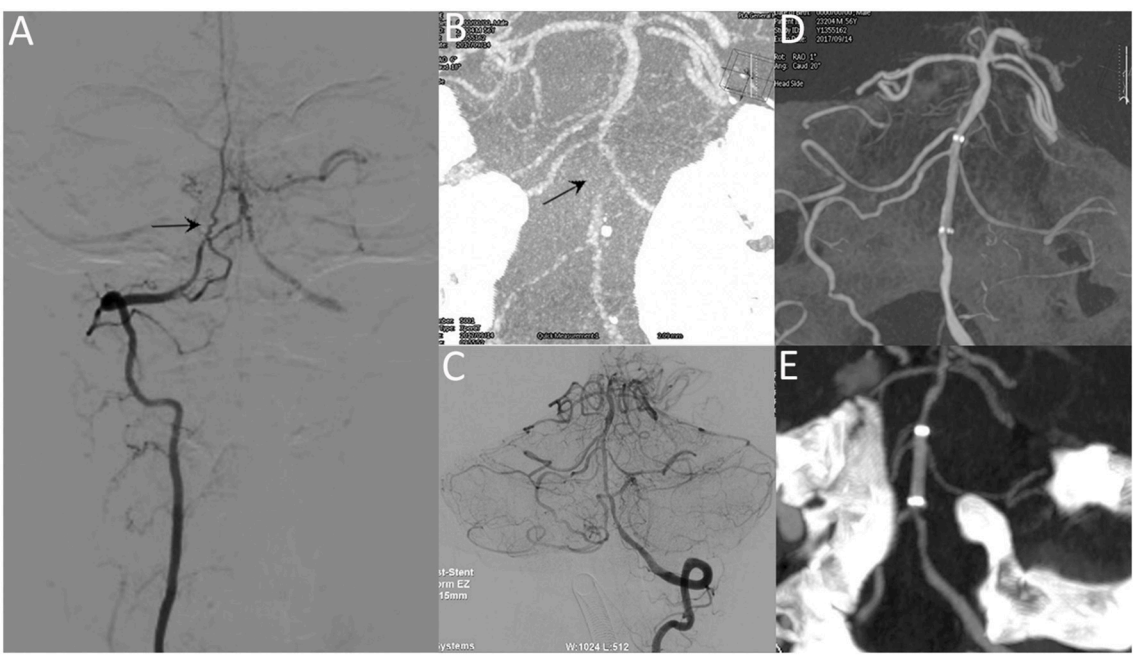

FIGURE 2 | A 53-year-old male with repeated episodes of posterior circulation transient ischemic attacks. Preprocedural DSA image **(A)** and VasoCT **(B)** reveal near-occlusion of the basilar artery (arrow). Postprocedural DSA images **(C)** reveal patency of the basilar artery. Postprocedural XperCT **(D)** demonstrates good wall apposition of the stent. Follow-up CTA image **(E)** reveals the patent stent with good apposition 6 months after the procedure.

left M1 segment. The procedure was performed uneventfully (Gateway 15/9 mm for pre-stent angioplasty, Neuroform EZ 3/20 mm for stenting), with a 20% residual stenosis of the artery. When the patient regained consciousness after general anesthesia, no neurological deficit was detected. Forty-eight hours after the procedure he began to develop numbness and weakness in his right leg and arm (4^{+}/5 power, NIHSS = 2). An urgent CT scan revealed no hemorrhagic

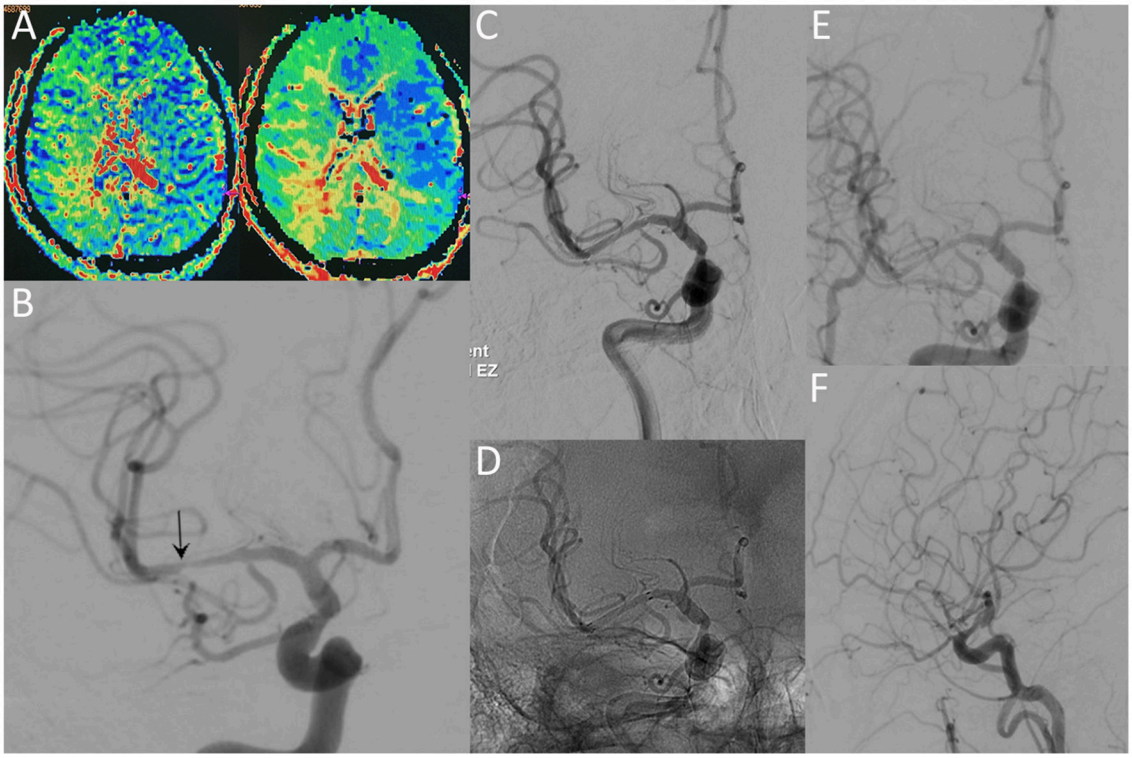

FIGURE 3 | A 36-year-old male with a significant stenosis in the right MCA. CT perfusion images **(A)** reveal a prolongation of MTT and TTP before the procedure. Preprocedural DSA image **(B)** demonstrates high-grade stenosis close to the MCA bifurcation (arrow). Postprocedural DSA images **(C,D)** reveal patency of the MCA without residual stenosis. The 12-month follow-up DSA images **(E,F)** reveal no ISR in the region of the originally stented lesion.

changes, and intravenous IIb/IIIa inhibitor (tirofiban) was administered. The patient deteriorated within 6 h after the symptom onset, MR images reveal new infarctions and hypoperfusion in the territories of the left MCA. He had 1/5 power in the right upper limb and 2/5 in the right lower limb with slurred speech (NIHSS = 14) before a second procedure. During the second procedure, DSA image demonstrates complete occlusion of the left MCA. After the intra-arterial administration of IIb/IIIa inhibitor and solitaire stent (6/20 mm) deployment, the occluded MCA was gradually recanalized (TICI 3). No significant improvement of neurological functions was achieved after the procedure. The patient was discharged 50 days later, maintained right-sided plegia and slurred speech (NIHSS = 10, mRS = 5) (**Figure 4**).

- Late complications: No procedure related permanent neurologic morbidity and mortality rate beyond 30 days was noted during 8.6 months of mean follow-up.

DISCUSSION

Neuroform EZ: A Promising Optional Device for ICAS Stenting

As a self-expanding intracranial stent, the Neuroform stent was initially developed to assist the coiling of wide-necked intracranial aneurysms (8). Subsequently, the Wingspan stent was developed for the endovascular treatment of ICAS as a design variant with an optimized delivery system and radial force (9). However, the Gateway-Wingspan system failed in the SAMMPRIS trial for creating too many complications (4). Yet, despite advances in medical therapy, patients with recalcitrant ICAS may continue to experience TIAs and strokes, especially for the Asian population (10). It is these patients for whom the endovascular therapy was mandatory, even, recent examination in large trials showed no benefit of this intervention. Regarding various salient features of ICAS lesions, a lesion-specific design of procedures with dedicated devices might help to resolve this issue, instead of the exclusive option for devices approved by the Food and Drug Administration (FDA). As an alternative, the Neuroform stent had been used for ICAS in several case series (11–13). Thus, for the relatively small sample size (3 trials, 14 patients totally), beyond the scope of the indicated uses outlined in the device manual, the experience of the Neuroform EZ stenting for ICAS was still limited. In the present study, our results revealed that selected ICAS stenting with Neuroform EZ stent was safe and efficacious. Moreover, focused analysis of lesions of this series would help neurointerventionists in selecting the most appropriate device for ICAS stenting on the basis of individualized decision making.

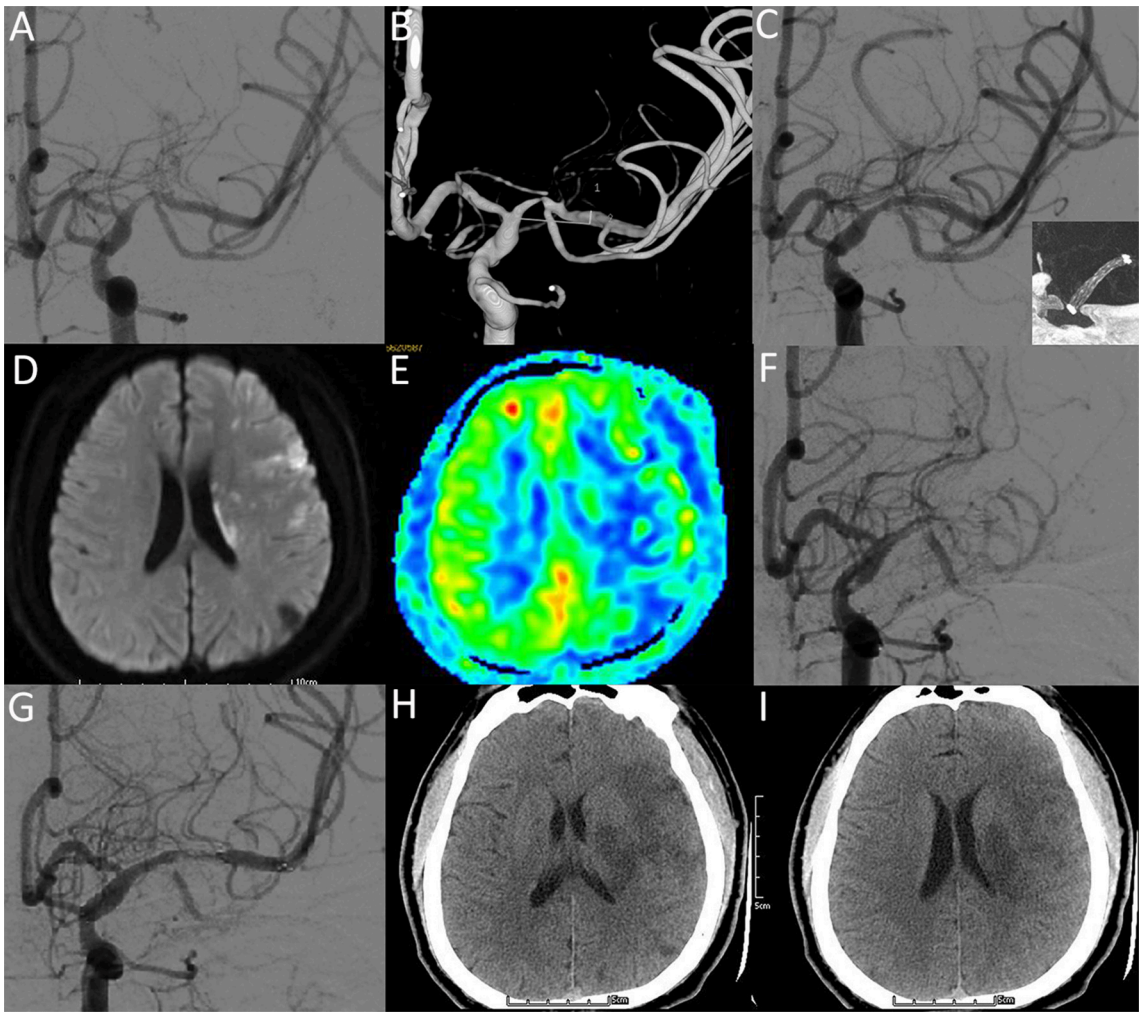

FIGURE 4 | A 28-year-old male with a significant symptomatic stenosis of the left M1 segment. **(A,B)** Preprocedural DSA image demonstrates high-grade stenosis. **(C)** Postprocedural DSA image demonstrates a 20% residual stenosis (NIHSS: 0). Insert: VasoCT showing patent stent lumen with good stent vessel apposition. **(D-F)** Two days after stenting, DWI **(D)** and ASL **(E)** images reveal new infarctions and hypoperfusion in the territories of the left MCA (NIHSS: 14). DSA image **(F)** demonstrates complete occlusion of the left MCA. After the intra-arterial administration of IIb/IIIa inhibitor and solitaire stent deployment, DSA image **(G)** demonstrates recanalized flow of MCA (NIHSS: 14). Five days after recanalization, CT images **(H,I)** reveal hypointense lesions within the territories of the left MCA (NIHSS: 10).

Neuroform EZ for ICAS Stenting:Relationship Between Device Physical Properties and Procedural Outcome

In the prematurely halted SAMMPRIS trial, poor outcomes are largely attributable to ischemic stroke secondary to perforator branch occlusion (4, 15). The mechanism of perforator stroke has mainly been demonstrated by plaque shift after deployment of a stent with relative higher radial force (16). Although higher radial force may result in larger lumen for achieving improved flow, the atheromatous debris of the plague entrapped between expanding stent struts and the arterial wall might be forced into perforator ostia (**Figure 5**), which was termed "snowplowing" effect and may pose a major risk of perforator occlusion related to stenting. Hence, device-related complications should be carefully taken into consideration in the stents selection for ICAS. In an *in vitro* examination, while expanding the vessel diameter at about 85% of the labeled diameter, the Wingspan stent produces nearly a 0.5-fold increase in chronic radial strength as compared with Neuroform (17). Theoretically, given the physical properties, a stent with appropriate radial force might help to solve the "snowplowing" problem. In the present series, as we expected, with the utilization of Neuroform EZ stent, our results revealed that the periprocedural complication rates reduced to 2.2% (1), especially for a 7.2% drop of perforator event compare with the SAMMPRIS subgroup [15 [7.2%] of 21 [10.1%] for ischemic complications] (15). The rationale behind the present results might be that the Neuroform EZ stent was more flexible than Wingspan, exert reduced outward radial force. In another post-SAMMPRIS prospective trial for the individualized treatment of ICAS, with the exclusion criteria of perforator territory strokes

before the procedure, positive results were also yielded in a subgroup with device selection limited to Wingspan (18). Thus, in our study, patients presented with perforator territory strokes were not excluded (55.6%), the outcome was even better than previous studies. This suggested that Neuroform EZ stenting may be beneficial in the selected subset of ICASs with a higher risk of procedure-related perforator infarct.

Another major influence on the outcome of ICAS stenting trials was the in-stent restenosis (ISR). As a device-related trigger of ISR, intimal hyperplasia may be stimulated by the outward radial force of the stent. The Wingspan stent is a self-expandable stent (SES) with a relatively high radial opening force. In contrast, the Neuroform EZ stent is a SES with reduced radial force compared to the Wingspan stent (19, 20). In this study, the angiographically demonstrated pre-procedural stenosis rate was 86.5 ± 8.7%, imaging follow-up (mean 7.3 months) revealed no ISR occurred, which was lower than published trials with stents of higher radial force (21, 22). In another group of patients treated with a drug-eluting coronary stent (DES), a substantially lower ISR of 3.8% could be achieved with an acceptable procedural complication rate of 0.9%. However, 7% of the procedures failed due to the high rigidity of the stent system (23). Under the hypothesis that more flexible stents will be less likely to result in ISR than one with high radial force, the Enterprise stent or the Solitaire stent also have been used in several series. Yet, compared to our results, the rate of ISR in these studies (24.7% for Enterprise, 11.4% for Solitaire) was not significantly lower (20, 24). Mechanically, appropriate rigidity should be taken into account when the more flexible device was adopted in ICAS stenting, so as to exert adequate radial force to resist the elastic recoil of the target vessel while promoting the ability to navigate in tortuous vessels. Certainly, there is no stent that is superior in all clinical and technical requirements. Therefore, clinical advantages of ICAS stenting should be based on the focused analysis of location and morphology of the ICAS lesions as well as device physical properties.

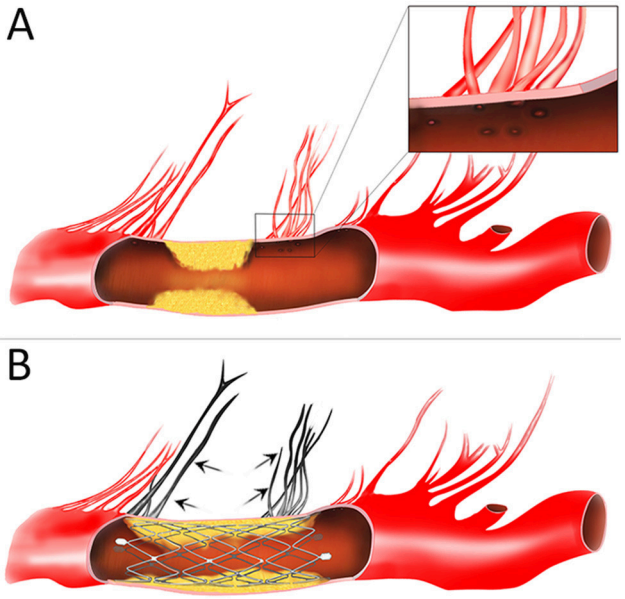

FIGURE 5 | Schematic diagram of the "snow-plowing" effect. **(A)** An intracranial atherosclerotic arterial stenosis with perforator vessels. Inset: the magnified view of perforator ostia. **(B)** After stent deployment, forceful displacement of the plaque causes occlusion of the perforator vessels (arrow).

Neuroform EZ for ICAS Stenting:Preliminary Lesion-Specific Recommendations And Modified Techniques

The features of ICAS lesions is likely diversiform in nature. Different types of symptomatic intracranial stenosis may respond differently to interventional strategy. Even for skilled

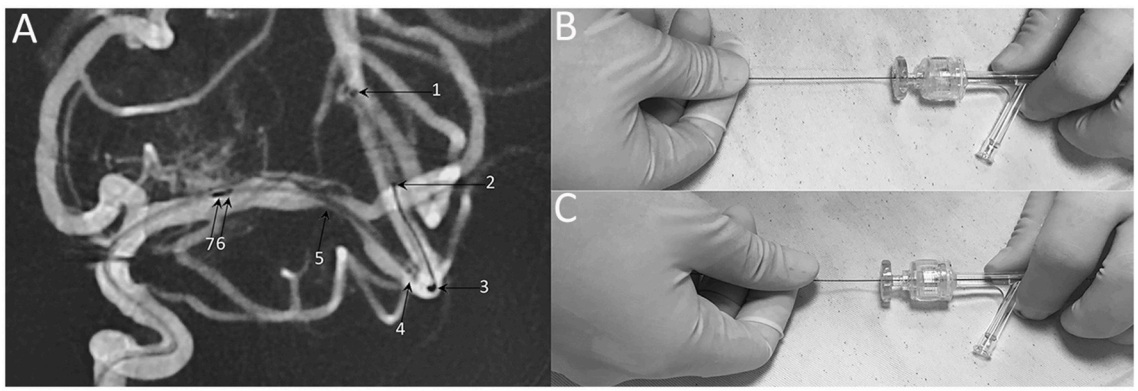

FIGURE 6 | Technical note of Neuroform EZ stent deployment. **(A)** Representative DSA image of stent deploying, demonstrating the radiopaque markers of 1: XT-27 microcatheter tip, 2: distal tip of the delivery wire, 3: distal bumper, 4: distal stent markers, 5: stenosis 6: stent proximal markers, 7: proximal bumper. **(B)** When the stent was ready to be deployed, holding the stent delivery wire at a sufficient distance (about 8-10 cm) from the RHV. **(C)** Insufficient distance may cause unnecessary hand movement and poor stent apposition.

neurointerventionists, in case of ICAS stenting, positive outcomes would depend not only on patient selection, but also the procedural techniques with given specific devices. Based on our experience with the use of the Neuroform EZ stents for ICAS, the lesion-specific recommendations and modified techniques are preliminarily summarized as follows:

Lesion-specific recommendations: (1) lesions with tortuous access vessel (**Figure 1**), (2) lesions involving small vessels (**Figure 2**), (3) lesions close to or across a bifurcation (**Figure 3**).

Modified techniques: (1) balloon and stent size selection: balloon sizes were selected to be similar to at least 80% of the diameter of the vessel either proximally or distally to the stenosis; the stent diameter was sized to exceed the diameter of the proposed artery by 0.5–1.0 mm, the stent length was selected to exceed the length of the lesion by at least 3 mm on both sides; (2) microcatheter position: the tip of XT-27 microcatheter should be distal enough to the lesion to preserve sufficient length of landing zone to accommodate the distal tip (19 mm) of the stent delivery wire (**Figure 6A**); (3) stent deployment: when the stent was ready to be deployed, holding the stent delivery wire at a sufficient distance (about 8–10 cm) from the RHV to avoid unnecessary hand movement during stent deployment (**Figures 6B,C**).

LIMITATIONS OF THIS STUDY

First, this retrospective study was more prone to a certain bias compared with the prospective randomized trial. Second, our study was conducted at a single institution, and the population-specific experiences may not be globally generalized. Certainly, multicenter studies with larger sample size and long-term follow-up period are needed to confirm the clinical and angiographic results of this study.

CONCLUSION

The off-label use of Neuroform EZ stent might lower procedural complications in stenting for many medically refractory ICASs. Our initial experience provides feasibility and safety data to guide future alternative procedures with Neuroform EZ in ICAS stenting. Due to the respective nature of this study, longer-term follow-up and further randomized trials are still mandatory to determine the durability and viability of our promising results.

ETHICS STATEMENT

This study was performed with approval from the institutional ethics committee of Chinese PLA General Hospital (NO:S2018-060-01). All patients or their authorized representative were explicitly informed and gave written informed consent to the off-label use of the Neuroform EZ stent.

AUTHOR CONTRIBUTIONS

ZD and JM performed the analysis and wrote the paper. SY and CT contributed to data analysis. JW, ZD, XC, and XL performed the interventions and were responsible for patients care and management. RM, RZ, and BL contributed to acquisition of data. JW contributed to the study design and critical revision of the manuscript.

REFERENCES

1. Holmstedt CA, Turan TN, Chimowitz MI. Atherosclerotic intracranial arterial stenosis: risk factors, diagnosis, and treatment. *Lancet Neurol.* (2013) 12:1106–14. doi: 10.1016/S1474-4422(13)70195-9
2. Fiorella D, Levy EI, Turk AS, Albuquerque FC, Niemann DB, Aagaard-Kienitz B, et al. US multicenter experience with the Wingspan stent system for the treatment of intracranial atheromatous disease: periprocedural results. *Stroke* (2007) 38:881–7. doi: 10.1161/01.STR.0000257963.65728.e8
3. Fiorella D, Turk AS, Levy EI, Pride GL, Woo HH, Albuquerque FC, et al. US wingspan registry: 12-month follow-up results. *Stroke* (2011) 42:1976–81. doi: 10.1161/STROKEAHA.111.613877
4. Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med.* (2011) 365:993–1003. doi: 10.1056/NEJMoa1105335
5. Zaidat OO, Fitzsimmons BF, Woodward BK, Wang Z, Killer-Oberpfalzer M, Wakhloo A, et al. Effect of a balloon-expandable intracranial stent vs medical therapy on risk of stroke in patients with symptomatic intracranial stenosis: the VISSIT randomized clinical trial. *JAMA* (2015) 313:1240–8. doi: 10.1001/jama.2015.1693
6. Turan TN, Cotsonis G, Lynn MJ, Wooley RH, Swanson S, Williams JE, et al. Intracranial stenosis: impact of randomized trials on treatment preferences of US neurologists and neurointerventionists. *Cerebrovasc Dis.* (2014) 37:203–11. doi: 10.1159/000358120
7. Sangha RS, Naidech AM, Corado C, Ansari SA, Prabhakaran S. Challenges in the medical management of symptomatic intracranial stenosis in an Urban setting. *Stroke* (2017) 48:2158–63. doi: 10.1161/STROKEAHA.116.016254
8. Henkes H, Bose A, Felber S, Miloslavski E, Berg-Dammer E, Kühne D. *Endovascular coil* occlusion of intracranial aneurysms assisted by a novel self-expandable nitinol microstent (neuroform). *Interv Neuroradiol.* (2002) 8:107–19. doi: 10.1177/159101990200800202
9. Henkes H, Miloslavski E, Lowens S, Reinartz J, Liebig T, Kühne D. Treatment of intracranial atherosclerotic stenoses with balloon dilatation and self-expanding stent deployment (WingSpan). *Neuroradiology* (2005) 47:222–8. doi: 10.1007/s00234-005-1351-2
10. Mehndiratta MM, Khan M, Mehndiratta P, Wasay M. Stroke in Asia: geographical variations and temporal trends. *J Neurol Neurosurg Psychiatry* (2014) 85:1308–12. doi: 10.1136/jnnp-2013-306992
11. Turk AS, Ahmed A, Niemann DB, Aagaard-Kienitz B, Brooks N, Levine RL. Utilization of self-expanding stents in the treatment of intracranial atherosclerotic disease in the distal small cerebral vessels. *Neuroradiology* (2007) 49:659–63. doi: 10.1007/s00234-007-0229-x
12. Rohde S, Seckinger J, Hähnel S, Ringleb PA, Bendszus M, Hartmann M. Stent design lowers angiographic but not clinical adverse events in stenting of symptomatic intracranial stenosis - results of a single center study with 100 consecutive patients. *Int J Stroke* (2013) 8:87–94. doi: 10.1111/j.1747-4949.2011.00715.x
13. Hähnel S, Ringleb P, Hartmann M. Treatment of intracranial stenoses using the neuroform stent system: initial experience in five cases. *Neuroradiology* (2006) 48:479–85. doi: 10.1007/s00234-006-0081-4
14. Samuels OB, Joseph GJ, Lynn MJ, Smith HA, Chimowitz MI. A standardized method for measuring intracranial arterial stenosis. AJNR Am *J Neuroradiol.* (2000) 21:643–6.
15. Fiorella D, Derdeyn CP, Lynn MJ, Barnwell SL, Hoh BL, Levy EI, et al. Detailed analysis of periprocedural strokes in patients undergoing intracranial stenting in Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS). *Stroke* (2012) 43:2682–8. doi: 10.1161/STROKEAHA.112.661173

16. Fujimoto M, Shobayashi Y, Takemoto K, Tateshima S, Viñuela F. Structural analysis for wingspan stent in a perforator model. *Interv Neuroradiol.* (2013) 19:271–75. doi: 10.1177/159101991301900302
17. Krischek Ö, Miloslavski E, Fischer S, Shrivastava S, Henkes H. A comparison of functional and physical properties of self-expanding intracranial stents [Neuroform3, Wingspan, Solitaire, Leo(+), Enterprise]. *Minim Invasive Neurosurg.* (2011) 54:21–8. doi: 10.1055/s-0031-1271681
18. Miao Z, Song L, Liebeskind DS, Liu L, Ma N, Wang Y, et al. Outcomes of tailored angioplasty and/or stenting for symptomatic intracranial atherosclerosis: a prospective cohort study after SAMMPRIS. *J Neurointerv Surg.* (2015) 7:331–5. doi: 10.1136/neurintsurg-2014-011109
19. Kim M, Levy EI, Meng H, Hopkins LN. Quantification of hemodynamic changes induced by virtual placement of multiple stents across a wide-necked basilar trunk aneurysm. *Neurosurgery* (2007) 61:1305–12. doi: 10.1227/01.neu.0000306110.55174.30
20. Vajda Z, Schmid E, Güthe T, Klötzsch C, Lindner A, Niehaus L, et al. The modified Bose method for the endovascular treatment of intracranial atherosclerotic arterial stenoses using the Enterprise stent. *Neurosurgery* (2012) 70:91–101. doi: 10.1227/NEU.0b013e31822dff0f
21. Albuquerque FC, Levy EI, Turk AS, Niemann DB, Aagaard-Kienitz B, Pride GL Jr, et al. Angiographic patterns of Wingspan in-stent restenosis. *Neurosurgery* (2008) 63:23–7. doi: 10.1227/01.NEU.0000335067.53190.A2
22. Zhu SG, Zhang RL, Liu WH, Yin Q, Zhou ZM, Zhu WS, et al. Predictive factors for in-stent restenosis after balloon-mounted stent placement for symptomatic intracranial atherosclerosis. *Eur J Vasc Endovasc Surg.* (2010) 40:499–506. doi: 10.1016/j.ejvs.2010.05.007
23. Vajda Z, Aguilar M, Göhringer T, Horváth-Rizea D, Bäzner H, Henkes H. Treatment of intracranial atherosclerotic disease with a balloon-expandable paclitaxel eluting stent procedural safety, efficacy and mid-term patency. *Clin Neuroradiol.* (2012) 22:227–33. doi: 10.1007/s00062-011-0125-y
24. Duan G, Feng Z, Zhang L, Zhang P, Chen L, Hong B, et al. Solitaire stents for the treatment of complex symptomatic intracranial stenosis after antithrombotic failure: safety and efficacy evaluation. *J Neurointerv Surg.* (2016) 8:680–4. doi: 10.1136/neurintsurg-2015-011734

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CASE REPORT
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Optical Coherence Tomography of Spontaneous Basilar Artery Dissection in a Patient With Acute Ischemic Stroke

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The diagnosis of intracranial arterial dissection (IAD) may be challenging and multimodal imaging techniques are often needed to confirm the diagnosis. Previous studies have based their criteria for diagnosis of IAD on conventional angiography, computed tomography, or magnetic resonance imaging. We report a case with acute ischemic stroke due to spontaneous basilar artery dissection in which intravascular optical coherence tomography (OCT) was used to show features of IAD. A 59-years-old woman presented with symptoms of acute ischemic stroke. Thrombosis related to basilar artery (BA) stenosis was assumed on conventional angiography; however, no clot was retrieved after mechanical thrombectomy (MT) and a restored BA caliber was observed after a rescue recanalization with the detachment of a self-expanding stent was performed. Spontaneous IAD was suspected; however, angiographic findings were ambiguous for confirming IAD. The patient remained symptom-free until 18-months follow-up. At this point, angiography showed restenosis at the proximal tapered length of the stent. *In vivo* OCT was performed to assess the pathological changes of the restenosis and confirm the diagnosis of IAD.OCT revealed BA dissection with the presence of remnant transverse flap, double lumen and mural hematoma. Imaging at multiple levels identified intimal disruption that originated in the right vertebral artery and extended distally to the BA. The use of intravascular imaging with OCT enabled the accurate diagnosis of IAD. Care should be taken as the procedure may add additional risks to the patient. Future studies are needed to validate the safety of OCT in IAD.

Keywords: spontaneous intracranial arterial dissection, intravascular optical coherence tomography, acute ischemic stroke, imaging diagnosis, feasibility, safety

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BACKGROUND

Spontaneous intracranial artery dissection (IAD) is uncommon, with its incidence estimated to be lower than that of cervical artery dissection (2.6–3.0/100,000/year) among patients of European ethnic origin (1, 2). In Italy, the prevalence of IAD was 23/4400 (0.5%) among patients with a diagnosis of cerebral ischemia (3). Another study from France demonstrated spontaneous IAD to account for 3.3% (13/391) of patients with acute ischemic stroke due to large vessel occlusion

(LVO) (4). However, in Asia, IAD is not such a rare diagnosis with its reported prevalence of up to 20.5% (192/937) among patients with intracranial atherosclerotic narrowing on TOF-MRA (5). In Korea and Taiwan, IAD accounted for up to 67–78% of all cervicocephalic artery dissections (6, 7). Therefore, IAD may be an important cause of acute ischemic stroke and should be considered in young patients with acute intracranial LVO.

The diagnosis of IAD may be challenging due to the small size of intracranial arteries and non-specific radiological signs. Multimodal imaging techniques are often needed to confirm the diagnosis of IAD (8). In most cases, IAD is defined based on angiographic criteria rather than magnetic resonance imaging given its clinical presentation as an acute stroke (4, 8).The prevalence of the pathognomonic finding of IAD—the mural hematoma may be underdiagnosed by luminal examination alone and many Asian patients with IAD may be misclassified as having intracranial atherosclerotic disease (5). Intra-arterial Optical Coherence Tomography (OCT) is a novel catheter-based imaging technique that uses coherent light to capture micrometer-resolution with two—and three-dimensional images of the vessel wall. The sharp delineation of the luminal borders on OCT enables assessment of the vessel dissection, tissue prolapse, and stent-vessel interactions (9). Although it was initially approved for imaging of coronary arteries, OCT has been used to identify extracranial traumatic aneurysms (10), assess carotid arteries (11), and evaluate intracranial atherosclerotic disease (12). Nevertheless, *in vivo* imaging on IAD pathology has not been well described in the medical literature. In the present case, OCT was used to assess the intravascular changes of the intracranial arterial wall in a patient with basilar artery (BA) dissection. The utility and safety concern of OCT as an imaging modality in the diagnosis of IAD are discussed.

CASE PRESENTATION

History and Findings

A 59-years-old woman presented with sudden onset of lethargy, slurred speech, and left extremity weakness since 5 h. Neurological examination indicated right gaze preference, dysarthria, and decreased muscle strength on the left side (grade II). The patient had a NIHSS score of 8. Previously, the patient presented with paroxysmal dizziness for 1 year and had no history of brain trauma. No intravenous tissue plasminogen activator (tPA) was given since symptom onset was 5 h after presentation to the emergency room.

Angiography and Recanalization Approaches

The patient was admitted and transferred to the catheter room 5.5 h after the onset of symptoms. Digital subtraction angiography (DSA) demonstrated a filling defect caused by a long segment severe stenosis in the BA, which was first assumed to be intraluminal clot related to BA stenosis. After a 6Fr guiding catheter (Envoy, Cordis) was placed into the right vertebral artery (VA), a microcatheter (REBAR-21, Covidien) co-axially assembled with a 0.014-inch Synchro Standard microwire (Stryker, Neurovascular) was used to traverse through the lesion. A self-expanding stent retriever (SOLITAIRE AB 6–30 mm, Covidien) was deployed across the lesion. Mechanical thrombectomy (MT) was performed; however, no clot was found. Repeat DSA showed even worse antegrade flow. It was decided to deploy the stent retriever which lead to restored caliber of the BA. IAD rather than ICAS was suspected. Nevertheless, conventional DSA failed to confirm the diagnosis of IAD. After the procedure, the patient regained consciousness and speech without gaze preference. The muscle strength on the left side recovered to grade III. Intravenous platelet glycoprotein IIb/IIIa receptor inhibitors (Tirofiban, Yuanda Pharmaceuticals, Wuhan, China) was maintained (5 ml/h) for 18 h after the procedure. Double anti-platelet regimen (aspirin 100 mg plus clopidogrel 75 mg per day) was given for 3 months (aspirin 100 mg alone thereafter). Post-operative Diffusion-weighted imaging (DWI) showed acute infarctions in the right pons and occipital lobe (**Figure 1**). The patient had a NIHSS score of 2 at discharge and 0 at 3-months follow-up, respectively. The modified Ranking Score at 3 months was 1.

Follow-up Angiography

The patient had no recurrent symptoms until 18-months follow-up. She was transferred to our institute due to paroxysmal dizziness and blurred vision for the past month. In-sent restenosis was confirmed on follow-up angiography (85% based on WASID criteria) (13). The restenosis was located within the proximal tapered area of the SOLITAIRE stent (**Figure 2**).

Optical Coherence Tomography (OCT) Procedure and Interpretation

The need for further intervention of this restenosis was uncertain based on DSA alone. Therefore, OCT was performed in order to assess the underlying cause of restenosis and confirm the diagnosis of IAD. The patient has signed informed consent regarding the use of OCT which was approved by the local Institutional Review Board. The intravascular frequency-domain OCT system (ILUMIEN OPTIS, OCT Intravascular Imaging System; St. Jude Medical) was used. After conventional angiography, the patient was placed under general anesthesia. A bolus of 5,000 units of intravenous heparin was administrated. With a 6Fr intermediate catheter (NAVIEN 115 cm long, Covidien) placed in the right VA, a 0.014 inch 300 cm long microwire (PILOT 150, Abbott) co-axially assembled with a microcatheter (ECHELON-10, Covidien) was carefully advanced through the proximal stent marker, the area of restenosis, and placed in the right posterior cerebral artery (PCA). After that, the microcatheter was exchanged for a 2.7Fr OCT imaging catheter (Dragonfly Duo; LightLab Imaging, Inc., St. Jude Medical).The short "monorail" design of the Dragonfly catheter did not permit its proximal marker to enter the PCA despite many attempts. After the catheter was advanced as far as in the mid-BA, control angiography demonstrated the opacification of the BA dissection.

Imaging at multiple levels was performed along the BA with an automatic pullback speed (36 mm/s) during blood clearance by the injection of contrast medium. The OCT data were analyzed by the ILUMIEN OPTIS Imaging System. OCT imaging demonstrated visualization of a dissection and poor stent strut

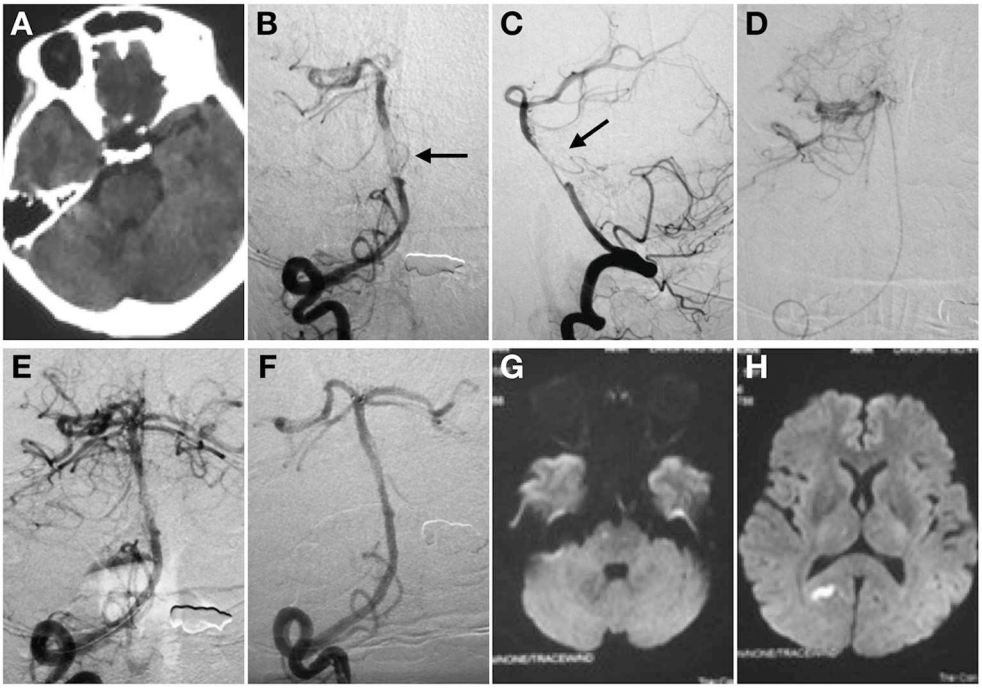

FIGURE 1 | Spontaneous basilar artery (BA) dissection causing acute ischemic stroke. Non-contrast CT **(A)**. Anterior **(B)**, and lateral **(C)** projection of angiography before stent deployment. There is a "non-occlusive thrombus" in the mid-BA with regular residual lumen **(C)**. Intracranial atherosclerotic stenosis was then suspected (black arrow). The super -selective angiography control was performed to confirm the tip of the microcatheter in the real lumen **(D)**. Angiography after the first mechanical thrombectomy maneuver **(E)**. No clot was found. Angiography immediately after stent detachment showed the stent restored the BA caliber **(F)**. The distal marker of the stent lined up with the BA tip whereas the proximal marker was located within the right vertebral artery. MRI in transverse DWI section showed acute infarctions in right pons **(G)** and occipital lobe **(H)** after procedure.

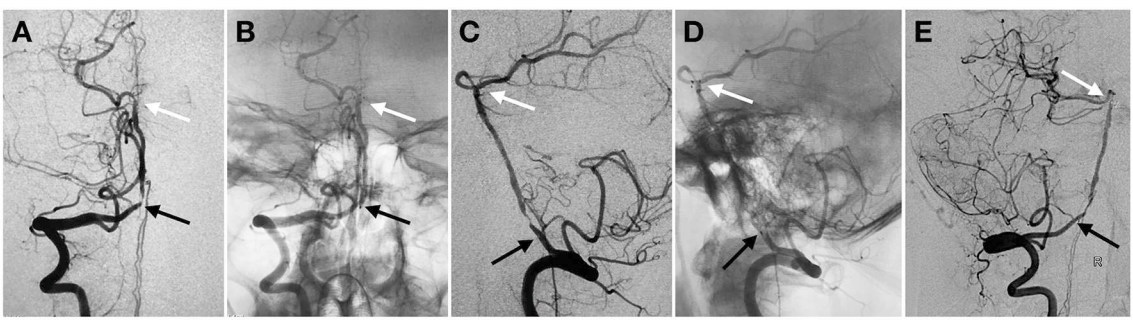

FIGURE 2 | Proximal in-stent restenosis on 18-months follow-up angiography. Anterior **(A,B)** and lateral **(C,D)** view of subtracted **(A,C)** and un-subtracted angiography **(B,D)** in right VA demonstrated proximal stenosis within the tapered length of the stent construct. Oblique view of the angiography **(E)**. Black and white arrow indicated proximal and distal markers of the stent, respectively.

wall apposition (**Figure 3**). The intimal disruption was limited to the VA and the false lumen extended into the BA. There were no clot formation or tissue prolapse within the stent. After the OCT imaging catheter was withdrawn, control angiography demonstrated rapid antegrade flow and improved lumen at the site of the previously demonstrated restenosis. No progressive stenosis or occlusion was noted after 10 min observation and no additional intervention was needed. The patient was given intravenous Tirofiban for 24 h after procedure. She had no symptoms and was discharged without neurological deficits 3 days after the procedure.

DISCUSSION

In vivo intravascular imaging of the vessel wall includes intravascular ultrasound (IVUS) and OCT. IVUS is the first intravascular imaging modality, which involves the advancement of a miniaturized ultrasound probe to the arteries. The probe

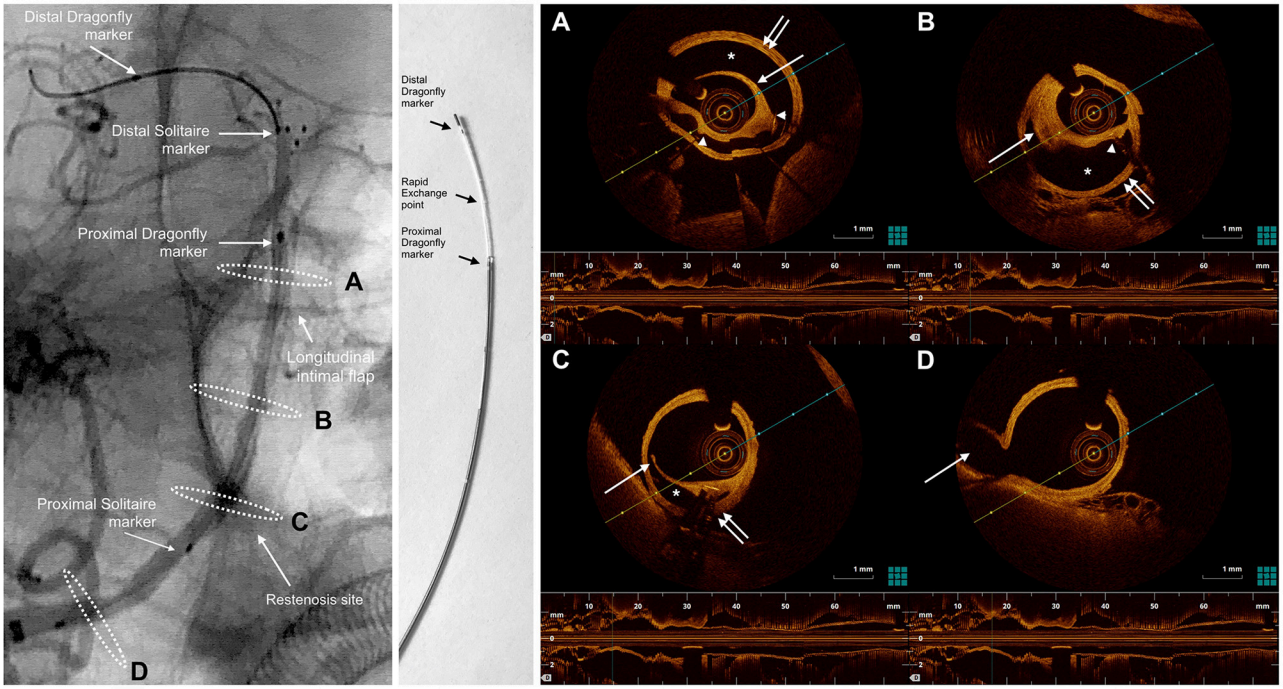

FIGURE 3 | oblique view from an un-subtracted angiography of the right vertebral artery shows right VA dissection extending to BA. The markers of the SOLITAIRE stent and the Dragonfly Duo OCT imaging catheter are noted in the left panel. White dashed ellipses on the left panel correspond to the cross-sections of the OCT acquisition (right). The Dragonfly Duo imaging catheter is illustrated in the middle. **(A)**, the OCT image demonstrated a severe dissection (*), between the intima (single white arrow) and media (double white arrow). Poor strut-wall apposition was noted (struts indicated by the white arrowheads). **(B)**, 10 mm proximal to the cross-section A, there was a mural hematoma (single white arrow) within the dissection. The intima was complete without disruption. The false lumen (*) between the intima and media (double white arrow) caused the moderate stenosis of the BA. **(C)**, at the level of restenosis in right VA within the tapered area of the SOLITAIRE stent, there is a disrupted transverse flap (single white arrow) and mural hematoma, suggesting the dissection originated in right VA and extended distally to BA. **(D)**, at the level of posterior inferior cerebral artery (PICA) origin, no dissection is visible on DSA or OCT. Single white arrow indicated PICA. The presence of remnant transverse flap, double lumen and mural hematoma were signs of intracranial BA dissection on OCT.

is attached to the distal end of the catheter and is able to emit ultrasound signals perpendicular to its axis allowing visualization of the arteries (14). OCT is a recently-developed imaging technique that utilizes a light source with a near-infrared spectrum to produce cross-sectional images of arteries by measuring the echo time delay and the intensity of backscattered light (15). In this respect, OCT is somehow analogous to ultrasound imaging; however, OCT is superior to IVUS due to its high spatial resolution (4–10 μm vs. 70–100 μm) to distinguish the intima, media and adventitia of the arterial wall (16). Because of its easy passage of imaging catheter through the carotid arteries, OCT has been more frequently used in the extracranial carotid artery diseases than that in the intracranial vasculature. However, the intracranial vasculature is better accessed with full extent of OCT because the circumferential tissue visualization of OCT is limited to 5 mm from the catheter. Prior studies have noted the importance of OCT. It has been used to image the vessel wall of intracranial aneurysms, inflammation and atherosclerosis. In 2005, OCT demonstrated cerebral aneurysm healing following coil embolization in a canine model (17). After that, the use of OCT to assess mal-apposition of flow diverters has been shown to be predictive of the 30-days healing rate in a rabbit model of aneurysms (18). Nevertheless, the application for intracranial lesions in humans was not reported until 2014 (12). The study by Given et al showed OCT has potential applications in the evaluation of ICAS after Wingspan stent placement (12). Since 2014, there has been no other reported use of OCT in other intracranial lesions.

In our case, OCT was used to evaluate one patient who presented with spontaneous IAD in BA. The diagnosis of IAD other than ICAS clot was not confirmed during the initial mechanical thrombectomy. In our center, the use of OCT as an adjunct to DSA was performed. The intravascular changes of IAD were visualized on OCT for the first time. Consistent with the current pathognomonic criteria, OCT revealed signs of mural hematoma, intimal flap, and double lumen (8). The intimal disruption was observed in the proximal segment of the stent, which was not visible on DSA. Therefore, the findings of OCT may not only help to diagnose IAD, but also to provide better understanding of IAD and eliminate differential diagnosis of intracranial narrowing.

The potential advantages of OCT include fast acquisition time that allows for repeated scans, and high spatial resolution and depth-resolved analysis that enables us to see the details of disease more accurately. Studies from coronary intervention have demonstrated that OCT not only helps to diagnose coronary

dissection, but can also guide endovascular treatment (19, 20). Stenting, as a salvage strategy, has been used to rescue patients with coronary dissection (21). Nevertheless, angiography-guided stenting of coronary dissection is often difficulty and carries additional risks. OCT-guided stenting is safe and effective in that it ensures the guidewire in the true lumen, allows for the accurate caliber of the stent, and enables the stent to cover the dissection on all its length. Nevertheless, as for patients with acute stroke due to IAD, the optimal treatment remains uncertain due to the limited case reports. In the study by Labeyrie et al. stenting of IAD was used as first-line approach to rescue patients with acute stroke due to intracranial large vessel occlusion. However, without the guidance of OCT, stenting of a circulating false lumen failed to recanalize the artery in 2 (25%) out of 8 patients (4). Therefore, one can expect that OCT-guided stenting may be secure and reliable to manage IAD because it may circumvent risk of stenting in a false lumen and achieve covering of dissection with full length.

It has to be kept in mind, though, that OCT is an invasive technique and should be used with caution. The image quality of OCT may also be hampered by the presence of red thrombus and hypercoagulability. In order to obtain reliable images, OCT procedures require injection of contrast media to wash out blood from the vessel lumen because the near-infrared light signals are attenuated by the presence of red blood cells. This procedure may aggravate the false lumen with high pressure contrast injection. Therefore, OCT should be only used in complex cases with ambiguous diagnosis that cannot be managed with conventional examinations. Once diagnosed with IAD, OCT may be helpful in select cases to guide endovascular treatment with stenting.

High-resolution MRI (HR-MRI), a non-invasive MR based technique, is a promising tool to directly evaluate the intracranial vascular wall in various conditions (22). Pathognomonic radiological findings of IAD consist of mural intimal flap, hematoma, and double lumen (8). In the study by Han et al. HR-MRI corroborated the final diagnosis in 94% of patients with intracranial vertebrobasilar artery dissection, in which intimal flaps were identified in 91.4% of patients on contrast-enhanced (CE) T1-Weighted (T1WI) HR-MRI (23). On T1WI MRI, mural hematomas are spontaneously hyperintense 48–72 h after onset, which are then best detected on T1WI and CE-T1WI (54.3%) with black-blood effect by using high resolution 3-Tesla imaging (23, 24). In our case, HR-MRI may be an alternative to OCT because numerous studies have shown its value in differentiating IAD from ICAS, moyamoya disease, vasculitis and reversible cerebral vasoconstriction syndrome (25). However, current HR-MRI has several limitations. Validation of HR-MRI imaging criteria of IAD with histological analysis appears difficult in view of the limited availability of histological specimens. Furthermore, HR-MRI can be time-consuming when we need high-resolution and evaluate small tortuous intracranial arteries. Sometimes, poor quality of imaging may be obtained due to patient motion and discomfort (26). At last, despite the successes and further technical developments, HR-MRI is limited by the lower spatial resolution (around 300 μm) when compared with OCT (10 μm) (16).

A recent study suggested the use of self-expanding stents to treat IAD as a first-line approach to recanalize IAD (4). In our case, there were two aspects that may explain the decreased efficacy of permanent stenting in the treatment of IAD. First, follow-up OCT demonstrated the intimal disruption within the tapered area of the stent. That indicated the dissection started from the right VA and extended into the BA. The initial deployment of one self-expandable stent (SOLITAIRE 6–30 mm) covered the proximal dissection only with the tapered end instead of the non-tapered portion of the stent. Therefore, the dissection was not completely healed. Ideally, proximal placement of an additional stent may have covered the intimal flap and prevented restenosis. Second, the SOLITAIRE stent has less radial force when compared to other intracranial stents. The proximal tapered 10 mm area (total length minus usable length) has even less radial force, which may delay the healing of IAD and cause subsequent restenosis despite administration of anti-platelet regimen. We observed, even after 18-months follow-up, that the false lumen persisted, suggesting poor interaction between the stent and the vessel wall. Moreover, OCT indicated a mural hematoma existed between the layers of intima and media, which has not dissolved after 18-months follow-up.

The visualization of IAD on OCT may be counterbalanced by the inherent risks during OCT procedures. The major challenges include vessel tortuosity and the monorail design of the imaging catheter. In our case, the combined use of microwire and microcatheter enabled the microwire to advance smoothly and avoided the risk of entering the circulating false lumen. In addition, an intermediate catheter with a stiff microwire (Pilot 150, Abbott) may achieve better support and facilitate advancing the imaging catheter through tortuous anatomy. However, the short monorail design of the rapid exchange of the Dragonfly catheter does not allow its distal marker going further, and left its proximal marker within the BA. *Given et al* described a similar condition, in which the proximal marker of the OCT catheter failed to advance into the PCA resulting in incomplete imaging of the BA (12). In addition, during our procedure, repeated attempts to navigate the catheter through the lesion together with high pressure contrast injections, probably caused the recurrence of the intimal flap and aggravation of the dissection on OCT. In view of the limitations of the monorail design of the current OCT catheter, it is empirically hypothesized OCT is feasible in patients with extracranial dissections and selective intracranial dissection, but not those with IAD beyond the siphon segment of internal carotid artery (ICA) or distally-located IAD. Although Lopes et al. devised a method to overcome the monorail design and inserted this catheter in the middle and posterior cerebral arteries of a fresh frozen cadaver, it has not been tested *in vivo* (27). Future observational series are needed to validate the safety of OCT in IAD.

OCT was initially designed for the evaluation of the coronary vasculature. The indications of OCT expanding from coronary to other vascular territories remain unknown. Currently, the Dragonfly Duo catheter may not be well compatible with intracranial vasculature. In the future, new, more flexible catheters, shorter scan distances, and smaller diameter may

overcome the intracranial tortuosity, ease the concern of the peri-procedural complications and result in better technical results.

CONCLUSION

OCT may be helpful to diagnose IAD where angiography is ambiguous. Understanding the role and careful use of OCT is expected to improve the diagnosis of IAD when clinically indicated.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of ethics committee of Xuanwu Hospital, Capital Medical University. The protocol was approved by the ethics committee of Xuanwu Hospital, Capital Medical University. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

PG drafted the initial manuscript. LJ and TK critically reviewed and revised the manuscript. LG performed the first mechanical thrombectomy for this patient. BY finished the OCT scan. All the authors reviewed and approved the final version of the manuscript.

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REFERENCES

1. Béjot Y, Daubail B, Debette S, Durier J, Giroud M. Incidence and outcome of cerebrovascular events related to cervical artery dissection: the dijon stroke registry. *Int J Stroke* (2014) 9:879–82. doi: 10.1111/ijs.12154
2. Lee VH, Brown RD, Mandrekar JN, Mokri B. Incidence and outcome of cervical artery dissection: a population-based study. *Neurology* (2006) 67:1809–12. doi: 10.1212/01.wnl.0000244486.30455.71
3. Giannini N, Ulivi L, Maccarrone M, Montano V, Orlandi G, Ferrari E, et al. Epidemiology and cerebrovascular events related to cervical and intracranial arteries dissection: the experience of the city of Pisa. *Neurol Sci.* (2017) 38:1985–91. doi: 10.1007/s10072-017-3084-5
4. Labeyrie MA, Civelli V, Reiner P, Aymard A, Saint-Maurice JP, Zetchi A, et al. Prevalence and treatment of spontaneous intracranial artery dissections in patients with acute stroke due to intracranial large vessel occlusion. *J Neurointerv Surg.* (2018) 10:761–64. doi: 10.1136/neurintsurg-2018-013763
5. Park MS, Cha J, Chung J-W, Seo W-K, Kim G-M, Bang OY. Arterial dissection as a cause of intracranial stenosis in East Asians. *J Am Coll Cardiol.* (2017) 70:2205–6. doi: 10.1016/j.jacc.2017.08.048
6. Huang YC, Chen YF, Wang YH, Tu YK, Jeng JS, Liu HM. Cervicocranial arterial dissection: experience of 73 patients in a single center. *Surg Neurol.* (2009) 72 (Suppl. 2):S20–7. doi: 10.1016/j.surneu.2008.10.002
7. Kwak JH, Choi JW, Park HJ, Chae EY, Park ES, Lee DH, et al. Cerebral artery dissection: spectrum of clinical presentations related to angiographic findings. *Neurointervention* (2011) 6:78–83. doi: 10.5469/neuroint.2011.6.2.78
8. Debette S, Compter A, Labeyrie MA, Uyttenboogaart M, Metso TM, Majersik JJ, et al. Epidemiology, pathophysiology, diagnosis, and management of intracranial artery dissection. *Lancet Neurol.* (2015) 14:640–54. doi: 10.1016/S1474-4422(15)00009-5
9. Bezerra HG, Costa MA, Guagliumi G, Rollins AM, Simon DI. Intracoronary optical coherence tomography: a comprehensive review clinical and research applications. *JACC Cardiovasc Interv.* (2009) 2:1035–46. doi: 10.1016/j.jcin.2009.06.019
10. Griessenauer CJ, Foreman PM, Deveikis JP, Harrigan MR. Optical coherence tomography of traumatic aneurysms of the internal carotid artery: report of 2 cases. *J Neurosurg.* (2016) 124:305–9. doi: 10.3171/2015.1.JNS142840
11. Harada K, Oshikata S, Kajihara M. Optical coherence tomography evaluation of tissue prolapse after carotid artery stenting using closed cell design stents for unstable plaque. *J Neurointerv Surg.* (2018) 10:229–34. doi: 10.1136/neurintsurg-2017-013004
12. Given CA, Ramsey CN, Attizzani GF, Jones MR, Brooks WH, Bezerra HG, et al. Optical coherence tomography of the intracranial vasculature and Wingspan stent in a patient. *BMJ Case Rep.* (2014) 2014:bcr2014011114. doi: 10.1136/bcr-2014-011114
13. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med.* (2005) 352:1305–16. doi: 10.1056/NEJMoa043033
14. Athanasiou L, Sakellarios AI, Bourantas CV, Tsirka G, Siogkas P, Exarchos TP, et al. Currently available methodologies for the processing of intravascular ultrasound and optical coherence tomography images. *Exp Rev Cardiovasc Ther.* (2014) 12:885–900. doi: 10.1586/14779072.2014.922413
15. Jang IK. *In vivo* characterization of coronary atherosclerotic plaque by use of optical coherence tomography. *Circulation* (2005) 111:1551–55. doi: 10.1161/01.CIR.0000159354.43778.69
16. Popescu DP, Choo-Smith LP, Flueraru C, Mao Y, Chang S, Disano J, et al. Optical coherence tomography: fundamental principles, instrumental designs and biomedical applications. *Biophys Rev.* (2011) 3:155. doi: 10.1007/s12551-011-0054-7
17. Thorell WE, Chow MM, Prayson RA, Shure MA, Jeon SW, Huang D, et al. Optical coherence tomography: a new method to assess aneurysm healing. *J Neurosurg.* (2005) 102:348–54. doi: 10.3171/jns.2005.102.2.0348
18. King RM, Brooks OW, Langan ET, Caroff J, Clarençon F, Tamura T, et al. Communicating malapposition of flow diverters assessed with optical coherence tomography correlates with delayed aneurysm occlusion. *J Neurointerv Surg.* (2017) 10:693–7. doi: 10.1136/neurintsurg-2017-013502
19. Alfonso F, Paulo M, Gonzalo N, Dutary J, Jimenez-Quevedo P, Lennie V, et al. Diagnosis of spontaneous coronary artery dissection by optical coherence tomography. *J Am Coll Cardiol.* (2012) 59:1073–9. doi: 10.1016/j.jacc.2011.08.082
20. Combaret N, Souteyrand G, Amonchot A, Coupez E, Motreff P. Contribution of guidance by optical coherence tomography (OCT) in rescue management of spontaneous coronary artery dissection. *Eur Heart J Cardiovasc Imaging* (2013) 14:714. doi: 10.1093/ehjci/jet015
21. Nishiguchi T, Tanaka A, Taruya A, Ozaki Y, Nakai M, Teraguchi I, et al. Prognosis of spontaneous coronary artery dissection treated by percutaneous coronary intervention with optical coherence tomography. *J Cardiol.* (2017) 70:524–9. doi: 10.1016/j.jjcc.2017.03.009
22. Alexander MD, Yuan C, Rutman A, Tirschwell DL, Palagallo G, Gandhi D, et al. High-resolution intracranial vessel wall imaging: imaging beyond the lumen. *J Neurol Neurosurg Psychiatry* (2016) 87:589–97. doi: 10.1136/jnnp-2015-312020
23. Han M, Rim NJ, Lee JS, Kim SY, Choi JW. Feasibility of high-resolution MR imaging for the diagnosis of intracranial vertebrobasilar artery dissection. *Eur Radiol.* (2014) 24:3017–24. doi: 10.1007/s00330-014-3296-5

24. Swartz RH, Bhuta SS, Farb RI, Agid R, Willinsky RA, Terbrugge KG, et al. Intracranial arterial wall imaging using high-resolution 3-tesla contrast-enhanced MRI. *Neurology* (2009) 72:627–34. doi: 10.1212/01.wnl.0000342470.69739.b3
25. Choi YJ, Jung SC, Lee DH. Vessel wall imaging of the intracranial and cervical carotid arteries. *J Stroke* (2015) 17:238–55. doi: 10.5853/jos.2015.17.3.238
26. Andre JB, Bresnahan BW, Mossa-Basha M, Hoff MN, Smith CP, Anzai Y, et al. Toward quantifying the prevalence, severity, and cost associated with patient motion during clinical MR examinations. *J Am Coll Radiol.* (2015) 12:689–95. doi: 10.1016/j.jacr.2015.03.007
27. Lopes DK, Johnson AK. Evaluation of cerebral artery perforators and the pipeline embolization device using optical coherence tomography. *J Neurointerv Surg.* (2012) 4:291–4. doi: 10.1136/neurintsurg-2011-010102

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SYSTEMATIC REVIEW
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Vessel-Wall Magnetic Resonance Imaging of Intracranial Atherosclerotic Plaque and Ischemic Stroke: A Systematic Review and Meta-Analysis

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Introduction: Vessel-wall magnetic resonance imaging (MRI) has been suggested as a valuable tool for assessing intracranial arterial stenosis with additional diagnostic features. However, there is limited conclusive evidence on whether vessel-wall MR imaging of intracranial atherosclerotic plaques provides valuable information for predicting vulnerable lesions. We conducted this systematic review and meta-analysis to evaluate which characteristics of intracranial-plaque on vessel-wall MRI are markers of culprit lesions.

Methods: The MEDLINE, EMBASE, and Cochrane Library of Clinical Trials databases were searched for studies reporting the association between vessel-wall MRI characteristics of intracranial plaque and corresponding stroke events. Odds ratios (ORs) for the prevalence of stroke with intracranial-plaque MRI characteristics were pooled in a meta-analysis using a random-effects model.

Results: Twenty studies were included in this review. We found a significant association between plaque enhancement (OR, 10.09; 95% CI, 5.38–18.93), positive remodeling (OR, 6.19; 95% CI, 3.22–11.92), and plaque surface irregularity (OR, 3.94; 95% CI, 1.90–8.16) with stroke events. However, no significant difference was found for the presence of eccentricity (OR, 1.22; 95% CI, 0.51–2.91).

Conclusion: Based on current evidence, intracranial plaque contrast enhancement, positive remodeling, and plaque irregularity on MRI are associated with increased risk of stroke events. Our findings support the design of future studies on intracranial-plaque MRI and decision making for the management of intracranial atherosclerotic plaques.

Keywords: magnetic resonance imaging, intracranial arteriosclerosis, plaque, brain ischemia–diagnosis, cerebrovascular accident, vessel wall imaging, high resolution imaging, systematic (literature) review

INTRODUCTION

During last two decades, a shift has taken place toward imaging for the assessment of atherosclerotic-plaque characteristics rather than the luminal stenosis measurement as a result of accumulating knowledge that the histopathologic composition of plaques is a major risk factor for ischemic symptoms independent of stenosis severity (1). This trend has been broadly applied to assess extracranial carotid stenosis; carotid vessel-wall magnetic resonance imaging (MRI) is emerging as the best candidate for assessing carotid stenosis with additional diagnostic features pertinent to patient management (2, 3).

Intracranial atherosclerotic stenosis (ICAS) is a major cause of ischemic stroke, to a comparable degree with extracranial atherosclerosis, worldwide especially in Asian populations accounting for 10% of transient ischemic attack and 30–50% of ischemic strokes (4, 5). However, vessel-wall imaging in ICAS is somewhat lagging compared to that in extracranial atherosclerosis due to technical limitations in the imaging of small structures and the lack of insight regarding intracranial atherosclerotic plaques. Recently, numerous interesting studies on intracranial-plaque imaging have been published, suggesting that the radiological characteristics of intracranial plaques may be an important predictor of vulnerability in addition to the degree of stenosis (2, 6). Despite recent reports advocating the benefit of intracranial-plaque vessel-wall MRI, there is limited conclusive evidence regarding whether vessel-wall MRI provides valuable information for predicting vulnerable lesions, and which characteristics are useful to judge the vulnerability among many different characteristics other than those previously suggested. Moreover, there is debate on how intracranial plaque morphology is related to the risk of stroke because imaging features had not been proven by histopathological specimens and the assumption of imaging markers has been suggested based on small populations in individual studies, thereby making it challenging to draw definite conclusion on the value of vessel-wall MRI for intracranial-plaque characterization.

Therefore, we considered it necessary to perform a quantitative synthesis of existing evidence to explore fully and present high-level evidence regarding the valuable characteristics of intracranial-plaque vessel-wall MRI. Furthermore, it is worth clarifying whether there are differences in the risk profiles of specific plaque characteristics. Gupta et al. (7) presented a systematic review of high-resolution MRI of intracranial atherosclerotic plaques but they only analyzed one image feature of plaque enhancement. As many pertinent studies have been published since the previous review, a meta-analysis using updated data is needed. In particular, a consensus on MRI characteristics of vulnerable plaques is needed for future prospective studies to determine the clinical benefit of vessel-wall MRI in ICAS and its clinical applications. Summarizing this knowledge might provide guidelines for prospective studies and can also be applied in the clinical field.

For these reasons, we conducted this systematic review and meta-analysis to evaluate whether the characteristics of intracranial-plaque vessel-wall MRI are markers of symptomatic lesions of corresponding ischemic events.

METHODS

Search Strategy

The meta-analysis was conducted in accordance with the guidelines for meta-analyses of observational studies in epidemiology (8). We conducted a systematic literature review of the PubMed, EMBASE, and Cochrane library databases from inception through June 30, 2018. To identify eligible studies, the following keywords, and entrée terms analogous to these, were used for searching in relevant combinations using the Boolean operators OR and AND: in combination with the words "intracranial atherosclerosis" or "plaque, atherosclerotic" and "stroke" or "brain ischemia," "magnetic resonance imaging" or "vessel wall imaging" (**Supplemental Data**: Search Strategy). In addition, we reviewed the reference lists of the included articles and background papers for potentially relevant studies.

Study Selection

Two researchers reviewed the content of the screened articles for the inclusion criteria listed as follows: studies that (1) enrolled patients with intracranial atherosclerosis, (2) enrolled patients who underwent high-resolution vessel-wall MRI of the intracranial arteries, (3) enrolled more than 10 subjects, and (4) assessed vessel-wall MRI findings of intracranial plaques and their relation to ischemic symptoms. We excluded studies that (1) reported duplicate data, (2) was limited in appropriate data, (3) included non-stenotic lesions (such as the contralateral side of lesions) as controls, and that (4) were markedly flawed with respect to the guidelines of reporting observational studies.

Data Extraction

Two reviewers independently extracted data from the selected studies that fulfilled the inclusion and exclusion criteria using a standardized form, and all disagreements were resolved by consensus. The following data were collected: report characteristics (first author's name, year of publication, country of the study), major inclusion/exclusion criteria, MRI protocol, basic demographics of subjects, the prevalence of stroke risk factors in the studied populations, including hypertension, diabetes, coronary artery disease, dyslipidemia, and smoking history; the definition of characteristic findings of intracranial plaque, and definitions of culprit and non-culprit lesions.

The quality of the included studies was also independently assessed by two reviewers using the "Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies," provided by the National Institutes of Health (9).

Statistical Analysis

Demographic characteristics and extracted covariates are summarized with standard descriptive statistics. Categorical variables are expressed as frequencies, and continuous variables are expressed as means with standard deviations. Continuous variables presented by median and intervals were converted to means and standard deviation (10).

Based on the collected data of the enrolled studies, we assessed the incidence of culprit lesions associated with characteristic plaque findings on vessel-wall MRI. To perform the pooled estimates, these characteristic findings were limited to those

present in three studies or more, and included the presence of contrast enhancement, positive remodeling (the ratio of the out-diameter at target lesion to that at reference artery—contralateral or proximal non-stenotic segment- is over 1.05), intraplaque hemorrhage (IPH; high signal intensity on T1-weighted MRI), plaque eccentricity, and irregularity of plaque surface. We defined culprit lesions as intracranial arterial stenosis with (1) corresponding ischemic stroke including transient ischemic attack (TIA) and/or ischemic lesions on MRI or (2) corresponding downstream embolic infarction (large-artery atherosclerosis by the TOAST classification) in the acute or subacute phase. Non-culprit lesions were defined as intracranial arterial stenosis (1) without recent neurologic symptoms relevant to the lesion or (2) with ipsilateral stroke caused by small-vessel occlusion.

Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were used to determine the associations between ischemic stroke and imaging findings on vessel-wall MRI. The pooled OR for dichotomous parameters was estimated with a random-effect weighted meta-analysis and a forest plot was generated. A continuity correction of 0.5 was applied for studies without event in one arm. Heterogeneity across studies in the meta-analysis was assessed using the I^2 test, with values higher than 50% considered to indicate substantial heterogeneity. If there was a possibility that the pooled estimates would be confounded by substantial heterogeneity among the studies, the results were not pooled in order to prevent misinterpretation. As for the evaluation of publication bias, it was estimated by contour enhanced funnel plot (11) and Begg's test (12). No publication bias was confirmed when the *p*-value for significance was higher than 0.05.

A subgroup analysis was used to determine whether study-related factors could account for heterogeneity. The subgroup analysis was conducted according to any binary variables that may have affected the consistency of a result across the enrolled studies. In order to assess the robustness of the observed outcomes, we further conducted sensitivity analyses by removing studies with the higher risks of bias, and with the "leave-one-out" method.

Meta-regression analysis investigated potential effects of hypertension, diabetes mellitus, dyslipidemia, current smoking status, and coronary ischemic disease on intracranial MRI characteristics associated with culprit lesions.

RESULTS

Study Selection

A total of 1,973 studies were identified during the initial search. Of these, review of the titles and abstracts identified 41 studies that presented the stroke rate and intracranial-plaque vessel-wall MRI findings. After reviewing the full texts, 20 studies were suitable for inclusion to this review (2, 6, 13–30). Two studies (2, 18) that were published from our institute were finally included in the current analysis, and these data were reanalyzed based on raw data including clinical records and images to obtain the necessary information to conduct the meta-analysis. Since we did not only review the published manuscripts but also retrospectively reanalyzed clinical data, we obtained the approval of the institutional review board and the requirement for informed consent was waived due to the retrospective nature of the study. A flow-diagram summarizing the literature search is presented as **Figure 1.**

Study Characteristics

The results of the quality assessment were satisfactory with all the studies satisfying at least 10 of the 14 domains. All studies showed a fatal flaw concerning the sample size justification. Eleven of twenty studies showed a high risk of bias by potential confounders which were not adjusted by logistic regression of other regression methods (2, 13–16, 19, 21–23, 25, 27) (**Supplemental Data: Table**).

The basic demographics and the prevalence of risk factors were summarized in **Table 1**. In total, A total of 1,233 intracranial stenosis lesions of 1,126 patients were eligible for the meta-analysis. In all studies, vessel-wall MRI was prospectively acquired from ICAS or stroke cohorts and was analyzed retrospectively. Fourteen (2, 6, 13–16, 18, 19, 22, 24, 25, 27, 28, 30) and three studies (23, 26, 29) enrolled only middle cerebral artery (MCA) plaques (one study including 7% internal carotid artery (ICA) plaques was enrolled) and only basilar artery (BA) plaques in accordance with their inclusion criteria, respectively, and three studies (17, 20, 21) enrolled both large- and medium-size intracranial arteries for their subjects. The proportion of MCA lesions and BA lesions to total lesions were 74.1%, 25.9%, respectively (**Table 1**).

In all studies, target lesions for vessel-wall MRI were assessed by MR angiography (MRA) before the acquisition of MRI, and 11 of 20 studies (13, 14, 16–20, 22, 23, 26, 30) enrolled only patients with moderate to severe stenosis. Although 14 studies (2, 6, 13, 14, 16–19, 22, 23, 25, 26, 29, 30) recruited subjects based on only stenotic lesions on angiographic imaging, six studies (15, 20, 21, 24, 27, 28) recruited subjects based on ischemic symptoms. Four of these six studies (15, 21, 27, 28) dichotomized subjects into infarction by large-artery atherosclerosis (downstream embolic infarction) and small-vessel occlusion according to the subtype of ischemic stroke at the ipsilateral side of the stenotic lesion (**Table 2**).

Most enrolled studies used 3.0 Tesla MRI units to acquire vessel wall MRI, acquired with sub-mm in-plane voxel resolution, lower than 0.6 × 0.6 mm. Intracranial plaques were assessed by high-resolution, multi-contrast vessel-wall MRI in 13 studies, of which seven studies (2, 6, 14, 15, 21, 22, 25) used three different sequences of T1-,T2- and proton density-weighted images and six studies (13, 16, 19, 23, 24, 29) included T1- and T2-weighted images. All studies included T1-weighted MRI with 14 studies using different block-blood techniques; six studies (2, 14, 15, 19, 24, 25) used 2-dimensional turbo spin echo or fast spin echo images; eight studies (6, 18, 20, 21, 23, 26, 27, 30) used 3-dimensional volume isotropic turbo spin echo acquisition or magnetization prepared rapid gradient echo or sampling perfection with application optimized contrasts using different flip angle evolution. All studies except one (20) involved more than one reader evaluating the vessel-wall MRI for ICAS (**Table 2**).

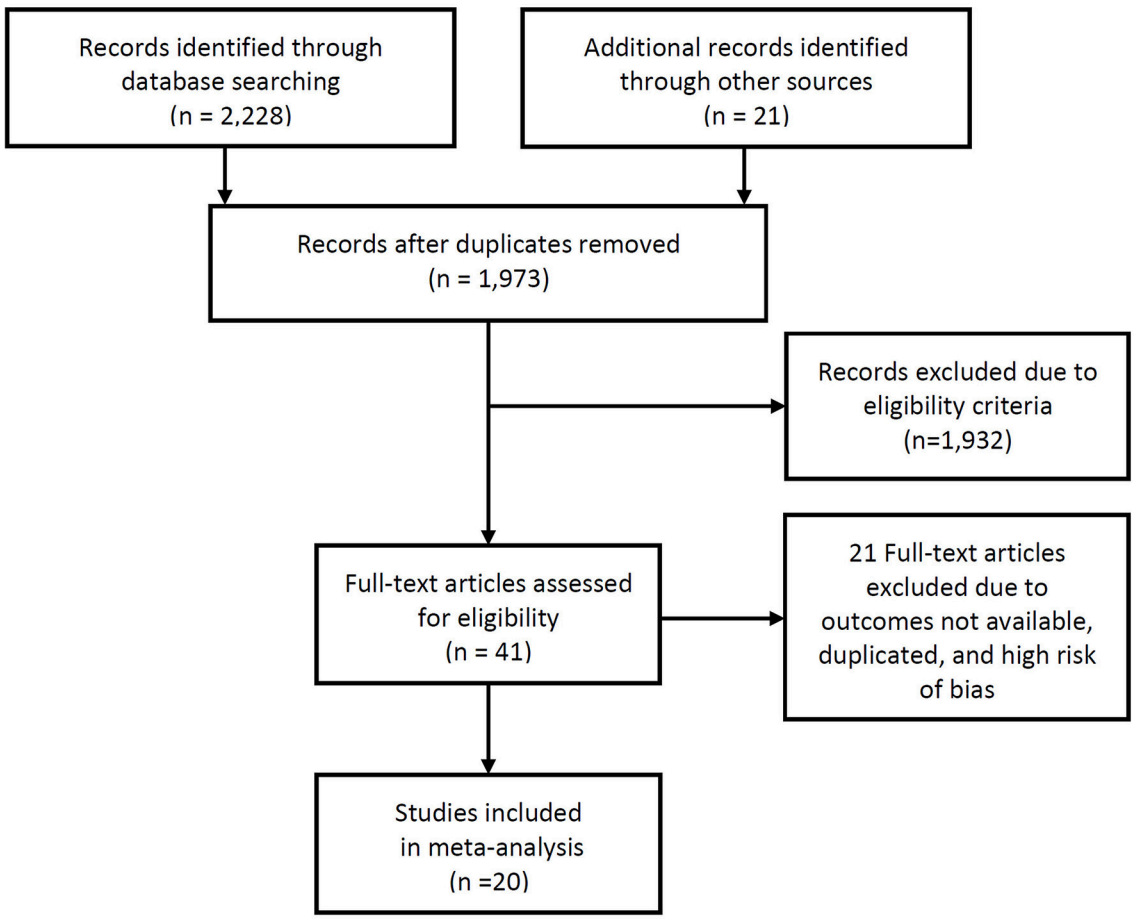


FIGURE 1 | PRISMA flow diagram of studies identification.

Stroke events were present in 11 studies evaluating the contrast enhancement of plaques. Six of 11 studies (15, 17, 18, 21, 22, 26) classified the degree of contrast enhancement as a two-level grading system (non-enhancement and enhancement) and five studies (20, 26–28, 30) classified it as a three-level grading system (0: enhancement was less than or equal to that of intracranial arterial walls without plaque, 1: less enhancement than the pituitary stalk, 2: enhancement greater than or equal to that of the pituitary stalk). To calculate the OR by binary group, we dichotomized the three-level grading system as grade 0 and grade 1 to 2.

Data Synthesis and Statistical Analysis

In terms of plaque contrast enhancement, 519 intracranial atherosclerotic lesions in 11 studies (15, 17–22, 26–28, 30) provided data eligible for the meta-analysis. We found a significantly higher prevalence of stroke events in plaques with contrast enhancement, with a random effect OR of 10.09 (95% CI, 5.38 to 18.93; $I^2 = 24.04\%$; **Figure 2A**).

Subgroup analysis was conducted for binary classifications according to (1) selecting indication for plaque location (MCA only vs. other intracranial arteries with/without the MCA), (2) the classifying method of culprit and non-culprit lesions (based on the presence of corresponding ischemic symptoms vs. based on TOAST subgrouping of ischemic stroke, large artery embolism and small vessel occlusion), and (3) the grading method of the degree of contrast enhancement (two- vs. three-level grading system). Pooled estimates showed a consistent strong positive correlation between ischemic stroke and plaque contrast enhancement regardless of subgrouping (**Table 3**).

Ten studies (2, 6, 14, 16, 19, 23, 26, 28–30) evaluating IPH reported data that could be included in the meta-analysis. However, we did not conduct OR pooled estimate because we observed significant heterogeneity in the analysis. Although five (16, 19, 23, 28, 29) of 10 studies presented higher prevalence of culprit lesions for positive IPH than for negative IPH, the other five (2, 6, 14, 26, 30) did not find a significant difference in culprit lesions related to IPH (**Figure 3**).

A total of 338 lesions in seven studies (2, 14, 21, 22, 24, 26, 30), 235 lesions in five studies (2, 6, 13, 14, 21), and 152 lesions in three studies (6, 14, 28) were meta-analyzed for eccentricity, positive remodeling, and plaque irregularity, respectively. The meta-analysis did not show any significant differences in ischemic events between the eccentricity and concentricity of stenosis (OR, 1.22; 95% CI, 0.51 to 2.91; $I^2 = 47.65\%$). However, we found a significant association between positive remodeling and plaque

TABLE 1 | Demographics and risk factor of enrolled studies.

References	Country	Subject No[a]	Mean age (years), SD	Male (%)	Lesion site	HTN (%)	DM (%)	Dyslipidemia (%)	Current smoking (%)	CAD (%)
Ryu et al. (2)	South Korea	16(14)	60.0 ± 8.5	57.1	MCA	78.6	50.0	50.0	14.3	7.1
Xu et al. (13)	China	61	62.4 ± 11.6	63.9	MCA	68.9	29.5	31.1	36.1	N/A
Chung et al. (14)	South Korea	30	65.8 ± 9.7	63.3	MCA	56.7	46.7	70.0	43.3	N/A
Kim et al. (15)	South Korea	26	65.2 ± 10.5	61.5	MCA	65.4	30.8	23.1	NA	23
W Xu et al. (16)	China	109(104)	56.7 ± 12.8	83.7	MCA	69.2	23.1	46.2	21.2	N/A
Vakil et al. (17)	United States	22(19)	68.7 ± 9.6	68.4	ICA, A2, BA, V4	89.5	47.4	84.2	10.5	N/A
Ryu et al. (18)	South Korea	36	69.7 ± 11.9	47.2	MCA	69.4	44.4	63.9	33.3	11.1
Yang et al. (19)	China	65(73)	63.0 ± 11.3	63.0	MCA	N/A	N/A	N/A	N/A	N/A
Qiao et al. (20)	United States	99(27)	56.8 ± 12.4	70.4	M1-2, A1-2, C3-4, P1-2, BA, V4	81.5	33.3	59.3	14.8	N/A
Ryoo et al. (21)	South Korea	80	64.5 ± 14.8	73.8	MCA (75.3%) BA (24.7%)	67.5	41.3	51.3	27.5	11.3
P Xu et al. (22)	China	32	65.8 ± 13.1	46.9	MCA	78.1	28.1	59.4	34.4	37.5
Yu et al. (23)	South Korea	73	72.4 ± 55.8	56.2	BA	46.6	27.4	34.2	23.3	16.4
Zhao et al. (6)	China	51	67.4 ± 8.8	58.8	MCA	64.7	35.3	N/A	31.4	N/A
Teng et al. (24)	China	165(139)	57.1 ± ?	64.7	MCA	71.2	34.5	N/A	29.5	9.4
Zhang et al. (25)	China	33	68.1 ± 11.8	81.8	MCA	81.8	51.5	N/A	57.6	N/A
Wang et al. (26)	China	57	59.4 ± 8.1	77.2	BA	63.2	52.6	21.1	49.1	N/A
Jang et al. (27)	South Korea	25	62.7 ± 6.19	40.0	MCA	48.0	76.0	80.0	28.0	N/A
Wu et al. (28)	China	74	54.7 ± 12.1	79.7	MCA (92%) ICA (8%)	75.7	21.6	40.5	52.7	N/A
Zhu et al. (29)	China	126	61.5 ± 10.0	65.1	BA	80.2	33.3	51.6	27.8	4.0
Lu et al. (30)	China	46	55.8 ± 15.2	67.4	MCA	76.1	28.3	47.8	28.3	N/A

SD, standard deviation; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; MCA, middle cerebral artery; ICA, internal carotid artery, A2, anterior cerebral artery segment 2; BA, basilar artery; V4, vertebral artery segment 4; M1-2; middle cerebral artery segment 1-2; A1-2, anterior cerebral artery segment 1-2; C3-4, cavernous and supraclinoid segments of internal carotid artery; P1-2, posterior cerebral artery segment 1-2; N/A, data not available.

[a]*Data indicates numbers of analyzed lesions with numbers of patients in parentheses.*

irregularity and stroke events within the corresponding vascular territory, with a random effect OR of 6.19 (95% CI, 3.22 to 11.92; $I^2 = 0\%$) and 3.94 (95% CI, 1.90 to 8.16; $I^2 = 0\%$), respectively (**Figures 2B–D**).

Sensitivity Analysis and Meta-Regression

Sensitivity analysis for studies with high risk of bias at (1) study population definition (2) exposure measurement and (3) outcome measurement, and the leave-one-out method showed that the conclusions were not drastically changed with these analyses. Contour enhanced funnel plots indicated that all studies were within the non-significant area (**Figure 4**) and significant publication bias was not observed based on Begg's test (**Table 4**) in any meta-analysis.

Meta-regressions were conducted only for studies evaluating plaque enhancement. Information regarding dyslipidemia was available in nine studies. Meta-regression showed a statistically significant negative association between the proportion of current smoking and culprit lesions (slope coefficient (standard error) = −0.062 (0.023), $p = 0.0006$). Information on hypertension, diabetes, and dyslipidemia were available in 10 studies, and meta-regression for these risk factors showed no statistically significant association between these proportion of risk factors and ORs of association between ischemic event and plaque enhancement.

DISCUSSION

Our meta-analysis, by pooling the available evidence, indicated that intracranial plaques with contrast enhancement, positive remodeling, and wall irregularity are significantly more likely to be associated with ischemic stroke at the corresponding territory. These findings were significantly different from the known vulnerability markers (including IPH, large lipid core, and thin fibrous cap) in the extracranial carotid plaque, suggesting

TABLE 2 | Inclusion/exclusion criteria, definition of ischemic event, and MRI protocols of enrolled studies.

References	Inclusion criteria		Exclusion criteria			Definition of culprit plaque	MRI protocols						
	Patient selection	Vessel stenosis degree and modality	Cardiac embolism	Extra-LAO	Non-atherosclerosis[a]	Culprit lesion, ipsilateral	Interval between symptom to MRI	MRI field strength (tesla)	High-resolution MRI sequences	T1-weighted imaging			
										Sequences	TR/TE (ms)	Voxel size (mm^3)	NEX
Ryu et al. (2)	Lesion	Any stenosis	O	O	O	Ischemic symptoms	1 week	3	T1W, T2W, PD	2D, BB, TSE	581/20	0.38 × 0.48 × 2	4
Xu et al. (13)	Lesion	>50% MRA	O	O	O	Ischemic symptoms	4 week	3	T1W, T2W	2D	800/12	0.25 × 0.25 × 2(ZFIP)	4
Chung et al. (14)	Lesion	>50% MRA	O	O	O	Ischemic symptoms and DWI restriction	N/A	3	T1W, T2W, PD	2D, BB, TSE	700/23	0.39 × 0.61 × 2	4
Kim et al. (15)	Symptom	N/A	O	O	O	Downstream lesion[b]	1 week	3	T1W, T2W, PD	2D, BB,	600/12	0.31 × 0.45 × 2	4
W Xu et al. (16)	Lesion	>70% MRA	O	O	O	DWI restriction	4 week	3	T1W, T2W	2D	800/12 520/12.2	0.25 × 0.25 × 2(ZFIP)	4
Vakil et al. (17)	Lesion	>70% MRA	N/A	O	N/A	Ischemic symptoms and DWI restriction	1day[c]	1.5	T1W	2D, spin echo	63/15	0.9 × 0.9 × 5	N/A
Ryu et al. (18)	Lesion	>70% MRA	O	O	O	Lesion on MRI	3days	3	T1W	3D, BB, VISTA	350/19.5	0.34 × 0.34 × 1	N/A
Yang et al. (19)	Lesion	>50% CA	O	O	O	Ischemic symptoms and DWI restriction	17days	3	T1W, T2W	2D, BB, FSE	1200-2000/50	0.5 × 0.5 × 2	4
Qiao et al. (20)	Lesion and symptom	>50% MRA, CTA, CA	O	O	O	Ischemic symptoms and lesion on MRI	21days[d]	3	T1W	3D, BB, VISTA	2000/38	0.4 × 0.4 × 0.4	1
Ryoo et al. (21)	Symptom	Any stenosis	O	O	O	Downstream lesion[b]	1 week	3	T1W, T2W, PD, FLAIR	3D, BB, VISTA	2100/10	0.25 × 0.25 × 2(ZFIP)	2
P Xu et al. (22)	Lesion	>50% MRA	N/A	N/A	O	DWI restriction	3days	3	T1W, T2W, PD	2D	600/12	0.22 × 0.22 × 2.5	4
Yu et al. (23)	Lesion	>50% MRA	N/A	O	O	Ischemic symptoms	2 week	3	T1W, T2W	2D, BB, TSE 3D, BB, MPRAGE	800/10	0.65 × 0.71 × 2	2
Zhao et al. (6)	Lesion	>30% MRA	O	O	O	Ischemic symptoms	1 week	3	T1W, T2W, PD	2D, BB T1W 3D, SPACE	700/26	0.55 × 0.55 × 2	2
Teng et al. (24)	Lesion and symptom	Any stenosis	O	O	O	Ischemic symptoms and lesion on MRI	3.3days[d]	3	T1W, T2W	2D, BB, FSE	567/16	0.31 × 0.39 × 2	2
Zhang et al. (25)	Lesion	>30% MRA	O	O	O	DWI restriction	1 week	3	T1W, T2W, PD	2D, BB	1000/9	0.44 × 0.56 × 2	2
Wang et al. (26)	Lesion	>50% MRA	O	N/A	O	Lesion on MRI	4 week	3	T1W	3D, BB, SPACE	900/15	0.5 × 0.5 × 0.5	N/A
Jang et al. (27)	Symptom	N/A	O	O	O	Downstream lesion[b]	3days	3	T1W	3D, BB, SPACE	700/12	0.9 × 0.9 × 0.9	1

(Continued)

TABLE 2 | Continued

References	Inclusion criteria		Exclusion criteria			Definition of culprit plaque	MRI protocols						
	Patient selection	Vessel stenosis degree and modality	Cardiac embolism	Extra-LAO	Non-atherosclerosis[a]	Culprit lesion, ipsilateral	Interval between symptom to MRI	MRI field strength (tesla)	High-resolution MRI sequences	T1-weighted imaging			
										Sequences	TR/TE (ms)	Voxel size (mm^3)	NEX
Wu et al. (28)	Symptom	Any stenosis	O	O	O	Downstream lesion[b]	2 week	3	T1W	3D, SPACE	900/15	0.5 × 0.5 × 0.5	N/A
Zhu et al. (29)	Lesion	>30% MRA, CTA, CA	O	N/A	O	Ischemic symptoms	12 week	3	T1W, T2W	2D, FSE	601/10	0.4 × 0.4 × 2	N/A
Lu et al. (30)	Lesion	>50% MRA	O	O	O	Ischemic symptoms and DWI restriction	1 week	3	T1W	3D, BB, SPACE	900/4.2	0.4 × 0.4 × 0.75	N/A

Extra-LAO, stenosis at extracranial carotid artery; TR, repetition time; TE, echo time; NEX, number of excitations; MRA, magnetic resonance angiography; CA, cerebral angiography; CTA, computed tomography angiography; DWI, diffusion-weighted magnetic resonance imaging; T1W, T1-weighted; T2W, T2-weighted; PD, proton density; FLAIR, fluid-attenuated inversion recovery; 2D, two dimensional; 3D, three dimensional; BB, black blood; TSE, turbo spin echo; VISTA, volume isotropic turbo spin echo acquisition; FSE, fast spin echo; MPRAGE, magnetization prepared rapid gradient echo; SPACE, sampling perfection with application optimized contrasts using different flip angle evolution; ZFIP, zero filled interpolation; N/A, data not available.

[a] *Nonatherosclerosis vasculopathy such as dissection, vasculitis or Moyamoya disease.*

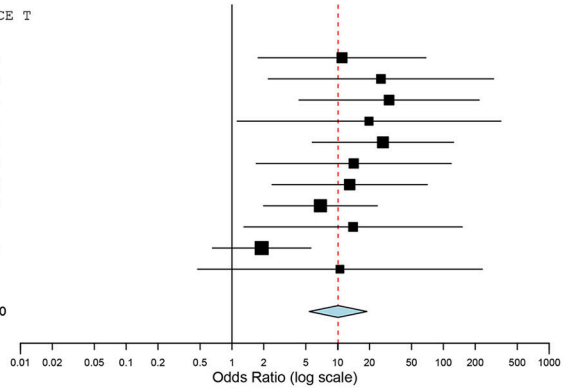
[b] *Downstream of culprit lesion indicates artery-to-artery embolic infarctions caused by intracranial atherosclerosis and corresponding non-culprit lesion means ipsilateral infarction caused by small-vessel occlusion.*

[c] *Data is limited to 16 of 19 patients.*

[d] *Data is median value of interval between onset of symptom to MRI scan.*

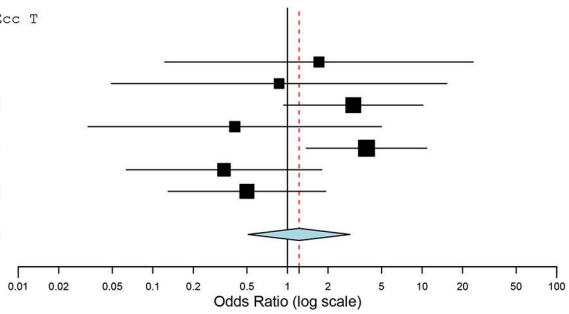
A Forest plot for contrast enhancement

Studies	Estimate (95% C.I.)	+CE Culp/+CE T	-CE Culp/-CE T
J Kim 2012	11.000 (1.770, 68.350)	9/12	3/14
P Vakil 2013	25.667 (2.207, 298.494)	7/8	3/14
C Ryu_2 2014	30.667 (4.312, 218.092)	23/25	3/11
Y Qiao 2014	19.794 (1.120, 349.805)	21/52	0/14
W Yang 2014	26.813 (5.754, 124.942)	39/43	4/15
S Ryoo 2015	14.192 (1.697, 118.666)	41/67	1/10
P Xu 2015	13.000 (2.398, 70.461)	12/16	3/16
W Wang 2017	6.873 (1.992, 23.717)	27/38	5/19
J Jang 2017	14.000 (1.299, 150.889)	14/19	1/6
F Wu 2018	1.912 (0.655, 5.585)	29/55	7/19
S Lu 2018	10.517 (0.474, 233.475)	30/44	0/2
Overall	**10.094 (5.382, 18.934)**	**252/379**	**30/140**
(I^2=24.04 % , P=0.215)			



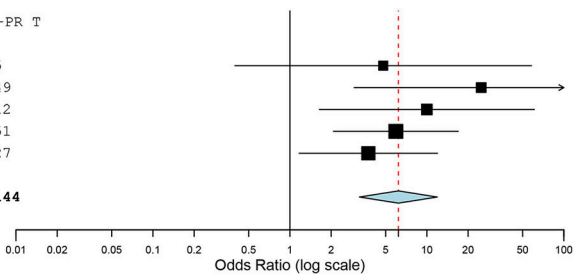
B Forest plot for eccentricity

Studies	Estimate (95% C.I.)	+Ecc Culp/+Ecc T	-Ecc Culp/-Ecc T
C Ryu 2009	1.714 (0.123, 23.939)	6/13	1/3
G Chung 2012	0.867 (0.049, 15.279)	13/28	1/2
S Ryoo 2015	3.083 (0.938, 10.136)	37/61	5/15
P Xu 2015	0.406 (0.033, 4.997)	13/29	2/3
Z Teng 2016	3.864 (1.381, 10.813)	35/57	7/24
W Wang 2017	0.338 (0.064, 1.795)	26/48	7/9
S Lu 2018	0.500 (0.130, 1.923)	18/30	12/16
Overall	**1.219 (0.510, 2.911)**	**148/266**	**35/72**
(I^2=47.65 % , P=0.075)			



C Forest plot for positive remodeling

Studies	Estimate (95% C.I.)	+PR Culp/+PR T	-PR Culp/-PR T
C Ryu 2009	4.800 (0.397, 58.013)	6/11	1/5
WH Xu 2010	24.933 (2.947, 210.938)	11/12	15/49
G Chung 2012	10.000 (1.641, 60.921)	12/18	2/12
S Ryoo 2015	5.937 (2.079, 16.954)	19/26	16/51
D Zhao 2015	3.740 (1.170, 11.962)	18/25	11/27
Overall	**6.192 (3.218, 11.915)**	**66/92**	**45/144**
(I^2=0 % , P=0.614)			



D Forest plot for surface irregularity

Studies	Estimate (95% C.I.)	+IR Culp/+IR T	-IR Culp/-IR T
G Chung 2012	8.333 (1.470, 47.226)	10/13	4/14
D Zhao 2015	3.643 (1.060, 12.523)	15/20	14/31
F Wu 2018	3.163 (1.102, 9.079)	15/22	21/52
Overall	**3.940 (1.903, 8.158)**	**40/55**	**39/97**
(I^2=0 % , P=0.638)			

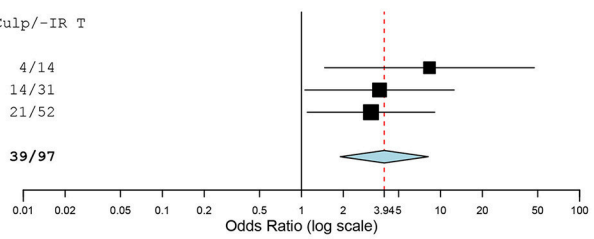


FIGURE 2 | Forest plots for association between vessel-wall MRI findings and ischemic event. Forest plots showing odds ratio (OR) presenting corresponding ischemic events of intracranial atherosclerotic plaques in comparison of positive and negative culprit signs on vessel-wall MRI. The size of the black box

(Continued)

FIGURE 2 | corresponding to each study is proportional to the sample size. The horizontal line shows the corresponding 95% confidence interval (CI) of the effect size (OR). The combined estimate is based on a randomized-effects model shown by the diamond. "Culp" and "T" indicate the number of culprit lesions and total lesions according to positive and negative signs of contrast enhancement (CE), eccentricity (Ecc), positive remodeling (PR), and surface irregularity (IR).
(A) Forest plot for contrast enhancement
(B) Forest plot for eccentricity
(C) Forest plot for positive remodeling
(D) Forest plot for surface irregularity.

TABLE 3 | Results of subgroup analyses of contrast enhancement of plaque for prediction of ischemic stroke.

Category	Subgroup	Studies no.	Odds ratio (95% CI)	I^2 (%)
Plaque location[a]	MCA only[b]	7	10.44(4.06–26.88)	48.7
	Other site[c]	4	10.65(4.21–26.93)	0
Classification of culprit and non-culprit	Ipsilateral stroke	7	14.70(7.34–29.43)	0
	TOAST subgroup[d]	4	6.12(1.89–19.86)	44.1
Degree of contrast enhancement	Two grading	6	18.55(8.65–39.76)	0
	Three grading	5	5.13(2.12–12.41)	21.3

CI, confidence interval; MCA, middle cerebral artery; ICA, intracranial artery; TOAST, trial of Org 10172 in acute stroke treatment.
*[a]Refer to 6th column of **Table 1**.*
[b]Data that evaluated 92% of middle cerebral artery and 8% of internal carotid artery by Wu et al. (28) was also included.
[c]Other intracranial arteries with or without middle cerebral artery.
*[d]Culprit lesion was defined as intracranial arterial stenosis with downstream embolic infarction caused by large-artery atherosclerosis and non-culprit lesion was defined as that with ipsilateral stroke caused by small-vessel occlusion (refer to 7th column of **Table 2**).*

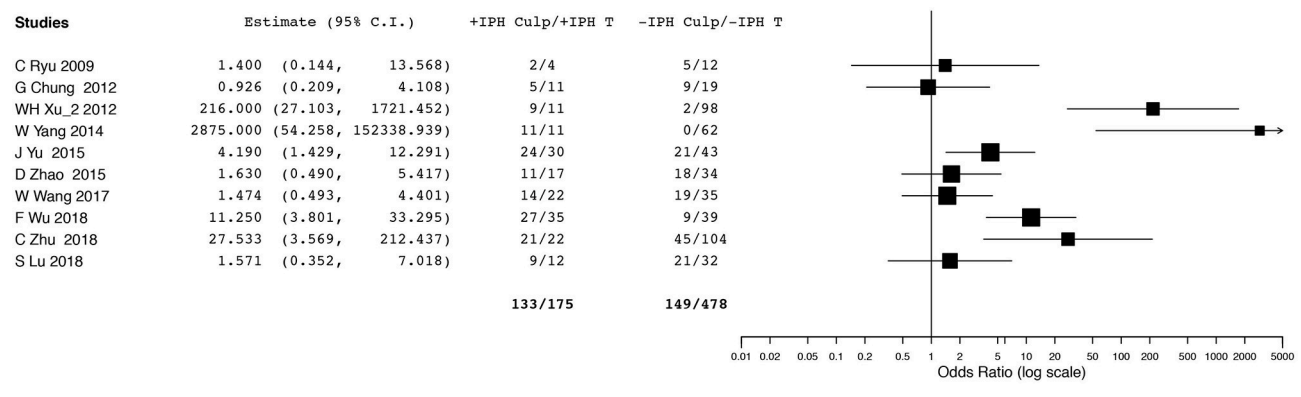


FIGURE 3 | Forest plot for association between intraplaque hemorrhage and ischemic event. Odd ratios and 95% confidence intervals demonstrating association between ischemic event and intraplaque hemorrhage in each enrolled study.

that unlike plaque imaging of the extracranial carotid artery, an independent imaging protocol should be provided to assess the intracranial plaque vulnerability, although intracranial plaque MRI studies have been benchmarked based on carotid plaque studies.

The current results identified vulnerable imaging markers for ICAS, and these could be used as a theoretical foundation for future research assessing the clinical benefit of intracranial vessel-wall MRI, such as monitoring of patients with ICAS or of their response to therapeutic intervention.

Additionally, our study illustrates important limitations of the current literature on MRI plaque characterization. Although there were many candidates for this review, only a limited number of studies were enrolled due to heterogeneity in methodology and selection indication for subjects. This review highlighted the need for more data to confirm and refine the standardization of methods assessing intracranial plaques using vessel-wall MRI.

Contrast Enhancement

Our meta-analysis revealed the strong association between plaque contrast enhancement and recent ischemic events. Although in line with the result of a previous meta-analysis that presented a pooled OR of 10.8 (95% CI 4.1–28.1) (7), our results differed from those of the previous study in many respects. One third of the studies we included were published after the previous meta-analysis. The relationship between contrast enhancement and ischemic symptoms was adjusted using subgroup analysis for vascular anatomy, grading method of contrast enhancement, and definition of culprit lesion. We excluded two studies that were included in the previous meta-analysis due to selection bias.

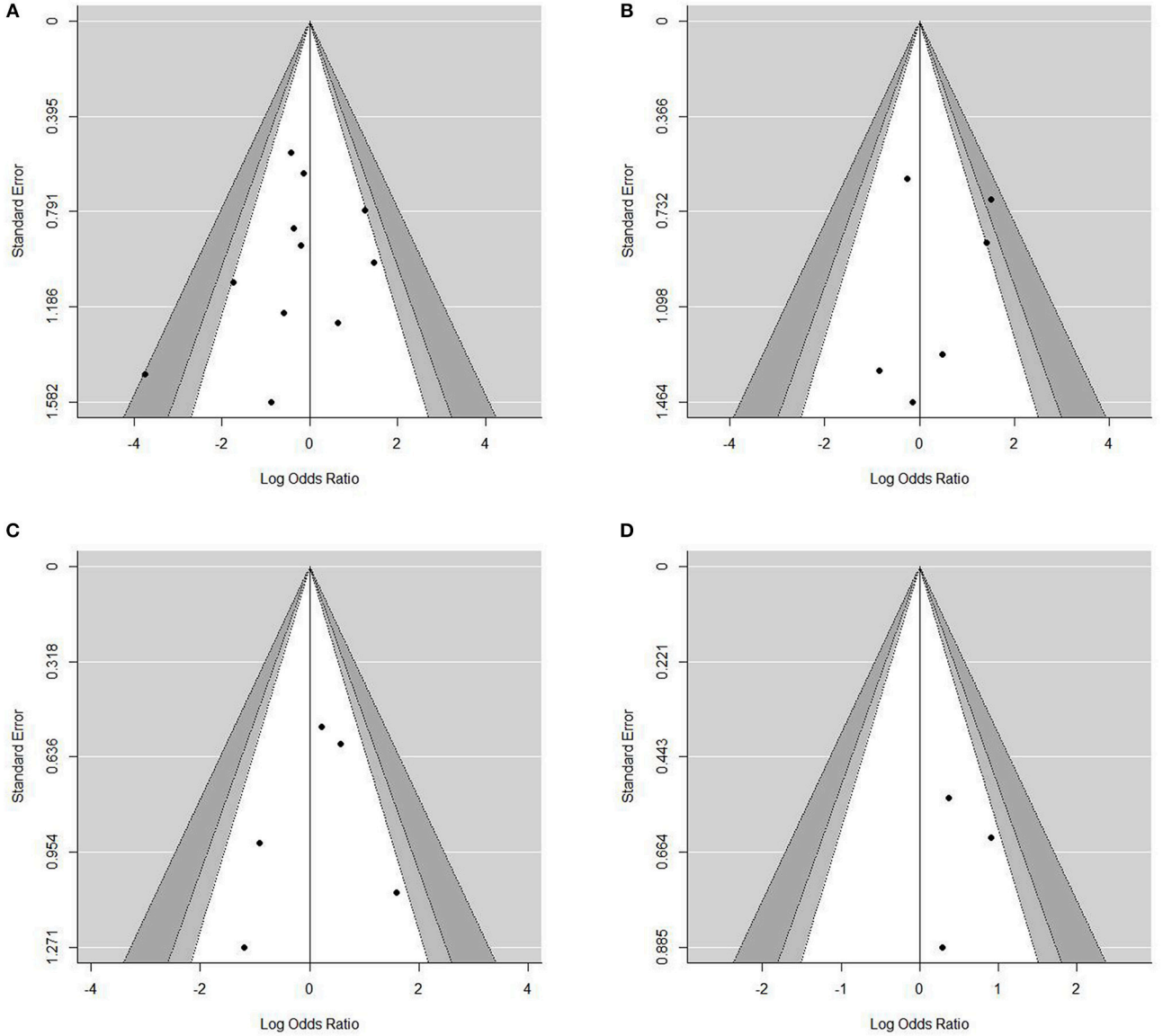


FIGURE 4 | Contour-enhanced funnel plots for the assessment of publication bias. Dots represent point estimates plotted over standard error. Shaded areas represent a given level of significances (*p*-values of 0.01, 0.05, 0.1).
(A) Funnel plot for contrast enhancement.
(B) Funnel plot for eccentricity
(C) Funnel plot for positive remodeling
(D) Funnel plot for surface irregularity.

As we demonstrated in our study, intracranial plaque enhancement has been known as an imaging marker for plaque vulnerability, and some studies have suggested that this enhancement can be independent of stenosis degree; its mechanism can be explained by vessel-wall neovascularization and inflammation (31). Although contrast enhancement also has been recognized as MRI sign of plaque vulnerability in extracranial carotid arteries, it serves as less precise marker of vulnerable plaque than IPH or thin fibrous cap showing on non-enhanced multi-contrast MRI. However, the present meta-analysis suggested that plaque enhancement might be highly reliable to predict high-risk plaques in intracranial arteries.

This meta-analysis also found that plaque enhancement was more significantly related to infarction caused by large-artery atherosclerosis than to infarction caused by small-vessel occlusion. This finding strengthened the assumption that plaque enhancement can help discriminate the subtype of stroke in ipsilateral stenotic lesions (27).

Arterial Remodeling

Arterial remodeling is an important mechanism in the pathogenesis of atherosclerosis and this mechanism has been explored in the carotid and coronary arteries (32, 33). Vascular remodeling is related to plaque area and plaque components,

TABLE 4 | Publication bias measures.

Characteristics of plaque on MRI	Publication bias (begg and mazumdar rank correlation)		
	Kendell τ	Z-value for τ	*P*-value
Contrast enhancement	0.109	0.467	0.640
Eccentricity	−0.190	0.601	0.548
Positive remodeling	0.100	0.245	0.807
Irregularity	0.667	1.044	0.296

supporting higher vulnerability in positive remodeling than negative remodeling with the same degree of stenosis (34). The present meta-analysis confirmed that positive remodeling can be a specific marker of vulnerability in intracranial plaques, in line with previous suggestions regarding the coronary arteries.

In our experience, there are several limitations in effective acquisition of vessel-wall MRI to monitor intracranial remodeling. It can be used for relatively larger-size arteries to obtain adequate resolution due to marginal blurring. It is necessary to identify the target lesion when obtaining the cross-sectional image.

IPH

A meta-analysis that analyzed longitudinal observational studies on extracranial carotid plaques with MRI found that the presence of IPH is a reliable predictor of subsequent stroke or transient ischemic attack (35). However, half of the enrolled studies in the current review did not report a statistically significant correlation between IPH and recent ischemic stroke, and we could not sum the OR of each study due to significant heterogeneity. A major limitation of IPH in intracranial plaques is that we cannot be certain whether high signal intensity within plaque on T1 weighted MRI is true IPH, because there has been no direct histological evidence for IPH on plaque MRI imaging. Another limitation of IPH detection through plaque vulnerability is the low prevalence of IPH at the site of the stenosis (16), suggesting low negative predictability. In carotid plaque imaging, multi-contrast MRI composed of four or more sequences (T1, T2, proton-density-weighted, the source images of time of flight MR angiography, and others) is recommended to delineate major imaging markers of vulnerability including IPH, lipid-rich necrotic core, and rupture of the fibrous cap. However, the present results suggested that pre-and post-contrast T1-weighted MRI and/or proton density MRI is sufficient to show major high-risk findings, contrast enhancement, degree of remodeling, and plaque irregularity.

LIMITATIONS

Our study illustrates several limitations of MRI plaque characterization related to ischemic stroke risk. First, all included studies had small sample sizes, with limited power for subgroup analyses. The pooled results of our meta-analysis need to be considered in the context of the included studies, in which the number of subjects in some of the subgroups was low. Second, the included studies employed different methodologies. There was variation in study design, eligibility of patient inclusion, and reporting outcomes. Although the statistical analysis of heterogeneity in effect sizes showed homogeneity among studies, the methodological diversity may have led to misinterpretation of the pooled estimates. Third, we could not adjust our estimates for the potentially confounding factors of plaque volume or degree of stenosis severity, which were not systematically specified in all included studies. This lack of data reduced the study's power and decreased estimate precision. In this study, we attempted to reduce the heterogeneity by presenting the results of subgroup analysis in patients with MCA lesions. The predictability of each finding may be meaningful, but more useful findings could not be determined.

CONCLUSION

In this study, by pooling the available evidence, we identified three imaging markers of culprit lesions for intracranial plaques: contrast enhancement, positive remodeling, and plaque irregularity, and these can lead to improved patient diagnosis and better decision-making for clinicians. Recently, the appearance of studies regarding intracranial vessel-wall MRI has been rapidly increasing in the literature, but they involve limitations in terms of research quality.

No obvious clinical benefit has been obtained from the use of intracranial vessel-wall MRI, since few of the published studies had a prospective design or involved controlled comparisons. Based on the present study, it is necessary to strengthen the theoretical basis for future prospective studies by developing a method of morphologic-characteristic description and standardization of imaging parameters of intracranial plaques.

AUTHOR CONTRIBUTIONS

C-WR conceived and designed the study, collected data, provided guidance, oversight of the study and manuscript, and drafted the manuscript. HNL collected data, performed the statistical analysis, and contributed to manuscript drafting. SJY collected data and performed the statistical analysis.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2018.01032/full#supplementary-material

REFERENCES

1. Kiechl S, Willeit J. The natural course of atherosclerosis. Part II: vascular remodeling. Bruneck Study Group. *Aarterioscler Thomb Vasc Biol*. (1999) 19:1491–8. doi: 10.1161/01.ATV.19.6.1491
2. Ryu CW, Jahng GH, Kim EJ, Choi WS, Yang DM. High resolution wall and lumen MRI of the middle cerebral arteries at 3 tesla. *Cerebrovasc Dis*. (2009) 27:433–42. doi: 10.1159/000209238
3. Millon A, Boussel L, Brevet M, Mathevet JL, Canet-Soulas E, Mory C, et al. Clinical and histological significance of gadolinium enhancement in carotid atherosclerotic plaque. *Stroke* (2012) 43:3023–8. doi: 10.1161/STROKEAHA.112.662692
4. Wityk RJ, Lehman D, Klag M, Coresh J, Ahn H, Litt B. Race and sex differences in the distribution of cerebral atherosclerosis. *Stroke* (1996) 27:1974–80. doi: 10.1161/01.STR.27.11.1974
5. Wong LK. Global burden of intracranial atherosclerosis. *Int J Stroke* (2006) 1:158–9. doi: 10.1111/j.1747-4949.2006.00045.x
6. Zhao DL, Deng G, Xie B, Ju S, Yang M, Chen XH, et al. High-resolution MRI of the vessel wall in patients with symptomatic atherosclerotic stenosis of the middle cerebral artery. *J Clin Neurosci*. (2015) 22:700–4. doi: 10.1016/j.jocn.2014.10.018
7. Gupta A, Baradaran H, Al-Dasuqi K, Knight-Greenfield A, Giambrone AE, Delgado D, et al. Gadolinium enhancement in intracranial atherosclerotic plaque and ischemic stroke: a systematic review and meta-analysis. *J Am Heart Assoc*. (2016) 5:e003816. doi: 10.1161/JAHA.116.003816
8. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* (2000) 283:2008–12. doi: 10.1001/jama.283.15.2008
9. National Heart Lung and Blood Institute. *Data From: Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies* (2014). Available online at: http://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort
10. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res*. (2018) 27:1785–805. doi: 10.1177/0962280216669183
11. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol*. (2008) 61:991–6. doi: 10.1016/j.jclinepi.2007.11.010
12. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* (1994) 50:1088–101. doi: 10.2307/2533446
13. Xu WH, Li ML, Gao S, Ni J, Zhou LX, Yao M, et al. *In vivo* high-resolution MR imaging of symptomatic and asymptomatic middle cerebral artery atherosclerotic stenosis. *Atherosclerosis* (2010) 212:507–11. doi: 10.1016/j.atherosclerosis.2010.06.035
14. Chung GH, Kwak HS, Hwang SB, Jin GY. High resolution MR imaging in patients with symptomatic middle cerebral artery stenosis. *Eur J Radiol*. (2012) 81:4069–74. doi: 10.1016/j.ejrad.2012.07.001
15. Kim JM, Jung KH, Sohn CH, Moon J, Han MH, Roh JK. Middle cerebral artery plaque and prediction of the infarction pattern. *Arch Neurol*. (2012) 69:1470–5. doi: 10.1001/archneurol.2012.1018
16. Xu WH, Li ML, Gao S, Ni J, Yao M, Zhou LX, et al. Middle cerebral artery intraplaque hemorrhage: prevalence and clinical relevance. *Ann Neurol*. (2012) 71:195–8. doi: 10.1002/ana.22626
17. Vakil P, Vranic J, Hurley MC, Bernstein RA, Korutz AW, Habib A, et al. T1 gadolinium enhancement of intracranial atherosclerotic plaques associated with symptomatic ischemic presentations. *AJNR Am J Neuroradiol*. (2013) 34:2252–8. doi: 10.3174/ajnr.A3606
18. Ryu CW, Jahng GH, Shin HS. Gadolinium enhancement of atherosclerotic plaque in the middle cerebral artery: relation to symptoms and degree of stenosis. *AJNR Am J Neuroradiol*. (2014) 35:2306–10. doi: 10.3174/ajnr.A4038
19. Yang WQ, Huang B, Liu XT, Liu HJ, Li PJ, Zhu WZ. Reproducibility of high-resolution MRI for the middle cerebral artery plaque at 3T. *Eur J Radiol*. (2014) 83:e49–55. doi: 10.1016/j.ejrad.2013.10.003
20. Qiao Y, Zeiler SR, Mirbagheri S, Leigh R, Urrutia V, Wityk R, et al. Intracranial plaque enhancement in patients with cerebrovascular events on high-spatial-resolution MR images. *Radiology* (2014) 271:534–42. doi: 10.1148/radiol.13122812
21. Ryoo S, Lee MJ, Cha J, Jeon P, Bang OY. Differential vascular pathophysiologic types of intracranial atherosclerotic stroke: a high-resolution wall magnetic resonance imaging study. *Stroke* (2015) 46:2815–21. doi: 10.1161/STROKEAHA.115.010894
22. Xu P, Lv L, Li S, Ge H, Rong Y, Hu C, et al. Use of high-resolution 3.0-T magnetic resonance imaging to characterize atherosclerotic plaques in patients with cerebral infarction. *Exp Ther Med*. (2015) 10:2424–8. doi: 10.3892/etm.2015.2815
23. Yu JH, Kwak HS, Chung GH, Hwang SB, Park MS, Park SH. Association of intraplaque hemorrhage and acute infarction in patients with basilar artery plaque. *Stroke* (2015) 46:2768–72. doi: 10.1161/STROKEAHA.115.009412
24. Teng Z, Peng W, Zhan Q, Zhang X, Liu Q, Chen S, et al. An assessment on the incremental value of high-resolution magnetic resonance imaging to identify culprit plaques in atherosclerotic disease of the middle cerebral artery. *Eur Radiol*. (2016) 26:2206–14. doi: 10.1007/s00330-015-4008-5
25. Zhang DF, Chen YC, Chen H, Zhang WD, Sun J, Mao CN, et al. A high-resolution MRI study of relationship between remodeling patterns and ischemic stroke in patients with atherosclerotic middle cerebral artery stenosis. *Front Aing Neurosci*. (2017) 9:140. doi: 10.3389/fnagi.2017.00140
26. Wang W, Yang Q, Li D, Fan Z, Bi X, Du X, et al. Incremental value of plaque enhancement in patients with moderate or severe basilar artery stenosis: 3.0 T high-resolution magnetic resonance study. *Biomed Res Int*. (2017) 2017:4281629. doi: 10.1155/2017/4281629
27. Jang J, Kim TW, Hwang EJ, Choi HS, Koo J, Shin YS, et al. Assessment of arterial wall enhancement for differentiation of parent artery disease from small artery disease: comparison between histogram analysis and visual analysis on 3-dimensional contrast-enhanced T1-weighted turbo spin echo MR images at 3T. *Korean J Radiol*. (2017) 18:383–91. doi: 10.3348/kjr.2017.18.2.383
28. Wu F, Song H, Ma Q, Xiao J, Jiang T, Huang X, et al. Hyperintense plaque on intracranial vessel wall magnetic resonance imaging as a predictor of artery-to-artery embolic infarction. *Stroke* (2018) 49:905–11. doi: 10.1161/STROKEAHA.117.020046
29. Zhu C, Tian X, Degnan AJ, Shi Z, Zhang X, Chen L, et al. Clinical significance of intraplaque hemorrhage in low- and high-grade basilar artery stenosis on high-resolution MRI. *AJNR Am J Neuroradiol*. (2018) 39:1286–92. doi: 10.3174/ajnr.A5676
30. Lu SS, Ge S, Su CQ, Xie J, Mao J, Shi HB, et al. MRI of plaque characteristics and relationship with downstream perfusion and cerebral infarction in patients with symptomatic middle cerebral artery stenosis. *J Magn Reson Imaging* (2018) 48:66–73. doi: 10.1002/jmri.25879
31. Kerwin WS, Oikawa M, Yuan C, Jarvik GP, Hatsukami TS. MR imaging of adventitial vasa vasorum in carotid atherosclerosis. *Magn Reson Med*. (2008) 59:507–14. doi: 10.1002/mrm.21532

32. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med*. (1987) 316:1371–5. doi: 10.1056/NEJM198705283162204
33. Birnbaum Y, Fishbein MC, Luo H, Nishioka T, Siegel RJ. Regional remodeling of atherosclerotic arteries: a major determinant of clinical manifestations of disease. *J Am Coll Cardiol*. (1997) 30:1149–64. doi: 10.1016/S0735-1097(97)00320-3
34. Rodriguez-Granillo GA, Serruys PW, Garcia-Garcia HM, Aoki J, Valgimigli M, van Mieghem CA, et al. Coronary artery remodelling is related to plaque composition. *Heart* (2006) 92:388–91. doi: 10.1136/hrt.2004.057810
35. Gupta A, Baradaran H, Schweitzer AD, Kamel H, Pandya A, Delgado D, et al. Carotid plaque MRI and stroke risk: a systematic review and meta-analysis. *Stroke* (2013) 44:3071–7. doi: 10.1161/STROKEAHA.113.002551

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer HSK declared a past co-authorship with one of the authors C-WR to the handling editor.

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ORIGINAL RESEARCH
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Solitaire Thrombectomy for Acute Stroke Due to Intracranial Atherosclerosis-Related Occlusion: ROSE ASSIST Study

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Background: Solitaire, a representative stent retriever, has shown high performance in removing embolic clots. However, its reperfusion potential in intracranial atherosclerotic stenosis (ICAS)-related occlusions has rarely been reported. In this ROSE ASSIST study, we hypothesized that Solitaire device is as effective and safe for removing *in situ* thrombi in ICAS-related occlusions as it is for removal of embolic occlusions.

Methods: Data from ASIAN KR, an observational multicenter registry ($n = 720$) enrolling patients who have undergone endovascular treatment for acute cervicocephalic artery occlusions, were retrospectively reviewed. Through blinded evaluations, occlusions were classified as ICAS-related (significant fixed focal stenosis observed at the occlusion site during endovascular treatment) or embolic (no or minimal stenosis observed). Among patients treated within 720 min after stroke onset, those who undertook Solitaire thrombectomy and whose underlying etiology was ICAS-related or embolic were included. The primary endpoint was immediate successful reperfusion (modified Treatment In Cerebral Ischemia 2b−3) after Solitaire stent retrieval. The safety endpoint included intracerebral hemorrhagic transformation and subarachnoid hemorrhage. Comparative analyses were performed between embolic and ICAS-related occlusions with 2:1 propensity score matching.

Results: In total, 303 patients (embolic, 228; ICAS-related, 75) were included in the analyses. As for the primary endpoint, the immediate successful reperfusion rate following Solitaire thrombectomy did not differ between the two etiologic groups after propensity score matching (73.1% embolic vs. 65.8% ICAS-related, $p = 0.261$). The final successful reperfusion grade was also similar in the two groups (79.3 vs. 72.0%, $p = 0.219$). The

grades and frequencies of intracerebral hemorrhagic transformation and subarachnoid hemorrhage did not differ between groups ($p = 0.134$ and $p = 0.269$, respectively).

Conclusions: The immediate reperfusion performance in terms of thrombus removal of Solitaire thrombectomy for ICAS-related occlusions was similar to that for embolic occlusions.

Keywords: cerebral infarction, stent, thrombectomy, intracranial atherosclerosis, intracranial embolism

INTRODUCTION

Mechanical thrombectomy with stent retrievers has achieved high level of evidence for the treatment for patients with acute ischemic stroke caused by intracranial large artery occlusion (1). The mechanical thrombectomy method utilizing stent retrievers results in both a high recanalization rate and a good prognosis in the embolic occlusion cases (2–5). As for a prototype stent retriever, the Solitaire device, its efficacy is well-known both in Asian (6–8) and Western (9, 10) countries. However, its effectiveness for large artery occlusions due to intracranial atherosclerotic stenosis (ICAS) and *in situ* thrombosis has rarely been reported.

In North America and Europe, acute cerebral infarctions from intracranial large artery occlusions are most often due to embolism. In contrast, in Asia, acute ischemic strokes from intracranial large artery occlusions are often caused by *in situ* atherosclerotic mechanisms (11–13). The frequency of ICAS-related occlusions is reported as 15.2% of intracranial large artery occlusions involving the anterior circulation (13) and as 37.5% of occlusions involving the posterior circulation (14). A French study reported that it accounted for only 5.5% of patients with stent retrieval treatment (15).

To date, the performance of stent retrievers is mostly proven for embolic occlusions. In a preliminary study, the Solitaire stent was efficient in removing *in situ* thrombi in ICAS-related occlusions (16). Additionally, Solitaire stent thrombectomy achieved immediate successful reperfusion in several consecutive patients. In this Role of Solitaire in Endovascular Treatment for Acute Serious Stroke Due to Intracranial *in situ* Thrombosis (ROSE ASSIST) study, we hypothesized that Solitaire thrombectomy is as effective and safe for thrombus removal in ICAS-related occlusions as it is for embolic occlusions and analyzed in a large retrospective registry.

METHODS

The ASIAN KR Registry and the ROSE ASSIST Study

The ASIAN KR registry was created for observational research and consists of consecutive patients, aged 18 years or older, who received endovascular treatment (EVT) for the treatment of acute ischemic stroke due to intracranial and/or extracranial large vessel occlusion (17). The type of EVT procedure was chosen at the discretion of the treating physician. Both de-identification and the allocation of study identification numbers were performed for all clinical data. After de-identification and blinding of clinical data, core laboratory imaging analyses were performed to ensure consistent grading and to eliminate bias. The data collection protocol was approved by the institutional review board of each respective hospital and implemented in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

The ROSE ASSIST study was designed for proving effectiveness and safety of Solitaire thrombectomy for thrombus removal in ICAS-related occlusions. Although being sponsored by Medtronic, the study was conducted independently from the company.

Etiologic Classification of Target Occlusive Lesions

The etiology of target large vessel occlusion was determined by stepwise angiographic analysis with procedural digital subtraction images (YHH, LJS) and postprocedural repeat angiographies obtained during admission (JSY) (14, 18–20). First, uncommon occlusive etiologies including dissection, Moyamoya disease and vasculitis, and the extracranial artery disease-related occlusions were excluded. Second, when the occluded vessel was completely recanalized, the etiology was classified as embolic occlusion. Third, remaining stenosis >70% or less-degree stenosis with a tendency of re-occlusion or flow impairment during the procedure and on final angiography was classified as ICAS-related occlusion. When recanalization could not be achieved during the procedure to determine the etiology, it was specifically classified as intractable occlusion cases, which were also excluded from the current study. In most cases, the classification of ICAS-related and embolic occlusion was not difficult by angiographic evaluations. However, for some cases, including mild stenosis, we determined the underlying etiology with consensus between YHH and JSL. Lastly, this mechanism was further evaluated by repeat angiography following EVT during admission (JSY).

Inclusion and Exclusion Criteria

A. Inclusion criteria:

- Patients with acute ischemic stroke who had intracranial large artery occlusion (arterial occlusive lesion grade 0) on baseline computed tomography (CT) or magnetic resonance angiography within the vascular territory corresponding to the neurologic deficit observed at the neurologic examination.
- Time from stroke onset to presentation <12 h.
- Patients who underwent the endovascular revascularization treatment with the Solitaire stent.

B. Exclusion criteria:

- Intracranial large artery occlusion due to uncommon stroke etiology including arterial dissection, Moyamoya disease, and vasculitis.
- Tandem intracranial large artery occlusions caused by extracranial arterial disease.
- Patients in whom the arterial lesion status could not be reliably assessed due to either persistent occlusion or incomplete recanalization.

Propensity Score Matching

To reduce the effects of selection bias and potential confounding between the two groups, we performed adjustments for significant differences in the baseline characteristics of the patients using propensity score matching. The propensity scores were estimated using multiple logistic-regression analysis. Variables chosen for inclusion in the model were age, sex, intravenous recombinant tissue plasminogen activator use, onset-to-puncture time, intracranial occlusion locations, and Solitaire use as primary vs. rescue treatment. After estimating the propensity score, the ICAS and embolic groups were matched at a ratio of one to two. This matching was performed using R version 3.4.1 with MatchIt package (version 3.0.2).

Endpoints

The primary endpoint was immediate successful reperfusion (modified Treatment In Cerebral Ischemia 2b−3) after Solitaire stent thrombectomy. The secondary safety endpoints included (1) degree and frequency of intracerebral hemorrhage on non-contrast CT or magnetic resonance imaging within 7 days, and (2) degree and frequency of subarachnoid hemorrhage on non-contrast CT within 24 h after EVT. Intracerebral hemorrhages were classified in accordance with criteria defined by the European Cooperative Acute Stroke Study (S.I.S.) (21). Subarachnoid hemorrhage was classified according to the modified Fisher scale (S.I.S.) (22).

Statistics

Differences between the groups were analyzed using χ^2 tests for categorical variables, the Mann-Whitney test for ordinal variables and Student's t-tests for continuous variables. After propensity score matching, independent statistics were also used due to incomplete pairing. For evaluating procedural outcomes on the primary use of Solitaire thrombectomy, variables were compared in embolic and ICAS groups without propensity score matching. $P < 0.05$ were considered significant. Statistical analysis was performed using the SPSS statistical package (version 22.0, Chicago, IL).

RESULTS

Baseline Characteristics and Propensity Score Matching

Seventy-five and 228 patients were included in the ICAS and embolic groups, respectively, based on the study criteria (**Figure 1**). The baseline characteristics and treatments are summarized in **Table 1**. Compared to those in the embolic group, patients in the ICAS group were younger (68.5 ± 13.4 vs. 64.3 ± 14.0 years, $p = 0.019$) and presented higher total cholesterol levels (163 ± 38 vs. 183 ± 41 mg/dL, $p < 0.001$), low-density lipoprotein levels (95 ± 34 vs. 115 ± 38 mg/dL,

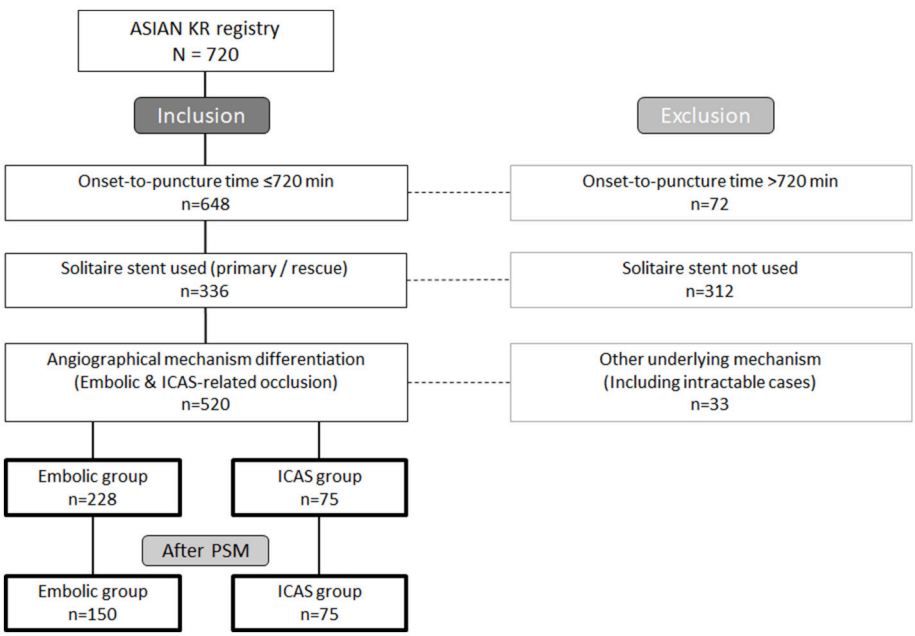

FIGURE 1 | Flowchart illustrating the current study. PSM, propensity score matching.

$p < 0.001$), and systolic (142 ± 26 vs. 149 ± 26 mmHg, $p = 0.034$) and diastolic (81 ± 15 vs. 85 ± 14 mmHg, $p = 0.040$) blood pressure. They were also more frequently male (47.8 vs. 64.0%, $p = 0.015$), more commonly smokers (16.2 vs. 32.0%, $p = 0.003$), and more frequently presented occlusions in the M1 portion of the middle cerebral artery (MCA) ($p < 0.001$). They also less commonly had atrial fibrillation as a comorbidity (59.6% vs. 22.7%, $p < 0.001$). When compared to those in the embolic group, patients in the ICAS group underwent intravenous recombinant tissue plasminogen activator treatment less frequently (64.9% vs. 44.0%, $p = 0.001$) and had significantly longer onset-to-puncture times (258 ± 132 min vs. 333 ± 164 min, $p < 0.001$).

After matching, the differences in age, sex, intravenous recombinant tissue plasminogen activator treatment, and onset-to-puncture time between the two groups were balanced. The proportions of MCA M1 and vertebrobasilar artery occlusions, however, were still higher in the ICAS group, while internal carotid artery terminal and MCA M2 occlusions were more frequent in the embolic group ($p < 0.001$). Solitaire thrombectomy was used in 79 patients (52.7%) as primary treatment and in 71 (47.3%) as rescue treatment in the embolic group, whereas it was employed in 38 patients (49.3%) as primary treatment and in 38 (50.7%) as rescue treatment in the ICAS group ($p = 0.637$).

Immediate Reperfusion Performance and Safety

The results of comparing outcomes are summarized in **Table 2**. The immediate successful reperfusion rate following Solitaire thrombectomy, which was the primary outcome, did not differ between the embolic and ICAS groups (73.1 vs. 65.8%, $p = 0.261$). Specifically, the immediate success rates were relatively higher in the ICAS-related occlusion cases when

TABLE 1 | Baseline characteristics and treatments used before and after propensity score matching.

	Before propensity score matching			After propensity score matching		
	Embolic	**ICAS**	***P***	**Embolic**	**ICAS**	***p***
Number	228	75		150	75	
Age, years	68.5 ± 13.4	64.3 ± 14.0	0.019	64.9 ± 14.0	64.3 ± 14.0	0.754
Male sex	109 (47.8%)	48 (64.0%)	0.015	90 (60.0%)	48 (64.0%)	0.561
Premorbid mRS, median [IQR]	0 [0–0]	0 [0–0]	0.880	0 [0–0]	0 [0–0]	0.695
Initial NIHSS score, median [IQR]	17 [13–20]	16 [12–20]	0.316	16.5 [13–20]	16 [12–20]	0.574
Baseline occlusion location			<0.001			<0.001
ICA T	94 (41.2%)	15 (20.0%)		63 (42.0%)	15 (20.0%)	
MCA M1	94 (41.2%)	46 (61.3%)		60 (40.0%)	46 (61.3%)	
MCA M2	23 (10.1%)	1 (1.3%)		15 (10.0%)	1 (1.3%)	
VBA	14 (6.1%)	13 (17.3%)		9 (6.0%)	13 (17.3%)	
Others	3 (1.3%)	0 (0%)		3 (2.0%)	0 (0%)	
Hypertension	142 (62.3%)	49 (65.3%)	0.635	89 (59.3%)	49 (65.3%)	0.384
Diabetes mellitus	47 (20.6%)	22 (29.3%)	0.118	31 (20.7%)	22 (29.3%)	0.149
Atrial fibrillation	136 (59.6%)	17 (22.7%)	<0.001	85 (56.7%)	17 (22.7%)	<0.001
Coronary artery occlusive disease	29 (12.7%)	6 (8.0%)	0.267	16 (10.7%)	6 (8.0%)	0.526
Smoking	37 (16.2%)	24 (32.0%)	0.003	30 (20.0%)	24 (32.0%)	0.047
Admission glucose level, mg/dl	136 ± 47	151 ± 63	0.058	132 ± 46	151 ± 63	0.021
Total cholesterol level, mg/dl	163 ± 38	183 ± 41	<0.001	163 ± 39	183 ± 41	0.001
Triglyceride level, mg/dl	110 ± 63	135 ± 141	0.136	116 ± 64	135 ± 141	0.180
High-density lipid level, mg/dl	48 ± 27	45 ± 10	0.357	49 ± 32	45 ± 10	0.349
Low-density lipid level, mg/dl	95 ± 34	115 ± 38	<0.001	95 ± 37	115 ± 38	<0.001
C-reactive protein level	0.74 ± 1.96	0.81 ± 1.96	0.775	0.74 ± 2.17	0.81 ± 1.96	0.811
Initial systolic blood pressure, mmHg	142 ± 26	149 ± 26	0.034	143 ± 27	149 ± 26	0.096
Initial diastolic blood pressure, mmHg	81 ± 15	85 ± 14	0.040	82 ± 15	85 ± 14	0.162
Intravenous thrombolysis	148 (64.9%)	33 (44.0%)	0.001	83 (55.3%)	33 (44.0%)	0.109
Onset to puncture time, min	258 ± 132	333 ± 164	<0.001	296 ± 144	333 ± 164	0.080
Puncture to final angiography time, min	80 ± 48	90 ± 48	0.138	87 ± 52	90 ± 48	0.710
Solitaire use as			0.142			0.637
Primary treatment	134 (59.0%)	37 (49.3%)		79 (52.7%)	37 (49.3%)	
Rescue treatment	93 (41.0%)	38 (50.7%)		71 (47.3%)	38 (50.7%)	

ICAS, intracranial atherosclerotic stenosis; mRS, modified Rankin Scale; NIHSS, national Institute of Health stroke scale; ICA, internal carotid artery; MCA, middle cerebral artery; VBA, vertebrobasilar artery.

Solitaire thrombectomy was used as primary treatment (79.7 vs. 75.7%, $p = 0.619$) than in cases wherein it was used as rescue treatment (65.2 vs. 55.6%, $p = 0.341$) (**Figure 2**). Representative cases are illustrated in **Figures 3**, **4**. Overall, EVT performed using all feasible methods resulted in similar final reperfusion rates in the two groups (embolic vs. ICAS, 79.3 vs. 72.0%, $p = 0.219$).

The degree and frequency of post-procedural intracerebral hemorrhage, which were the secondary (safety) endpoints, did not differ between the two groups ($p = 0.134$). In concordance, the degree and frequency of post-procedural subarachnoid hemorrhage did not differ between the groups ($p = 0.269$). Finally, also the rate of independent functional outcomes did not differ between the two groups (47.3 vs. 37.3%, $p = 0.154$).

Subgroup Analyses for the Primary Use of Solitaire

After primary thrombectomy with Solitaire device, immediate side effects and rescue treatments were evaluated (**Table 3**). In terms of immediate side effects following primary Solitaire thrombectomy, compared to the embolic group, target vessel injury (3.7 vs. 13.5%, $p = 0.025$) and reocclusion (1.5 vs. 24.3%, <0.001) more frequently occurred in the ICAS group whereas the occurrence of vasospasm and clot migration into another vessel did not differ. As for rescue treatments, tirofiban local infusion (7.5 vs. 40.5%, $p < 0.001$), intracranial balloon angioplasty (1.5 vs. 8.1%, $p = 0.034$) and intracranial stenting (3.7 vs. 16.2%, $p = 0.006$) were more frequently performed in the ICAS group. Procedural time was longer in the ICAS group (61.6 min vs. 79.6 min, $p = 0.012$).

DISCUSSION

In the current study, we investigated whether mechanical thrombectomy using the Solitaire stent had an immediate reperfusion performance in ICAS-related occlusions comparable to that in usual embolic occlusions. To minimize mismatching of baseline characteristics, we performed propensity score matching (23). The immediate reperfusion performance of Solitaire thrombectomy was substantial for ICAS-related occlusions when compared to embolic occlusions. Moreover,

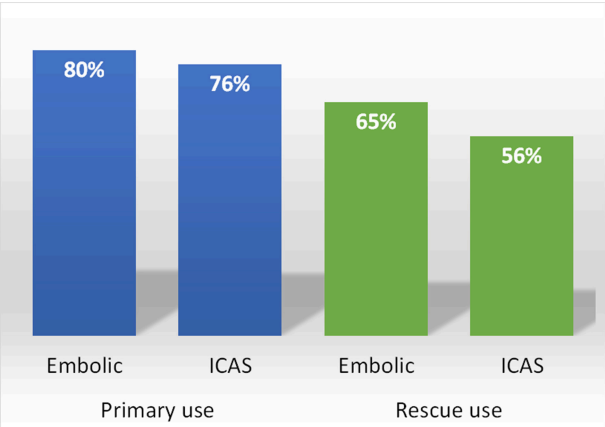

FIGURE 2 | Immediate successful reperfusion rates in embolic and ICAS-related occlusions after Solitaire thrombectomy used as either primary or rescue treatment.

TABLE 2 | Revascularization outcomes.

	Before propensity score matching			After propensity score matching		
	Embolic	**ICAS**	***P***	**Embolic**	**ICAS**	***p***
Immediate successful reperfusion by Solitaire	75.5%	65.8%	0.106	106 (73.1%)	48 (65.8%)	0.261
Final successful reperfusion	183 (80.3%)	54 (72.0%)	0.133	119 (79.3%)	54 (72.0%)	0.219
Post-procedural intracerebral hemorrhagic transformation			0.175			0.134
None	138 (60.5%)	56 (74.7%)		88 (58.7%)	56 (74.7%)	
Hemorrhagic transformation 1	18 (7.9%)	3 (4.0%)		10 (6.7%)	3 (4.0%)	
Hemorrhagic transformation 2	32 (14.0%)	6 (8.0%)		22 (14.7%)	6 (8.0%)	
Parenchymal hematoma 1	20 (8.8%)	3 (4.0%)		16 (10.7%)	3 (4.0%)	
Parenchymal hematoma 2	20 (8.8%)	7 (9.3%)		14 (9.3%)	7 (9.3%)	
Post-procedural subarachnoid hemorrhage			0.298			0.269
None	195 (85.5%)	70 (93.3%)		126 (84.0%)	70 (93.3%)	
Grade 1	15 (6.6%)	2 (2.7%)		10 (6.7%)	2 (2.7%)	
Grade 2	5 (2.2%)	0 (0%)		2 (1.3%)	0 (0%)	
Grade 3	4 (1.8%)	0 (0%)		4 (2.7%)	0 (0%)	
Grade 4	9 (3.9%)	3 (4.0%)		8 (5.3%)	3 (4.0%)	
Modified Rankin Scale 0–2 at 3 months	104 (45.8%)	28 (37.3%)	0.199	71 (47.3%)	28 (37.3%)	0.154
Mortality at 3 months	36 (15.9%)	12 (16.0%)	0.977	24 (16.0%)	12 (16.0%)	1.000

ICAS, intracranial atherosclerotic stenosis; IQR, interquartile range.

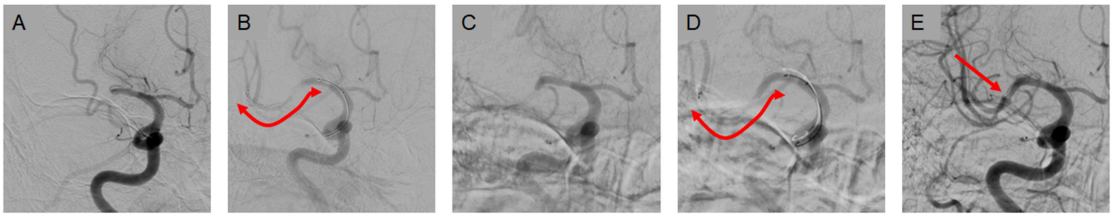

FIGURE 3 | A case of primary use of Solitaire thrombectomy in ICAS-related occlusions. **(A)** Occlusion is seen in the middle M1 segment of the middle cerebral artery prior to endovascular treatment. **(B)** The Solitaire stent was deployed for thrombectomy as primary treatment. **(C)** After the first pass, the clot was removed and partial recanalization was achieved, although focal stenosis was observed. **(D,E)** After 2 more passes, complete reperfusion was achieved despite the remaining focal stenosis.

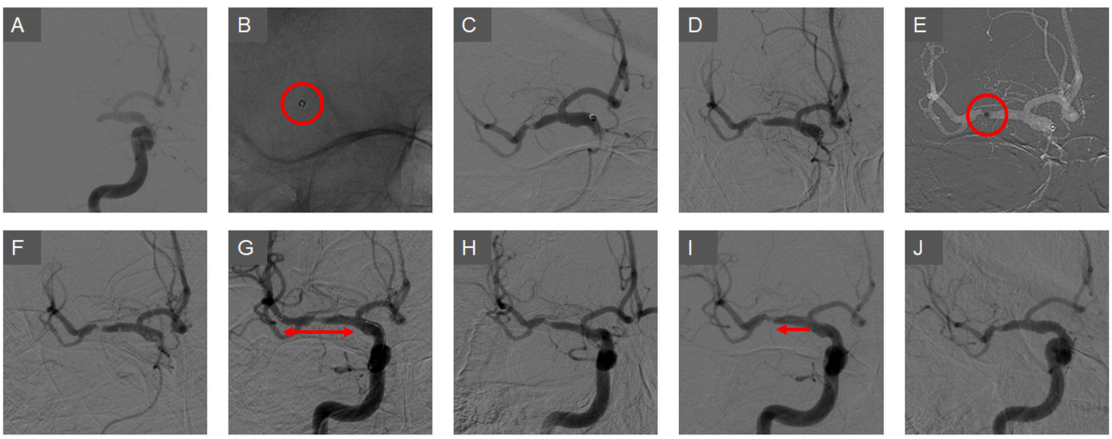

FIGURE 4 | A case of rescue treatment with the Solitaire stent in ICAS-related occlusions. **(A)** A right M1 occlusion is seen prior to the endovascular treatment. **(B)** The contact aspiration technique was used as the primary endovascular treatment. **(C)** The clot was removed, however, the focal stenosis was observed in the segment. **(D)** The vascular lesion appeared to be reoccluded soon after the treatment. **(E)** The aspiration catheter was placed further into the lesion and manipulated. **(F)** The vascular lesion appeared more aggravated and blood flow appeared to be impaired. **(G)** The Solitaire stent was deployed as a rescue treatment method. **(H)** After one pass, the vascular lesion was slightly improved and blood flow was somewhat restored. **(I)** After two more passes, the vessel was further recanalized. To prevent re-occlusion, low-dose tirofiban was infused. **(J)** In the final angiography, the vessel lesion appeared more stable and reperfusion was successfully achieved.

it was safe as shown by both the subarachnoid hemorrhage and intracerebral hemorrhagic transformation frequencies. Nevertheless, in subgroup analysis, ICAS-related occlusions were more associated with target vessel injury and immediate reocclusion than embolic occlusions, which resulted in an overall longer procedure time than embolic occlusions as they required more caution.

It has previously been suggested that thrombus formation and propagation are important pathomechanisms of neurological symptoms and signs resulting from ICAS-related occlusions in acute ischemic stroke (19). Moreover, previous anecdotal study suggested that the Solitaire stent retriever could be used to remove a thrombus in the ICAS-related occlusion (16). Nevertheless, the aforementioned findings needed further exploration in a larger population-based study with comparative analyses in standard embolic occlusion cases with baseline variable adjustments. Therefore, our group collected and combined multicenter registry data and evaluated the images in each imaging core lab. Our final outcome measures indicate that the rate of thrombus removal, which was represented by immediate reperfusion following the use of the Solitaire stent, was high for ICAS-related occlusions but not significantly different compared to that in the embolic occlusion cases. More specifically, the immediate reperfusion performance in the ICAS-related occlusion cases was nearly the same as that observed for embolic occlusions, when the Solitaire was used as a primary treatment method (76 vs. 80%).

Some physicians may become concerned that stent retrieval may induce vessel injury at the stenotic site. The Solitaire stent, which has an overlapping design, is expected to be smoothly retrieved through the stenotic vessel. Overall, the use of Solitaire thrombectomy during EVT did not have different outcomes in terms of subarachnoid hemorrhage occurrence in patients with ICAS-related occlusion compared to those with embolic occlusion. Nevertheless, target vessel injury following the primary use of Solitaire thrombectomy occurred more frequently in ICAS-related occlusion than in embolic occlusion. However, the relatively high frequency of those immediate side effects does

TABLE 3 | Procedural outcomes on the primary use of Solitaire thrombectomy (not matched).

	Embolic	ICAS	*P*
Number	134	37	
IMMEDIATE SIDE EFFECTS			
Vasospasm	4 (3.0%)	2 (5.4%)	0.479
Clot migration into another vessel	6 (4.5%)	3 (8.1%)	0.381
Target vessel injury	5 (3.7%)	5 (13.5%)	0.025
Immediate reocclusion	2 (1.5%)	9 (24.3%)	<0.001
RESCUE TREATMENTS			
Tirofiban local infusion	10 (7.5%)	15 (40.5%)	<0.001
Intracranial balloon angioplasty	2 (1.5%)	3 (8.1%)	0.034
Intracranial stenting	5 (3.7%)	6 (16.2%)	0.006
Procedural time (min)	61.6 ± 33.0	79.6 ± 48.9	0.012

not halt the primary use of Solitaire stent because its success rate of immediate reperfusion on ICAS-related occlusion was similar to that of embolic occlusion.

Several endovascular thrombectomy modalities, differing in stent retrieval, can be used for the treatment of the ICAS-related occlusion. However, these modalities were not addressed in the current study. For example, the contact aspiration technique is commonly used as a secondary treatment in cases intractable with stent retrieval, or vice versa (24). However, the switch between the two major types of thrombectomy techniques when stenosis is observed during a primary thrombectomy may be no longer needed. In a very recent study, up to four passes of stent retrieval achieved around 95% of reperfusion success for all types of intracranial large artery occlusions (25). It is experienced that a focal fixed stenosis can be mostly found within a few passes of stent retrieval for ICAS-related occlusions. We plan to further study the effectiveness and immediate side effects, such as vessel injury resulting from stent-retrieval thrombectomy vs. contact aspiration, when such techniques are used as primary treatments for ICAS-related occlusion.

Immediate reocclusion more frequently occurred in ICAS-related occlusion than in embolic occlusion in our subgroup analysis during the primary use of Solitaire thrombectomy. Reocclusion is associated with stent-retrieval failure as explained by truncal-type occlusion (26). The reocclusion rate of 24.3% in the current study is somewhat less than that reported previously. This reocclusion rate can vary based on different definitions. In the current study, the occurrence of reocclusion was evaluated only after the primary Solitaire thrombectomy. However, most cases of ICAS-related occlusions needed rescue treatments; therefore, the rate of reocclusion in the current analysis was calculated in a short time between the end of primary thrombectomy and the start of next rescue treatment, likely resulting in a lower rate. A recent study reported that the reocclusion rate accounted for 57.1% in ICAS-related occlusion and it was defined as an event occurring within at least 20 min after a sufficient recanalization (27). Another previous study showed reocclusion occurred in 65% cases of *in situ* thromboocclusions, which can be considered as ICAS-related occlusions (28). This study also defined reocclusion as the event count after recanalization. Another study reported 40% of instant reocclusion, which counted only the events that occurred during procedure only in M1 occlusion population (18). The tendency of reocclusion may also differ among vascular beds. On the other hand, delayed reocclusions that occurred after the procedure, was reported in 8 out of 40 patients (20%) in the above study (18). Another study showed delayed reocclusion in 15.7% of ICAS-related occlusions on repeat angiography (20). For further studies, it would be interesting if these reocclusion rates were compared according to primary thrombectomy methods.

Rescue treatment should be performed based on reocclusion tendency or tight stenosis in ICAS-related occlusions (19, 29). Local infusion of an antiplatelet agent may be one option. Tirofiban is an example of antiplatelet treatment, which is a glycoprotein 2b/3a inhibitor, and has been shown to be effective, at a low dose, in preventing reocclusion in patients with ICAS-related occlusions (28). In our population, the tirofiban local infusion was used in 40.5% of ICAS-related occlusions. Although the indication for tirofiban infusion was not prespecified in the current retrospective study, it might be used for reocclusion event or the prevention of reocclusion on stenosis. The relative lower rate of reocclusion (24.3%) in our study might be attributed to the preventive tirofiban infusion. On the other hand, considering that in coronary artery occlusive disease both angioplasty and stenting can be used, it has been suggested that these techniques may also be feasible for the treatment of ICAS-related occlusions (30). Although previous negative results from randomized control studies of intracranial stenting for preventing recurrent stroke may discourage from using this procedure (31–33), a very recent study showed that both local tirofiban infusion and angioplasty/stenting treatments were similarly effective and safe in emergent ICAS-related occlusion (34). In another study, permanent stent deployment as a rescue therapy for cases with thrombectomy failure, situations that possibly include substantial number of ICAS-related occlusions, showed better outcomes compared to no deployment (35, 36). When the intracranial angioplasty was optimally performed (residual stenosis $<50\%$), acute reocclusion rate was less compared to suboptimal cases (residual stenosis over 50%) (2.6 vs. 71.4%). After reviewing these retrospective study results, we concluded that appropriate combination of local antiplatelet infusion and intracranial angioplasty with or without stenting could improve the recanalization and clinical outcomes. There is still, however, a need to further prospectively study this treatment approach in patients with ICAS-related occlusions as it could potentially be used as another rescue treatment option following a Solitaire thrombectomy.

This study has a few limitations. First, the retrospective study design is an inherent limitation. However, ICAS-related occlusions cannot be diagnosed prior to EVT. Additionally, physicians can only see the presentation of intracranial large artery occlusions on baseline angiography, which is not sufficient to distinguish ICAS-related occlusions. To overcome this limitation, a large amount of registry data were collected and matching of baseline variables was performed. We therefore believe that both the reperfusion performance and the safety of Solitaire thrombectomy in the ICAS-related occlusions described

here are relevant. Second, although propensity score matching was used, all variables could not be matched; occlusion location was unbalanced even after matching. On the other hand, because of a large sample size difference between the two groups, 2:1 group matching was performed. Possibly due to these two factors, paired statistical tests were not performed in our analyses. Accordingly, we inevitably used independent statistical methods in the matched group comparisons (37). Additionally, our primary endpoint was not a clinical disability scale. Instead, we focused on the feasibility of Solitaire device in ICAS-related occlusions compared to embolic occlusions. The current findings must be cautiously interpreted, especially with respect to the main purpose. Last but not the least, we are unable to suggest what the best primary EVT method is for ICAS-related occlusions based on the results of the current study. Based on previously reported evidence, stent retrievers are supported by sufficient positive trial data as a tool for successful removal of clots in intracranial large artery occlusions (2–5, 10, 38, 39). Therefore, the first step for the treatment of ICAS-related occlusions should be to prove that stent retrievers have comparable performance and are safe compared to the usual embolic occlusions. In the current study, a prototype stent was selected for the evaluation among several similar stent retriever designs. The next step will be to compare both the reperfusion performance and the safety between stent retrieval and clot aspiration methods for the ICAS-related occlusions.

In conclusion, the Solitaire stent was shown to have both similar reperfusion performance and safety profile in the treatment of ICAS-related occlusions compared to embolic occlusions. Nevertheless, cases with minor vessel injuries and/or reocclusion tendencies needed further rescue treatments. Further studies evaluating technical approaches for the treatment of ICAS-related occlusions while addressing aforementioned limitations and issues should be conducted to improve patient outcomes.

AUTHOR CONTRIBUTIONS

JSL, S-JL, JH, JC, JY, J-HH, C-HK, Y-WK, D-HK, Y-SK, Y-HH, and S-IS contributed conception and design of the study; JSL, Y-HH, and S-IS organized the database; JSL, S-JL, and JY performed the statistical analysis; JSL wrote the first draft of the manuscript; S-JL and JY wrote sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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REFERENCES

1. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* (2018) 49:e46–110. doi: 10.1161/STR.0000000000000158
2. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med.* (2015) 372:1009–18. doi: 10.1056/NEJMoa1414792
3. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med.* (2015) 372:1019–30. doi: 10.1056/NEJMoa1414905
4. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med.* (2015) 372:2296–306. doi: 10.1056/NEJMoa1503780
5. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-PA vs. *t*-PA alone in stroke. *N Engl J Med.* (2015) 372:2285–95. doi: 10.1056/NEJMoa1415061
6. Kim JE, Kim AR, Paek YM, Cho YJ, Lee BH, Hong KS. Safety and efficacy of mechanical thrombectomy with the Solitaire device in large artery occlusion. *Neurol India* (2012) 60:400–5. doi: 10.4103/0028-3886.100701
7. Yoon YH, Yoon W, Jung MY, Yim NY, Kim BC, Kang HK. Outcome of mechanical thrombectomy with Solitaire stent as first-line intra-arterial treatment in intracranial internal carotid artery occlusion. *Neuroradiology* (2013) 55:999–1005. doi: 10.1007/s00234-013-1205-2
8. Baek JM, Yoon W, Kim SK, Jung MY, Park MS, Kim JT, et al. Acute basilar artery occlusion: outcome of mechanical thrombectomy with Solitaire stent within 8 hours of stroke onset. *AJNR Am J Neuroradiol.* (2014) 35:989–93. doi: 10.3174/ajnr.A3813
9. Roth C, Papanagiotou P, Behnke S, Walter S, Haass A, Becker C, et al. Stent-assisted mechanical recanalization for treatment of acute intracerebral artery occlusions. *Stroke* (2010) 41:2559–67. doi: 10.1161/STROKEAHA.110.592071
10. Saver JL, Jahan R, Levy EI, Jovin TG, Baxter B, Nogueira RG, et al. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. *Lancet* (2012) 380:1241–9. doi: 10.1016/S0140-6736(12)61384-1
11. Bang OY. Intracranial atherosclerosis: current understanding and perspectives. *J Stroke* (2014) 16:27–35. doi: 10.5853/jos.2014.16.1.27
12. Kim JS, Bonovich D. Research on intracranial atherosclerosis from the East and west: why are the results different? *J Stroke* (2014) 16:105–13. doi: 10.5853/jos.2014.16.3.105
13. Lee JS, Hong JM, Lee KS, Suh HI, Demchuk AM, Hwang YH, et al. Endovascular Therapy of cerebral arterial occlusions: intracranial atherosclerosis versus embolism. *J Stroke Cerebrovasc Dis.* (2015) 24:2074–80. doi: 10.1016/j.jstrokecerebrovasdis.2015.05.003
14. Kim YW, Hong JM, Park DG, Choi JW, Kang DH, Kim YS, et al. Effect of intracranial atherosclerotic disease on endovascular treatment for patients with acute vertebrobasilar occlusion *AJNR Am J Neuroradiol.* (2016) 37:2072–8. doi: 10.3174/ajnr.A4844
15. Gascou G, Lobotesis K, Machi P, Maldonado I, Vendrell JF, Riquelme C, et al. Stent retrievers in acute ischemic stroke: complications and failures during the perioperative period. *AJNR Am J Neuroradiol.* (2014) 35:734–40. doi: 10.3174/ajnr.A3746
16. Lee JS, Hong JM, Lee KS, Suh HI, Choi JW, Kim SY. Primary stent retrieval for acute intracranial large artery occlusion due to atherosclerotic disease *J Stroke* (2015) 18:96–101. doi: 10.5853/jos.2015.01347
17. Lee JS, Lee SJ, Hong JM, Choi JW, Hong JH, Chang HW, et al. Temporal changes in care processes and outcomes for endovascular treatment of acute ischemic stroke: retrospective registry data from three Korean Centers. *Neurointervention* (2018) 13:2–12. doi: 10.5469/neuroint.2018.13.1.2

18. Hwang YH, Kim YW, Kang DH, Kim YS, Liebeskind DS. Impact of target arterial residual stenosis on outcome after endovascular revascularization. *Stroke* (2016) 47:1850–7. doi: 10.1161/STROKEAHA.116.013046
19. Lee JS, Hong JM, Kim JS. Diagnostic and therapeutic strategies for acute intracranial atherosclerosis-related occlusions. *J Stroke* (2017) 19:143–51. doi: 10.5853/jos.2017.00626
20. Lee JS, Lee SJ, Yoo JS, Hong JH, Kim CH, Kim YW, et al. Prognosis of acute intracranial atherosclerosis-related occlusion after endovascular treatment. *J Stroke* (2018) 20:394–403. doi: 10.5853/jos.2018.01627
21. Fiorelli M, Bastianello S, von Kummer R, del Zoppo GJ, Larrue V, Lesaffre E, et al. Hemorrhagic transformation within 36 hours of a cerebral infarct: relationships with early clinical deterioration and 3-month outcome in the European Cooperative Acute Stroke Study I (ECASS I) cohort. *Stroke* (1999) 30:2280–4. doi: 10.1161/01.STR.30.11.2280
22. Frontera JA, Claassen J, Schmidt JM, Wartenberg KE, Temes R, Connolly ES Jr, et al. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. *Neurosurgery* (2006) 59:21–7. doi: 10.1227/01.NEU.0000218821.34014.1B
23. Austin PC. A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003. *Stat Med.* (2008) 27:2037–49. doi: 10.1002/sim.3150
24. Kang DH, Kim YW, Hwang YH, Park J, Hwang JH, Kim YS. Switching strategy for mechanical thrombectomy of acute large vessel occlusion in the anterior circulation. *Stroke* (2013) 44:3577–9. doi: 10.1161/STROKEAHA.113.002673
25. Baek JH, Kim BM, Heo JH, Nam HS, Kim YD, Park H, et al. Number of stent retriever passes associated with futile recanalization in acute stroke. *Stroke* (2018) 49:2088–95. doi: 10.1161/STROKEAHA.118.021320
26. Baek JH, Kim BM, Kim DJ, Heo JH, Nam HS, Song D, et al. Importance of truncal-type occlusion in stentriever-based thrombectomy for acute stroke. *Neurology* (2016) 87:1542–50. doi: 10.1212/WNL.0000000000003202
27. Baek JH, Kim BM, Heo JH, Kim DJ, Nam HS, Kim YD. Outcomes of endovascular treatment for acute intracranial atherosclerosis-related large vessel occlusion. *Stroke* (2018) 49:2699–705. doi: 10.1161/STROKEAHA.118.022327
28. Kang DH, Kim YW, Hwang YH, Park SP, Kim YS, Baik SK. Instant reocclusion following mechanical thrombectomy of *in situ* thromboocclusion and the role of low-dose intra-arterial tirofiban. *Cerebrovasc. Dis.* (2014) 37:350–5. doi: 10.1159/000362435
29. Kim BM. Causes and solutions of endovascular treatment failure. *J Stroke* (2017) 19:131–42. doi: 10.5853/jos.2017.00283
30. Yoon W, Kim SK, Park MS, Kim BC, Kang HK. Endovascular treatment and the outcomes of atherosclerotic intracranial stenosis in patients with hyperacute stroke. *Neurosurgery* (2015) 76:680–6. doi: 10.1227/NEU.0000000000000694
31. Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med.* (2011) 365:993–1003. doi: 10.1056/NEJMoa1105335
32. Fiorella D, Derdeyn CP, Lynn MJ, Barnwell SL, Hoh BL, Levy EI, et al. Detailed analysis of periprocedural strokes in patients undergoing intracranial stenting in stenting and aggressive medical management for preventing recurrent *stroke* in intracranial stenosis (SAMMPRIS). *Stroke* (2012) 43:2682–8. doi: 10.1161/STROKEAHA.112.661173
33. Zaidat OO, Fitzsimmons BF, Woodward BK, Wang Z, Killer-Oberpfalzer M, Wakhloo A, et al. Effect of a balloon-expandable intracranial stent vs medical therapy on risk of stroke in patients with symptomatic intracranial stenosis: the VISSIT randomized clinical trial. *JAMA* (2015) 313:1240–8. doi: 10.1001/jama.2015.1693
34. Kang DH, Yoon W, Kim SK, Baek BH, Lee YY, Kim YW, et al. Endovascular treatment for emergent large vessel occlusion due to severe intracranial atherosclerotic stenosis. *J Neurosurg.* (2018) 1–8. doi: 10.3171/2018.1.JNS172350. [Epub ahead of print].
35. Baek JH, Kim BM, Kim DJ, Heo JH, Nam HS, Yoo J. Stenting as a rescue treatment after failure of mechanical thrombectomy for anterior circulation large artery occlusion. *Stroke* (2016) 47:2360–3. doi: 10.1161/STROKEAHA.116.014073
36. Chang Y, Kim BM, Bang OY, Baek JH, Heo JH, Nam HS, et al. Rescue stenting for failed mechanical thrombectomy in acute ischemic *stroke*: a multicenter experience. *Stroke* (2018) 49:958–64. doi: 10.1161/STROKEAHA.117.020072
37. Stuart EA. Developing practical recommendations for the use of propensity scores: discussion of 'A critical appraisal of propensity score matching in the medical literature between 1996 and 2003' by Peter Austin, Statistics in Medicine. *Stat Med.* (2008) *27*:2062–5. doi: 10.1002/sim.3207
38. Nogueira RG, Lutsep HL, Gupta R, Jovin TG, Albers GW, Walker GA, et al. Trevo versus merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial. *Lancet* (2012) 380:1231–40. doi: 10.1016/S0140-6736(12)61299-9
39. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med.* (2015) 372:11–20. doi: 10.1056/NEJMoa1411587

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CTA-Based Truncal-Type Occlusion Is Best Matched With Postprocedural Fixed Focal Stenosis in Vertebrobasilar Occlusions

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Background: Differentiation of embolic and atherosclerotic occlusions is difficult prior to endovascular treatment (EVT) of acute ischemic stroke due to intracranial large artery occlusions. CTA-determined occlusion type has been reported to be associated with a negative cardiac embolic source and stent retriever failure, a potential of intracranial atherosclerosis (ICAS)-related occlusions. In this study, we evaluated the agreement between preprocedural identification of CTA-determined truncal-type occlusion (TTO) and postprocedural evaluation of underlying fixed focal stenosis (FFS) in the occlusion site.

Methods: Patients who underwent intracranial EVT for acute ischemic stroke within 24 h of onset and who had baseline CTA were identified from a multicenter registry collected between January 2011 and May 2016. Preprocedural occlusion type was classified as TTO (target artery bifurcation saved) or branching-site occlusion (bifurcation involved) on CTA. As for postprocedural identification, FFS was evaluated by stepwise analyses of procedural and postprocedural angiographies. The agreement between TTO and FFS was evaluated in respective intracranial vascular beds. Receiver operating characteristics analyses were also performed.

Results: A total of 509 patients were included [intracranial internal carotid artery (ICA): 193, middle cerebral artery (MCA) M1: 256, and vertebrobasilar artery (VBA): 60]. In preprocedural identification, 33 (17.1%), 41 (16.0%), and 29 patients (48.3%) had TTOs, respectively. TTOs had good agreement with angiographic FFS in M1 (positive predictive value: 63.4%, negative predictive value: 83.2%, likelihood ratio: 5.42, $P_{multivariate} < 0.001$) and VBA (72.4%, 96.8%, and 4.54, respectively, $P_{multivariate} = 0.004$), but not in intracranial ICA occlusions ($P_{multivariate} = 0.358$). The area under the receiver operating characteristics

curve was the largest for VBA (0.872, $p < 0.001$), followed by MCA M1 (0.671, $p < 0.001$), and intracranial ICA (0.551, $p = 0.465$).

Conclusions: Agreement between preprocedural TTO and postprocedural FFS, both of which are surrogate markers for ICAS-related occlusions, is highest for VBA, followed by MCA M1 occlusions. There is no significant association in intracranial ICA.

Keywords: endovascular treatment, computed tomographic angiography, intracranial atherosclerotic stenosis, truncal-type occlusion, intracranial atherosclerosis

INTRODUCTION

The recent success of several randomized controlled trials of endovascular treatment (EVT) (1–7) has resulted in adoption of EVT as standard therapy for acute stroke due to intracranial large artery occlusion. Contemporary endovascular therapy focuses on removal of intraluminal emboli through stent retrieval or direct aspiration (8–11). Nevertheless, a substantial fraction of intracranial occlusions are possibly caused by intracranial atherosclerotic stenosis (ICAS)-related occlusions, especially in the Asian population (12–17). Although EVT for ICAS-related occlusion is reported to be as safe and effective as for embolic occlusions (13, 16, 18, 19), treatment refractoriness and reocclusion (15, 20) during the procedure is frequently reported, resulting in procedure time elongation and relatively poor prognosis (14, 17). Furthermore, because ICAS-related occlusion cannot be easily differentiated by baseline imaging prior to the procedure, the effectiveness of EVT is difficult to confirm in a randomized prospective trial.

As an etiological approach, ICAS-related occlusions with EVT cannot be confirmed by pathological evaluations. Thus, a definitive method has not been developed for confirming the underlying ICAS in intracranial large artery occlusions either prior to or after the procedure. Instead, surrogate markers have been suggested by several studies. Two surrogate markers for ICAS-related occlusion have been reported: fixed focal stenosis (FFS) and truncal-type occlusion (TTO).

Postprocedural identification of ICAS can be performed by digital subtraction angiography (DSA) images taken during EVT (14). This method focuses on the presence of significant FFS (12), which is revealed during or after the procedure by transfemoral cerebral angiography. Because of its intuitiveness, this method has been used widely in previous studies (13, 19, 21). However, target residual stenosis may not always be the culprit underlying the occlusion because some thrombotic remnant stenoses can mimic ICAS (20). Intraprocedural complications, including vasospasm or dissections, may also complicate the etiological classification. Therefore, a stepwise approach to diagnose ICAS-related occlusion is necessary, incorporating both procedural DSA and postprocedural repeat non-invasive vascular imaging (17, 22).

An important issue regarding ICAS-related occlusion is its preprocedural identification (23, 24). DSA-determined TTO is another surrogate marker of ICAS-related occlusion that can potentially address this issue. Kim, Baek and colleagues had previously performed impressive studies on occlusion types, TTOs and branching-site occlusions (BSOs), in intracranial large arteries. In 2016, they reported that the DSA-determined TTO type at the time of deployment of the stent retriever during EVT was significantly associated with stent retriever failure (25). Moreover, the TTO type was associated with the absence of embolic sources, which were thoroughly investigated by postprocedural etiological approaches such as echocardiography, cardiac computed tomography (CT), and aortic arch atheroma imaging (25). In 2017, they reported that these occlusion types could be applied to computed tomographic angiography (CTA). Through their internal validation, the BSO type on preprocedural CTA corresponded well to the same type on DSA-based evaluations (26). This dichotomized analysis would be practically useful because it can also be assessed by baseline CTA (26), a time-sparing and widely-used imaging tool in EVT for acute stroke.

We hypothesized that the predictive ability of the preprocedural CTA-based identification of occlusion types may differ among occlusive vascular beds due to variations in their branching locations and in levels of collaterals. Therefore, in this study, we aimed to evaluate the agreement between the TTO, a preprocedural occlusion type, and the FFS, a postprocedural surrogate marker of ICAS-related occlusion, in the three most common occlusion sites targeted by EVT, including the intracranial internal carotid artery (ICA), the middle cerebral artery M1 portion (MCA M1), and the vertebrobasilar artery (VBA), using a retrospective multicenter EVT database.

MATERIALS AND METHODS

The ASIAN KR Registry

The Acute Stroke due to Intracranial Atherosclerotic occlusion and Neurointervention—Korean Retrospective (ASIAN KR) registry is a three-center retrospective database consisting of consecutive patients ages 18 or older who underwent EVT for treatment of acute ischemic stroke due to intracranial and/or extracranial large vessel occlusion (27). The registry focuses on revealing the clinical and procedural characteristics of ICAS-related occlusion, a frequent etiology in Asian population, yet in which interventional outcomes are less well-defined. The data collection protocol was approved by the Institutional Review Board of each hospital and was implemented in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. All EVT procedures were performed at the discretion of the treating

physician. The datasets generated in this study are available on reasonable request to the corresponding author. The current study was retrospectively performed with comparative and descriptive analyses based on the ASIAN KR registry.

Core Lab Imaging Evaluations

After de-identification and blinding of clinical data, core laboratory imaging analyses were performed to ensure consistent grading and eliminate bias. The location of the initial large vessel occlusion was identified on baseline angiography (S-JL). Alberta Stroke Program Early CT scores (ASPECTS) were classified on non-contrast CT (S-IS). Successful reperfusion was classified as modified Treatment In Cerebral Ischemia (mTICI) grade 2b−3 (JSL, Y-HH) (28). Arterial recanalization was also classified by the Arterial Occlusive Lesion (AOL) score to grade recanalization degree or residual stenosis of target occlusive lesions (JSL, Y-HH) (29). Parenchymal hematoma type 2 (30) and/or modified Fisher scale grade 3–4 subarachnoid hemorrhages (31) were regarded as serious postprocedural hemorrhagic complications (S-IS).

Preprocedural Identification of Truncal-Type Occlusion

Based on baseline CTA, occlusion types were classified as either TTO or BSO according to previous reports (25, 26), by two individual interventional neurologists (S-JL, 4 years of clinical experience; JY, 5 years of clinical experience). For the current study, it was classified as TTO if the very next bifurcation site was clearly visible beyond the occlusion segment. Occlusion types that involved the bifurcation sites of the vascular beds and/or major branches were classified as BSOs. Cases in which CTA images were not of sufficient quality to differentiate between the two occlusion types were classified as inconclusive and were excluded from the analysis. For the MCA M1, if the bifurcation point and most proximal point of both M2 segments were visible, it was regarded as a TTO. In intracranial ICA occlusions, a T-type occlusion that involves both the ICA bifurcation point, M1 proximal, and A1 portion was classified as BSO, while an I-type occlusion with occlusion of only the distal ICA with visualization of the proximal anterior cerebral artery (ACA) A1 and MCA junction through collaterals was classified as TTO. If the top of the basilar artery was involved in a basilar artery occlusion, it was regarded as a BSO. By contrast, if the top was saved, it was regarded as a TTO. Likewise, the basilar bifurcation was also evaluated in the case of dominant V4 occlusions resulting in major posterior circulation syndromes.

The CTA was obtained according to the protocol of each hospital. At center A, the CT scans (SOMATOM Sensation 16; SOMATOM Definition Edge [128-channel] Siemens, Erlangen, Germany), including non-contrast and postcontrast axial parenchymal images, were acquired with contiguous 5-mm thick axial sections (120 kV, 270 mAs). For CTA, a maximum of 90 mL (1.2 mL/kg) of iodinated contrast agent was injected at 4 mL/s, immediately followed by a 15 mL saline bolus. A bolus tracking technique was used with a minimum delay of 3-s. CTA images were acquired from the aortic arch to the vertex with the following parameters: 100 kV, 180 mAs, 0.5 s per rotation, 0.5 pitch, and a 0.75-mm section thickness. The CT source images were postprocessed to create coronal, sagittal, and axial multiplanar reformats in maximum intensity projection (MIP) images (10-mm slab and 2-mm interval) and volume-rendered 3D images.

At center B, (Optima CT 660 [64-channel]; Revolution EVO [128-channel], GE, Boston, MA) non-contrast CT was acquired with 2.5-mm thickness and 2.5-mm interval (tube voltage of 120 kV). CT angiography was performed using 2.5-mm slice thickness, 2.5-mm reconstruction interval, 100 kV, 100–300 mAs. A maximum of 80 mL (2 mL/kg) of iodinated contrast agent was injected at 4 mL/s, immediately followed by a 50 mL saline bolus. The CT source images were postprocessed to create coronal, sagittal, and axial multiplanar reformats in MIP images (10-mm slab and 2-mm interval) and volume-rendered 3D images. MIP images were obtained after May 2012 at center B.

At center C (SOMATOM Definition Flash [128-channel], Siemens, Erlangen, Germany), non-contrast CT was taken with 5-mm thickness and 5-mm interval (tube voltage of 120 kV). The first phase of the multiphase CTA is from the aortic arch to the vertex using a multidetector CT scanner, acquired in the late arterial phase with scanning triggered by contrast bolus monitoring in the aortic arch with average dose length product of 700–800 mGy cm. The scan time is <10 s. Images were acquired with a 0.625-mm section thickness. The second phase was acquired after a delay of 4 s that allows for table repositioning to the skull base. The scanning duration for each additional phase was 3.4 s. Thus, the 3 phases were each 8 s apart. A total of 70 mL of contrast material was injected at a rate of 5 mL/s, and was followed by a 50-mL normal saline chase at a rate of 4 mL/s. (FOV 200*200, 100–300 mAs). The CT source images were postprocessed to create coronal, sagittal, and axial multiplanar reformats in MIP images (24-mm slab and 4-mm interval) and volume-rendered 3D images. MIP images and multiphase CT was performed after June 2014 at center C.

Postprocedural Identification of FFS

An FFS was identified by several steps of angiographical analysis and was evaluated and determined based on the consensus of a vascular neurologist (Y-HH, over 10 years of clinical experience) and an interventional neurologist (JSL, 10 years of clinical experience) (14, 22): (1) uncommon stroke etiologies such as dissection, Moyamoya disease, and vasculitis were evaluated by DSA performed just prior to EVT. (2) If the occluded vessel was completely recanalized after primary thrombectomy, the etiology was determined to be embolic occlusion. (3) A focal stenosis >70% or lower-degree stenosis with tendency of re-occlusion or flow impairment during the procedure was defined as a meaningful FFS. (4) Repeat DSAs were often performed up to 20 min after final recanalization, to evaluate residual stenosis, further recanalization, or reocclusion. (5) Any postprocedural non-invasive angiographies performed (CT or MR) were reviewed to evaluate possible changes to the classification (JY).

In our preliminary analysis, the tentative identification of FFS until the 4th step was changed into embolism in 0.4% of included patients at the 5th step, and embolism into FFS in 1.9% (17). **Figure 1** shows two example cases that presented with TTO

(upper row) and BSO (lower row) types on CTA, and were, respectively, classified as FFS and embolic occlusion through stepwise angiographic analysis. If no recanalization could be achieved during the procedure to determine the etiology, it was specifically classified as intractable occlusion. If a FFS was present, the detailed location with the most severe stenosis in the occlusive vessel was further evaluated (i.e., proximal, middle, or distal segment).

Inclusion and Exclusion Criteria

For the current study, the following criteria were applied: (1) occlusion in the intracranial ICA portion, the MCA M1 segment, or the vertebrobasilar artery were included, while M2 or distal locations were excluded. Patients were also included when (2) onset-to-puncture time was within 24 h, and when (3) baseline angiographic evaluation was performed by CTA. Sole extracranial targets treated were excluded while tandem occlusions were included.

Statistical Analysis

Clinical characteristics, endovascular findings, and procedures were compared between patients with TTOs and BSOs at three respective occlusion sites, the intracranial ICA, MCA M1, and VBA. Differences between the groups were analyzed using χ^2 tests for categorical variables and Student's *t*-tests for continuous variables. For each occlusive vascular bed, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of preprocedural identification of TTO and postprocedural identification of FFS were investigated through univariate and multivariate analysis. Receiver operating characteristics (ROC) curve analyses of the association of TTO with FFS were performed for the three respective occlusive sites. The impact of the detailed location (i.e., proximal, middle, or distal segment) regarding the FFS on CTA occlusion types was further evaluated according to each vascular bed. A $p < 0.05$ was considered to be significant. Statistical analysis was performed using the SPSS statistical package (version 22.0; SPSS Inc., Chicago, IL).

RESULTS

A total of 525 patients were included. After excluding 16 patients due to inconclusive CTA, 509 were included in the final analysis (ICA T: 193, MCA M1: 256, and VBA: 60). In the included patients, the CTAs consisted of single-phase CTA MIP images + reconstruction images in 356 (69.9%), multiphase CTA MIP images + reconstruction images in 71 (13.9%), and CTA-enhanced images + reconstruction images in 82 (16.1%). Of these, 33 (17.1%), 41 (16.0%), and 29 patients (48.3%) demonstrated TTOs on baseline CTA in the ICA, MCA, and VBA, respectively. A total of 406/509 (79.8%) patients were

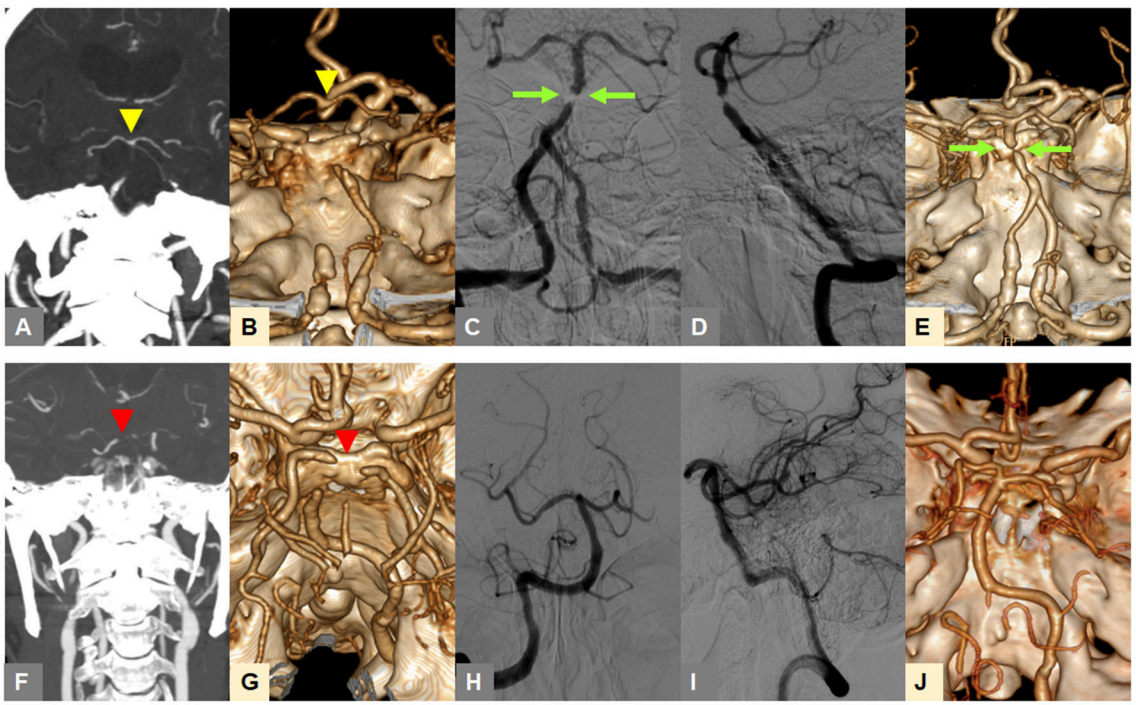

FIGURE 1 | Representative cases for classification of occlusion types on baseline CTA and angiography-revealed fixed focal stenosis. **(A,B)** A truncal-type occlusion of the basilar artery, with clearly visible bifurcation point at the top of the basilar artery (yellow arrowheads) is observed on baseline CTA. **(C,D)** Digital subtraction angiography after reperfusion treatment reveals >70% residual stenosis (green arrow). **(E)** Post-procedure CTA shows underlying atherosclerotic lesion (green arrow). **(F,G)** A branch-site occlusion of the basilar artery with involvement of the top of the basilar portion and P1 segments (red arrowheads) is observed. **(H,I)** Complete recanalization after primary thrombectomy is seen, suggestive of embolic etiology. **(J)** Post-procedure CTA also shows complete recanalization. CTA, computed tomographic angiography.

TABLE 1 | Comparison of clinical characteristics and endovascular procedure findings according to preprocedural occlusion types in intracranial internal carotid artery occlusions.

	TTO (n = 33)	BSO (n = 160)	p-value
CLINICAL CHARACTERISTICS			
Age, years	71 ± 11	68 ± 13	0.183
Male sex	22 (66.7%)	73 (45.6%)	0.028
Diabetes mellitus	10 (30.3%)	46 (28.7%)	0.858
Hypertension	21 (63.6%)	99 (61.9%)	0.849
Atrial fibrillation	18 (54.5%)	93 (58.1%)	0.705
CAOD	5 (15.2%)	22 (13.8%)	0.833
Hypercholesterolemia	11 (33.3%)	44 (27.5%)	0.499
Smoking	8 (24.2%)	31 (19.4%)	0.526
Admission NIHSS score, median [IQR]	15.0 [11.5–19.0]	18.0 [15.0–21.0]	0.002
ASPECTS, median [IQR]	9.0 [8.0–10.0]	5.5 [3.0–8.0]	<0.001
REPERFUSION TREATMENT			
IV thrombolysis	18 (54.5%)	92 (57.5%)	0.755
Onset-to-puncture time (min)	353 ± 220	303 ± 214	0.222
Procedure time (min)	83 ± 63	77 ± 48	0.502
Reocclusion after primary treatment	1 (3.7%)	8 (5.2%)	0.742
Tirofiban infusion	4 (12.1%)	12 (7.5%)	0.381
Intracranial balloon	1 (3.0%)	3 (1.9%)	0.671
Intracranial stenting	0 (0.0%)	16 (10.0%)	0.058
Number of techniques	2.0 [1.0–3.0]	2.0 [1.0–3.0]	0.620
Final AOL grade			0.109
0	4 (12.9%)	11 (6.9%)	
1	0 (0.0%)	6 (3.8%)	
2	5 (16.1%)	10 (6.3%)	
3	22 (71.0%)	133 (83.1%)	
Successful reperfusion	29 (87.9%)	123 (76.9%)	0.159
Post-procedure reocclusion	1/27 (3.7%)	3/123 (2.4%)	0.712
ANGIOGRAPHIC ANALYSIS OF ETIOLOGY			**0.097**
Complete recanalization	25 (75.8%)	137 (85.6%)	
Significant fixed focal stenosis	5 (15.2%)	14 (8.8%)	
Intractable	2 (6.1%)	9 (5.6%)	
Others	1 (3.0%)	0 (0.0%)	
OUTCOMES			
Serious hemorrhagic complications	2 (6.1%)	32 (20.0%)	0.056
3-month mRS 0–2	17 (51.5%)	67 (41.9%)	0.309

The data are presented as the mean ± standard deviation, number (%), or median [interquartile range]. TTO, truncal-type occlusion; BSO, branching-site occlusion; CAOD, coronary artery obstructive disease; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT score; IV, intravenous; AOL, arterial occlusive lesion; mRS, modified Rankin Scale.

TABLE 2 | Comparison of clinical characteristics and endovascular procedure findings according to preprocedural occlusion types in middle cerebral artery M1 occlusions.

	TTO (n = 41)	BSO (n = 215)	p-value
CLINICAL CHARACTERISTICS			
Age, years	62 ± 12	66 ± 13	0.074
Male sex	23 (56.1%)	122 (56.7%)	0.939
Diabetes mellitus	11 (26.8%)	59 (27.4%)	0.936
Hypertension	21 (51.2%)	131 (60.9%)	0.246
Atrial fibrillation	9 (22.0%)	104 (48.4%)	0.002
CAOD	0 (0.0%)	21 (9.8%)	0.037
Hypercholesterolemia	7 (17.1%)	57 (26.5%)	0.201
Smoking	17 (41.5%)	42 (19.5%)	0.002
Admission NIHSS score, median [IQR]	14.0 [8.5–20.5]	16.0 [12.0–20.0]	0.734
ASPECTS, median [IQR]	6.5 [4.0–9.0]	7.0 [5.0–9.0]	0.573
REPERFUSION TREATMENT			
IV thrombolysis	21 (51.2%)	113 (52.6%)	0.875
Onset-to-puncture time (min)	386 ± 258	328 ± 233	0.157
Procedure time (min)	75 ± 33	69 ± 42	0.381
Reocclusion after primary treatment	12 (31.6%)	18 (8.5%)	<0.001
Tirofiban infusion	19 (46.3%)	22 (10.2%)	<0.001
Intracranial balloon	3 (7.3%)	3 (1.4%)	0.022
Intracranial stenting	2 (4.9%)	7 (3.3%)	0.605
Number of techniques	2.0 [1.0–2.0]	1.0 [1.0–2.0]	0.001
Final AOL grade			<0.001
0	6 (14.6%)	15 (7.0%)	
1	9 (22.0%)	16 (7.5%)	
2	16 (39.0%)	37 (17.3%)	
3	10 (24.4%)	146 (68.2%)	
Successful reperfusion	30 (73.2%)	160 (74.4%)	0.867
Post-procedure reocclusion	2/38 (5.3%)	13/191 (6.8%)	0.725
ANGIOGRAPHIC ANALYSIS OF ETIOLOGY			**<0.001**
Complete recanalization	13 (31.7%)	163 (75.8%)	
Significant fixed focal stenosis	26 (63.4%)	36 (16.7%)	
Intractable	2 (4.9%)	16 (7.4%)	
OUTCOMES			
Serious hemorrhagic complications	3 (7.3%)	12 (5.6%)	0.665
3-month mRS 0–2	24 (58.5%)	114 (53.3%)	0.535

The data are presented as the mean ± standard deviation, number (%), or median [interquartile range]. TTO, truncal-type occlusion; BSO, branching-site occlusion; CAOD, coronary artery obstructive disease; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT score; IV, intravenous; AOL, arterial occlusive lesion; mRS, modified Rankin Scale.

TABLE 3 | Comparison of clinical characteristics and endovascular procedure findings according to preprocedural occlusion types in vertebrobasilar artery occlusions.

	TTO ($n = 29$)	BSO ($n = 31$)	p-value
CLINICAL CHARACTERISTICS			
Age, years	67 ± 9	67 ± 10	0.892
Male sex	18 (62.1%)	18 (58.1%)	0.752
Diabetes mellitus	10 (34.5%)	7 (22.6%)	0.307
Hypertension	22 (75.9%)	18 (58.1%)	0.144
Atrial fibrillation	9 (31.0%)	16 (51.6%)	0.106
CAOD	2 (6.9%)	2 (6.5%)	0.945
Hypercholesterolemia	10 (34.5%)	9 (29.0%)	0.650
Smoking	11 (37.9%)	5 (16.1%)	0.056
Admission NIHSS score, median [IQR]	20.0 [13.5–26.5]	19.0 [11.0–27.0]	0.960
REPERFUSION TREATMENT			
IV thrombolysis	12 (41.4%)	20 (64.5%)	0.073
Onset-to-puncture time (min)	406 ± 240	349 ± 303	0.427
Procedure time (min)	79 ± 46	62 ± 40	0.143
Reocclusion after primary treatment	12 (42.9%)	1 (3.2%)	<0.001
Tirofiban infusion	7 (24.1%)	1 (3.2%)	0.017
Intracranial balloon	8 (27.6%)	0 (0.0%)	0.002
Intracranial stenting	3 (10.3%)	2 (6.5%)	0.586
Number of techniques	2.0 [1.0–2.0]	1.0 [1.0–2.0]	0.044
Final AOL			<0.001
0	2 (6.9%)	5 (16.1%)	
1	2 (6.9%)	1 (3.2%)	
2	17 (58.6%)	0 (0.0%)	
3	8 (27.6%)	25 (80.6%)	
Successful reperfusion	26 (89.7%)	25 (80.6%)	0.329
Post-procedure reocclusion	4/25 (16.0%)	2/26 (7.7%)	0.357
ANGIOGRAPHIC ANALYSIS OF ETIOLOGY			**<0.001**
Complete recanalization	7 (24.1%)	26 (83.9%)	
Significant fixed focal stenosis	21 (72.4%)	1 (3.2%)	
Intractable	1 (3.4%)	3 (9.7%)	
Others	0 (0.0%)	1 (3.2%)	
OUTCOMES			
Serious hemorrhagic complications	2 (7.1%)	1 (3.2%)	0.494
3-month mRS 0–2	8 (27.6%)	17 (54.8%)	0.032

The data are presented as the mean ± standard deviation, number (%), or median [interquartile range]. TTO, truncal-type occlusion; BSO, branching-site occlusion; CAOD, coronary artery obstructive disease; NIHSS, National Institutes of Health Stroke Scale; IV, intravenous; AOL, arterial occlusive lesion; mRS, modified Rankin Scale.

classified as BSOs. The overall k-value of interrater reliability was 0.844. The k-value for intracranial ICA was 0.929, 0.727 for MCA M1, and 0.933 for VBA.

Among the occlusion sites, the statistical significance between the preprocedural occlusion types and the angiographic analyses of etiology was somewhat different. **Table 1** shows the comparison between TTOs and BSOs in the intracranial ICA occlusions. TTOs were significantly associated with lower NIHSS scores and higher ASPECTS scores. However, there were no significant differences in the angiographic analysis of etiology ($p = 0.097$). **Table 2** shows the comparison between TTOs and BSOs in the MCA M1 portion occlusions. There were fewer patients with atrial fibrillation and coronary artery obstructive disease in the TTO group, while smoking was more common. During the procedure, reocclusion after primary reperfusion treatment was more frequent (31.6 vs. 8.5%, $p < 0.001$) and adjunctive treatments, such as intra-arterial tirofiban or angioplasty, were more frequently used. In the angiographic analysis of etiology, TTO was significantly associated with fewer complete recanalization and more frequently revealed a FFS ($p < 0.001$). **Table 3** shows the comparison between TTOs and BSOs in the VBA occlusions. There were no significant differences in clinical characteristics. During the procedure, reocclusion after primary reperfusion treatment was more frequent (42.9 vs. 3.2%, $p < 0.001$) and adjunctive treatments were more frequently needed in the TTO group. In the angiographic analysis of etiology, TTO was associated with fewer complete recanalizations and more frequently revealed a FFS ($p < 0.001$).

When the agreement between TTO and FFS was evaluated (**Table 4**), the performance was high in overall included vascular beds with moderate sensitivity (50.5%) and high specificity (87.4%) and a positive likelihood ratio of 4.02 ($p < 0.001$). Specifically, the association was significant in multivariate analysis in both MCA M1 ($p < 0.001$) and VBA ($p = 0.004$) occlusions, along with atrial fibrillation as a significant predictor while age, gender, and smoking history were insignificant. By contrast, there was no significance in intracranial ICA occlusion ($p = 0.358$). In the ROC curve analysis (**Figure 2**), the area under the ROC curve was the largest for the VBA (0.872, $p < 0.001$), followed by the MCA M1 (0.671, $p < 0.001$) and intracranial ICA (0.551, $p = 0.465$).

If a significant FFS was present, a subgroup analysis based on the culprit stenotic segment was performed to identify the impact of the location of FFS on the CTA occlusion type (**Table 5**). In the intracranial ICA occlusions, a substantial number of culprit stenoses were located in the communicating segment or even the MCA M1 in the BSO group, while the culprit stenosis was more frequently seen in the ophthalmic segment in the TTO group ($p = 0.026$). Overall, underlying M1 FFS was common (57.9%), resulting in frequent BSOs. In the M1 occlusions, stenosis in the proximal or the mid-M1 segment was more frequently seen in the TTO group, while distal M1 or M2 stenosis was more frequently seen in the BSO group ($p = 0.012$). Overall, the stenosis was frequently located in the distal M1 (50.0%), and a significant number of patients presented with BSOs. In VBA occlusions,

TABLE 4 | The predictive power of CTA-based truncal-type occlusions for angiography-revealed significant fixed focal stenosis, and comparison with initial reports and other imaging modalities.

References	Population	Univariate P	Multivariate P	Sensitivity	Specificity	PPV	NPV	Accuracy	+LR	–LR
Truncal-type occlusions in prediction of angiography-revealed significant fixed focal stenosis										
Current study	ICA + MCA + VBA	<0.001	<0.001*	50.5%	87.4%	50.5%	87.4%	80.0%	4.02	0.57
	Intracranial ICA	0.261	0.358*	26.3%	83.9%	15.2%	91.3%	78.2%	1.64	0.88
	MCA M1	<0.001	<0.001*	41.9%	92.3%	63.4%	83.2%	80.1%	5.42	0.63
	VBA	<0.001	0.004*	95.5%	79.0%	72.4%	96.8%	85.0%	4.54	0.06
CTA truncal-type occlusions in prediction of SR failure										
Baek et al. (26)†	ICA + MCA + VBA			48.2%	90.8%	60.5%	85.6%	81.1%	5.21	0.57
Truncal-type occlusions after STENT deployment in prediction of SR failure										
Baek et al. (25)†	ICA+MCA+VBA			30.5%	97.6%	–	–	–	12.6	0.71
Other imaging predictors										
Negative susceptibility vessel sign in prediction of ICAS-related occlusion										
Kim et al. (23)	MCA	<0.001		100.0%	67.1%	42.9%	100.0%	73.6%	3.04	0.00
Suh et al. (24)†	ICA+MCA	0.239		28.6%	75.0%	–	–	–	1.14	0.95
Negative multi-segment clot sign in prediction of large artery atherosclerosis										
Chen et al. (32)†	ICA+MCA	<0.001		90.7%	52.7%	42.9%	93.5%	63.4%	1.92	0.18

**Multivariate analysis was performed with age, gender, smoking, and atrial fibrillation as covariates.* †*Predictive values from these articles have been calculated through statistical analysis of data presented in the literature. CTA, computed tomographic angiography; PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; –LR, negative likelihood ratio; ICA, internal carotid artery; MCA, middle cerebral artery; VBA, vertebrobasilar artery; SR, stent retriever; ICAS, intracranial atherosclerotic stenosis.*

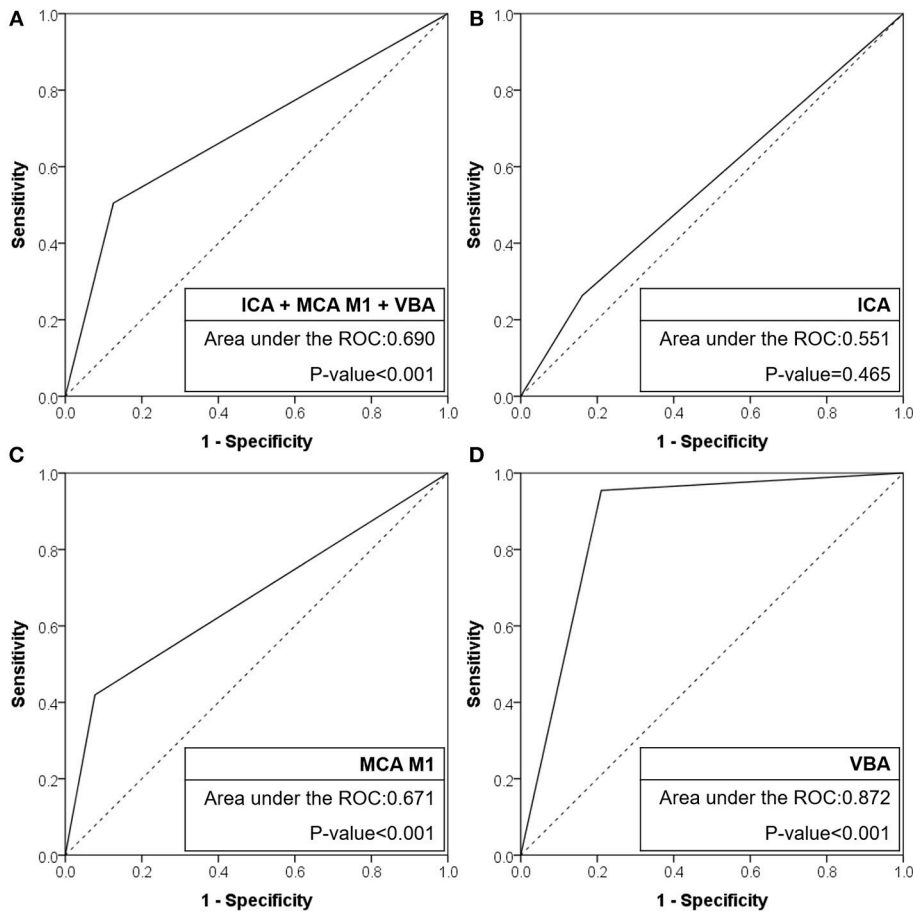

FIGURE 2 | Receiver operating characteristic curves of CTA-based truncal-type occlusions for angiography revealed fixed focal stenosis. **(A)** ICA + MCA M1 + VBA occlusions. **(B)** ICA occlusions. **(C)** MCA M1 occlusions. **(D)** VBA occlusions. CTA, computed tomographic angiography; ICA, internal carotid artery; MCA, middle cerebral artery; VBA, vertebrobasilar artery; ROC, receiver operating characteristic.

TABLE 5 | Comparison of culprit stenotic segments according to occlusion types in each vascular bed in the fixed focal stenosis positive subgroup.

	Overall	TTO	BSO	*P*-value
Intracranial ICA occlusions	***n* = 19**	***n* = 5**	***n* = 14**	**0.026**
Cavernous	1 (5.3%)	0 (0.0%)	1 (7.1%)	
Ophthalmic	5 (26.3%)	4 (80.0%)	1 (7.1%)	
Communicating	2 (10.5%)	0 (0.0%)	2 (14.3%)	
M1 without ACA collaterals	4 (21.1%)	1 (20.0%)	3 (21.4%)	
M1 with ACA collaterals	7 (36.8%)	0 (0.0%)	7 (50.0%)	
MCA M1 occlusions	***n* = 62**	***n* = 26**	***n* = 36**	**0.012**
Proximal M1	6 (9.7%)	5 (19.2%)	1 (2.8%)	
Mid M1	23 (37.1%)	13 (50.0%)	10 (27.8%)	
Distal M1	31 (50.0%)	8 (30.8%)	23 (63.9%)	
M2	2 (3.2%)	0 (0.0%)	2 (5.6%)	
Vertebrobasilar occlusions	***n* = 22**	***n* = 21**	***n* = 1**	**0.015**
V4 portion	7 (31.8%)	7 (33.3%)	0 (0.0%)	
Proximal basilar	6 (27.3%)	6 (28.6%)	0 (0.0%)	
Mid basilar	7 (31.8%)	7 (33.3%)	0 (0.0%)	
Distal basilar	2 (9.1%)	1 (4.8%)	1 (100.0%)	

TTO, truncal-type occlusion; BSO, branching-site occlusion; ICA, internal carotid artery; ACA, anterior cerebral artery; MCA, middle cerebral artery.

more proximal involvement was associated with TTOs, while 1 FFS case with distal basilar occlusion showed a BSO ($p = 0.015$). However, distal basilar stenosis was not common, and the majority presented with TTO. Representative cases are seen in **Figure 3**.

DISCUSSION

The results of the current study show that preprocedural identification of TTO highly agreed with postprocedural identification of FFS, but the degree of agreement differed among occlusion sites. This agreement was the highest in VBA occlusions, followed by M1 occlusions. While the TTO showed insignificant power in intracranial ICA occlusions, it showed moderate sensitivity with higher specificity and positive likelihood ratios in the MCA M1 segment, and both high sensitivity and specificity in the VBA. The area under the ROC curve was the largest in the VBA occlusions followed by MCA M1 occlusions, while the area was insignificant in ICA T occlusions. Although a definitive method for evaluating ICAS-related occlusion was not used, the high agreement between both preprocedural and postprocedural surrogate markers may suggest potentials in practical use.

The agreement between TTO and FFS depended on the vascular bed. This finding may be explained by differences in nearby collateral systems and the frequent location of culprit stenotic segments and their distances from the bifurcation. In VBA occlusions, in which the area under the curve analysis was the largest, culprit segments were predominant in the V4 to the mid-basilar segments, with some distance from the bifurcation. Furthermore, arterial filling distal to the occlusive portion is supplied by both the circle of Willis and leptomeningeal collaterals, and may have resulted in the high sensitivity in the occlusion type analysis. In the MCA, however, the culprit stenotic segment was most frequent in the distal M1, adjacent to the bifurcation point, possibly resulting in a BSO-type occlusion morphology. Furthermore, it is supplied only by leptomeningeal collaterals, which may affect blood stasis and *in situ* thrombosis propagation distal to the culprit ICAS lesion (33) resulting in masking of these occlusions as BSOs rather than visualizing the true stenotic segment. In ICA occlusions, a substantial number of culprit segments were located in the M1 segment in reality, with thrombus propagation proximally and impaired filling of the distal ICA. Furthermore, tortuous cavernous ICA segments can be prone to occlusions due to large emboli (34). For these reasons, both sensitivity and specificity might be unsatisfactory in this group, and the predictive power was insignificant.

Some differences in the methodology for evaluating CTA-based identification of TTO and BSO between the current study and the initial reports might also have affected the predictive power. First, tandem occlusions were included in this study, while their inclusion is uncertain in the original reports. In ICA occlusions, proximal ICA occlusions and ICA-I type occlusions are difficult to differentiate through CT images in some cases, while both may show TTOs, complicating the etiologic analysis of intracranial targets. Accordingly, sole extracranial targets were excluded in a retrospective manner in the current study. Second, TTO was not defined in detail for the vertebrobasilar junction occlusions in the initial reports; therefore, we further defined this situation. Third, while intractable cases were included in the dichotomized analysis in the initial reports, they were classified as intractable apart from complete recanalization and significant FFS in the current study. An interesting finding is that intractability was not more common in TTOs in the current study. Failure of primary reperfusion modalities may not always result from ICAS-related occlusion (35, 36). Factors such as organization, fibrin-rich thrombi (37), longer thrombus length (36), and collateral status (38) are all additional factors potentially associated with reperfusion failure apart from occlusive etiology. Such factors should be also considered when occlusions refractory to EVT are encountered.

Interrater reliability appeared to also differ among vascular beds. The interrater reliability was very high in the VBA (0.993) and intracranial ICA (0.929) but relatively low in the MCA M1 (0.727). In the MCA, a number of variant forms can exist, such as trifurcation patterns, large anterior temporal artery patterns, etc. Furthermore, there are variations in the length of the M1 segment itself (39). Such variations, and the frequent distal bifurcations masquerading as M1 bifurcations may have led to the lower interrater reliability. In the ICA and VBA, the anatomical morphology and location of the bifurcation is more straightforward, and likely contributed to the higher reliability. In the ICA, hypoplasia of the A1 and A1 occlusion can sometimes be difficult to differentiate, resulting in disagreement. In the VBA, a dominant fetal type posterior cerebral artery with hypoplastic P1 could result in some disagreement. However, the incidences of such disagreement were limited.

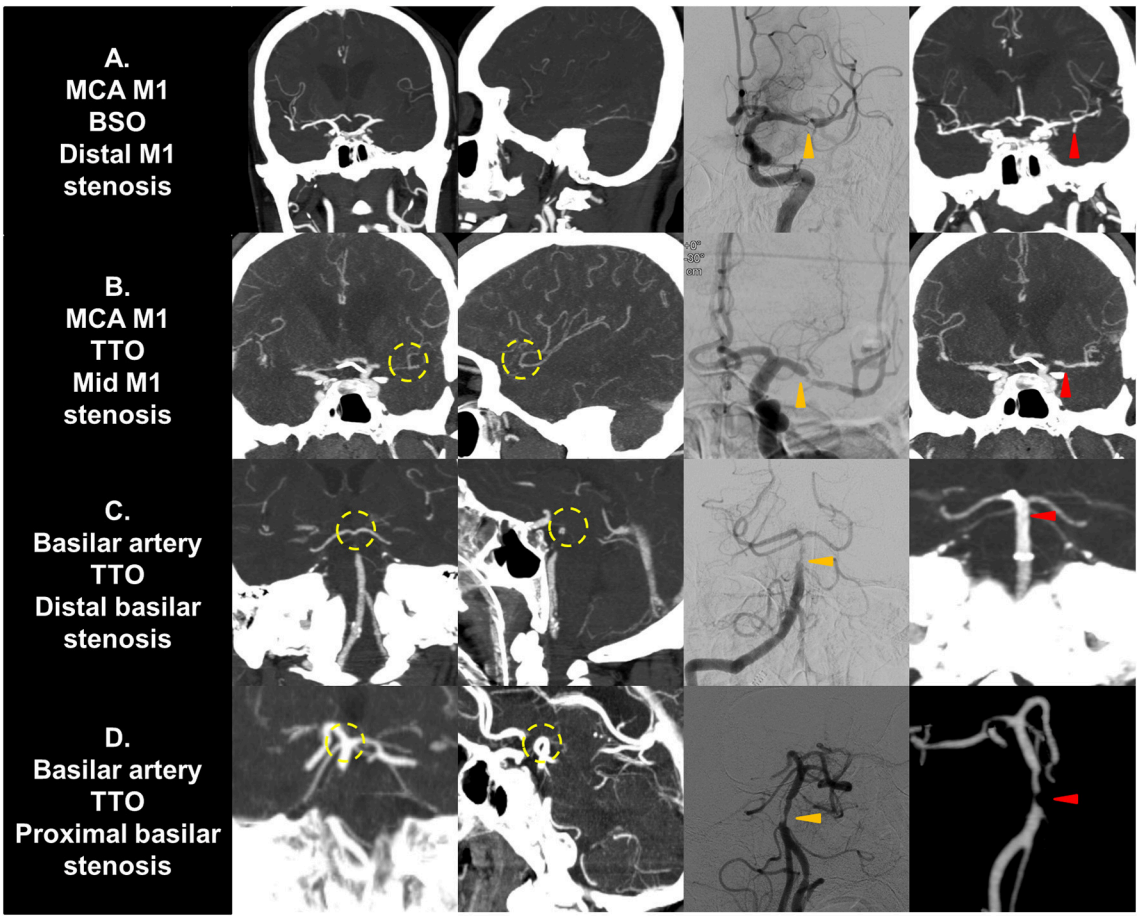

FIGURE 3 | Representative cases of culprit stenotic segment analysis. **(A)** A MCA M1 occlusion with fixed focal stenosis in the distal M1 segment is seen. The shorter distance from culprit stenosis to bifurcation results in a BSO. **(B)** A M1 occlusion with fixed focal stenosis in the mid M1 segment is seen. The distance from stenosis to bifurcation is longer, resulting in a TTO. **(C)** A vertebrobasilar occlusion with fixed focal stenosis in the distal basilar segment is seen. It may present as TTO due to collateral filling from the circle of Willis. **(D)** A vertebrobasilar occlusion with fixed focal stenosis in the proximal basilar segment is seen. The distance from stenosis to bifurcation is longer, resulting in a TTO. Yellow circle, truncal-type occlusions; Orange arrows, fixed focal stenosis in digital subtraction angiography; Red arrows, confirmation in postprocedural non-invasive imaging. MCA, middle cerebral artery; BSO, branch-site occlusion; TTO, truncal-type occlusion.

While CTA analysis of occlusion types is very practical for early identification of ICAS-related occlusions, our analysis shows that it is limited by a moderate overall sensitivity; a substantial number of FFS did not show TTO. Accordingly, a more sensitive marker may further aid prediction. In this regard, other predictive imaging parameters deserve attention (data outlined in **Table 4**). Among these, methods that use magnetic resonance imaging (MRI)-based visualization of the thrombus burden or red blood cell-dominancy through gradient echo sequences have been reported (40). Such hypointense signal changes, referred to as susceptibility vessel signs (41), have been shown to be associated with cardioembolic stroke (42). In consecutive MCA occlusion patients, a "negative susceptibility vessel sign" was shown to be a sensitive marker of predicting underlying atherosclerotic stenosis with a high negative predictive value (23). However, the predictive power of negative susceptibility vessel signs were somewhat different in another study (24), showing moderate sensitivity and a lack of statistical power in identifying ICAS-related occlusion. Other studies have also reported the presence of susceptibility vessel signs in stroke due to cerebral atherosclerosis (42). While MRI-based parameters may allow visualization of thrombus burden, treatment delay in door-to-reperfusion time should be reduced (43). Recently, a dynamic CTA-based imaging parameter, the "multisegment clot sign," was reported to be significantly associated with cardioembolism in patients who received thrombolytic therapy with or without EVT (32). In this report, the absence of the multisegment clot sign was highly sensitive for large artery atherosclerosis, with a modest positive predictive value. While more rapid and precise identification methods should be sought, such parameters may be used in the future to supplement occlusion types in the preprocedural diagnosis of ICAS-related occlusion.

There are some considerations worth mentioning in the current study. First, the comparison between occlusion types and FFS performed in this study should be interpreted with caution,

because the best determination method of occlusion type utilizes stent retriever deployment during DSA (25). However, our primary focus was to evaluate occlusion type as a preprocedural surrogate, and analyzed the CTA-determined occlusion type. Because contact aspiration thrombectomy was performed in many cases ($n = 301$, 59.1%), we could not perform DSA-based TTO analysis to support our findings. Likewise, the methods of MIP reconstruction differs from the original reports (26), and also differs from center to center. Differences in MIP slice thickness may change a TTO to BSO, or vice versa. Accordingly, we cannot be sure that our CTA based occlusion type readings may be highly predictive of DSA based occlusion types, and this may be a potential limitation of this study. Second, due to the retrospective nature of this study and changes in CT imaging protocols, not all images could be clearly dichotomized to TTOs or BSOs. Nevertheless, only 16/525 (3.0%) of the total population were classified as inconclusive, showing that occlusion type analysis is applicable in most cases. Third, advances in CT protocols may change one occlusion type to another. In this study, CTA-enhanced images + reconstruction images without MIP images were used in a portion of patients, and may have resulted in a less sensitive analysis, while multiphase CT was used in a number of patients in the later years of the study. Protocols such as multiphase or dynamic CTA can acquire images at later phases after contrast injection, possibly resulting in delayed filling of bifurcation portions distal to the occlusive portion. In theory, such changes might affect the classification between TTO and BSO (26), resulting in a more accurate visualization of thrombus burden (44). Thus, the predictive values reported in this study are liable to changing in future studies, likely increasing the predictive ability of CTA-based occlusion type analysis. Fourth, some patients with TTO in the intracranial ICA with underlying intracranial atherosclerosis might not have been included in our registry because their MCA and ACA were spared; consequently, their initial neurological condition would not be sufficiently severe for EVT to be indicated. Therefore, the findings in the intracranial ICA group should be interpreted with particular caution.

In conclusion, we examined whether the agreement between preprocedural identification of CTA-based TTO and postprocedural identification of FFS may differ among occlusion sites. The identification of TTO in the VBA appeared to have high interrater agreement and the highest agreement with FFS. TTO in the MCA M1 showed relatively low interrater agreement but relatively high agreement with FFS. As for TTO in the intracranial ICA, while interrater agreement was high, the agreement with FFS was low. We believe that our results can aid the selection of patients for prospective randomized trials to address ICAS-related occlusion in the near future.

AUTHOR CONTRIBUTIONS

S-JL and JSL contributed to the conception and design of the study, acquisition and analysis of data, and preparation of the manuscript. Y-HH, S-IS, JMH, JWC, D-HK, Y-WK, Y-SK, J-HH, JY, and C-HK contributed to acquisition and analysis of data.

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REFERENCES

1. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. (2015) 372:11–20. doi: 10.1056/NEJMoa1411587
2. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. (2015) 372:1009–18. doi: 10.1056/NEJMoa1414792
3. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. (2015) 372:1019–30. doi: 10.1056/NEJMoa1414905
4. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med*. (2015) 372:2296–306. doi: 10.1056/NEJMoa1503780
5. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med*. (2015) 372:2285–95. doi: 10.1056/NEJMoa1415061
6. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. (2018). 378:1849–50. doi: 10.1056/NEJMoa1713973
7. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. (2018) 378:11–21. doi: 10.1056/NEJMoa1706442
8. Roth C, Papanagiotou P, Behnke S, Walter S, Haass A, Becker C, et al. Stent-assisted mechanical recanalization for treatment of acute intracerebral artery occlusions. *Stroke* (2010) 41:2559–67. doi: 10.1161/strokeaha.110.592071
9. Kang DH, Hwang YH, Kim YS, Park J, Kwon O, Jung C. Direct thrombus retrieval using the reperfusion catheter of the penumbra system: forced-suction thrombectomy in acute ischemic stroke. *AJNR Am J Neuroradiol*. (2011) 32:283–7. doi: 10.3174/ajnr.A2299
10. Nogueira RG, Lutsep HL, Gupta R, Jovin TG, Albers GW, Walker GA, et al. Trevo versus merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial. *Lancet* (2012) 380:1231–40. doi: 10.1016/S0140-6736(12)61299-9
11. Saver JL, Jahan R, Levy EI, Jovin TG, Baxter B, Nogueira RG, et al. Solitaire flow restoration device versus the merci retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. *Lancet* (2012) 380:1241–9. doi: 10.1016/S0140-6736(12)61384-1
12. Lee JS, Hong JM, Lee KS, Suh HI, Demchuk AM, Hwang YH, et al. Endovascular therapy of cerebral arterial occlusions: intracranial atherosclerosis versus embolism. *J Stroke Cerebrovasc Dis*. (2015) 24:2074–80. doi: 10.1016/j.jstrokecerebrovasdis.2015.05.003
13. Yoon W, Kim SK, Park MS, Kim BC, Kang HK. Endovascular treatment and the outcomes of atherosclerotic intracranial stenosis in patients with hyperacute stroke. *Neurosurgery* (2015) 76:680–6. doi: 10.1227/NEU.0000000000000694
14. Kim YW, Hong JM, Park DG, Choi JW, Kang DH, Kim YS, et al. Effect of intracranial atherosclerotic disease on endovascular treatment for patients with acute vertebrobasilar occlusion. *AJNR Am J Neuroradiol*. (2016) 37:2072–8. doi: 10.3174/ajnr.A4844.
15. Baek JH, Kim BM, Heo JH, Kim DJ, Nam HS, Kim YD. Outcomes of endovascular treatment for acute intracranial

atherosclerosis-related large vessel occlusion. *Stroke* (2018) 49:2699–705. doi: 10.1161/STROKEAHA.118.022327
16. Kang DH, Yoon W, Kim SK, Baek BH, Lee YY, Kim YW, et al. Endovascular treatment for emergent large vessel occlusion due to severe intracranial atherosclerotic stenosis. *J Neurosurg*. (2018). doi: 10.3171/2018.1.jns172350. [Epub ahead of print].
17. Lee JS, Lee S-J, Yoo JS, Hong J-H, Kim C-H, Kim Y-W, et al. Prognosis of acute intracranial atherosclerosis-related occlusion after endovascular treatment. *J Stroke* (2018) 20:394–403. doi: 10.5853/jos.2018.01627
18. Lee JS, Hong JM, Lee KS, Suh HI, Choi JW, Kim SY. Primary stent retrieval for acute intracranial large artery occlusion due to atherosclerotic disease. *J Stroke* (2015) 18:96–101. doi: 10.5853/jos.2015.01347
19. Jia B, Feng L, Liebeskind DS, Huo X, Gao F, Ma N, et al. Mechanical thrombectomy and rescue therapy for intracranial large artery occlusion with underlying atherosclerosis. *J Neurointerv Surg*. (2018) 10:746–50. doi: 10.1136/neurintsurg-2017-013489
20. Hwang YH, Kim YW, Kang DH, Kim YS, Liebeskind DS. Impact of target arterial residual stenosis on outcome after endovascular revascularization. *Stroke* (2016) 47:1850–7. doi: 10.1161/STROKEAHA.116.013046
21. Al Kasab S, Almadidy Z, Spiotta AM, Turk AS, Chaudry MI, Hungerford JP, et al. Endovascular treatment for AIS with underlying ICAD. *J Neurointerv Surg*. (2017) 9:948–51. doi: 10.1136/neurintsurg-2016-012529
22. Lee JS, Hong JM, Kim JS. Diagnostic and therapeutic strategies for acute intracranial atherosclerosis-related occlusions. *J Stroke* (2017) 19:143–51. doi: 10.5853/jos.2017.00626
23. Kim SK, Yoon W, Heo TW, Park MS, Kang HK. Negative susceptibility vessel sign and underlying intracranial atherosclerotic stenosis in acute middle cerebral artery occlusion. *AJNR Am J Neuroradiol*. (2015) 36:1266–71. doi: 10.3174/ajnr.A4280
24. Suh HI, Hong JM, Lee KS, Han M, Choi JW, Kim JS, et al. Imaging predictors for atherosclerosis-related intracranial large artery occlusions in acute anterior circulation stroke. *J Stroke* (2016) 18:352–4. doi: 10.5853/jos.2016.00283
25. Baek JH, Kim BM, Kim DJ, Heo JH, Nam HS, Song D, et al. Importance of truncal-type occlusion in stentriever-based thrombectomy for acute stroke. *Neurology* (2016) 87:1542–50. doi: 10.1212/WNL.0000000000003202
26. Baek JH, Kim BM, Yoo J, Nam HS, Kim YD, Kim DJ, et al. Predictive value of computed tomography angiography-determined occlusion type in stent retriever thrombectomy. *Stroke* (2017) 48:2746–52. doi: 10.1161/STROKEAHA.117.018096
27. Lee JS, Lee SJ, Hong JM, Choi JW, Hong JH, Chang HW, et al. Temporal changes in care processes and outcomes for endovascular treatment of acute ischemic stroke: retrospective registry data from three korean centers. *Neurointervention* (2018) 13:2–12. doi: 10.5469/neuroint.2018.13.1.2
28. Tomsick T, Broderick J, Carrozella J, Khatri P, Hill M, Palesch Y, et al. Revascularization results in the interventional management of stroke II trial. *AJNR Am J Neuroradiol*. (2008) 29:582–7. doi: 10.3174/ajnr.A0843
29. Khatri P, Neff J, Broderick JP, Khoury JC, Carrozzella J, Tomsick T, et al. Revascularization end points in stroke interventional trials: recanalization versus reperfusion in IMS-I. *Stroke* (2005) 36:2400–3. doi: 10.1161/01.STR.0000185698.45720.58
30. Fiorelli M, Bastianello S, von Kummer R, del Zoppo GJ, Larrue V, Lesaffre E, et al. (1999). Hemorrhagic transformation within 36 hours of a cerebral infarct: relationships with early clinical deterioration and 3-month outcome in the European Cooperative Acute Stroke Study I (ECASS I) cohort. *Stroke* 30, 2280–2284.
31. Frontera JA, Claassen J, Schmidt JM, Wartenberg KE, Temes R, Connolly ESJr, et al. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. *Neurosurgery* (2006) 59:21–7. doi: 10.1227/01.NEU.0000218821.34014.1B
32. Chen Z, Shi F, Zhang M, Gong X, Lin L, Lou M. Prediction of the multisegment clot sign on dynamic CT angiography of cardioembolic stroke. *AJNR Am J Neuroradiol*. (2018) 39:663–8. doi: 10.3174/ajnr.A5549
33. Cho KH, Yoon Y, Sohn SI, Kim JS. Susceptibility vessel signs on T2*-weighted gradient echo images in patients with cerebral atherosclerosis. *Int J Stroke* (2014) 9:E32. doi: 10.1111/ijs.12318
34. Hong JM, Lee SE, Lee SJ, Lee JS, Demchuk AM. Distinctive patterns on CT angiography characterize acute internal carotid artery occlusion subtypes. *Medicine* (2017) 96:e5722. doi: 10.1097/MD.0000000000005722
35. Kim BM. Causes and solutions of endovascular treatment failure. *J Stroke* (2017) 19:131–42. doi: 10.5853/jos.2017.00283
36. Yoo AJ, Andersson T. Thrombectomy in acute ischemic stroke: challenges to procedural success. *J Stroke* (2017) 19:121–30. doi: 10.5853/jos.2017.00752
37. Gunning GM, McArdle K, Mirza M, Duffy S, Gilvarry M, Brouwer PA. Clot friction variation with fibrin content; implications for resistance to thrombectomy. *J Neurointerv Surg*. (2018) 10:34–8. doi: 10.1136/neurintsurg-2016-012721
38. Liebeskind DS, Jahan R, Nogueira RG, Zaidat OO, Saver JL, Investigators S. Impact of collaterals on successful revascularization in Solitaire FR with the intention for thrombectomy. *Stroke* (2014) 45:2036–40. doi: 10.1161/STROKEAHA.114.004781
39. Goyal M, Menon BK, Krings T, Patil S, Qazi E, McTaggart RA, et al. What constitutes the M1 segment of the middle cerebral artery? *J Neurointerv Surg*. (2016) 8:1273–7. doi: 10.1136/neurintsurg-2015-012191
40. Liebeskind DS, Sanossian N, Yong WH, Starkman S, Tsang MP, Moya AL, et al. CT and MRI early vessel signs reflect clot composition in acute stroke. *Stroke* (2011) 42:1237–43. doi: 10.1161/strokeaha.110.605576
41. Rovira A, Orellana P, Alvarez-Sabin J, Arenillas JF, Aymerich X, Grive E, et al. Hyperacute ischemic stroke: middle cerebral artery susceptibility sign at echo-planar gradient-echo MR imaging. *Radiology* (2004) 232:466–73. doi: 10.1148/radiol.2322030273
42. Cho KH, Kim JS, Kwon SU, Cho AH, Kang DW. Significance of susceptibility vessel sign on T2*-weighted gradient echo imaging for identification of stroke subtypes. *Stroke* (2005) 36:2379–83. doi: 10.1161/01.STR.0000185932.73486.7a
43. Lee JS, Demchuk AM. Choosing a hyperacute stroke imaging protocol for proper patient selection and time efficient endovascular treatment: lessons from recent trials. *J Stroke* (2015) 17:221–8. doi: 10.5853/jos.2015.17.3.221
44. Kaschka IN, Kloska SP, Struffert T, Engelhorn T, Golitz P, Kurka N, et al. Clot burden and collaterals in anterior circulation stroke: differences between single-phase CTA and multi-phase 4D-CTA. *Clin Neuroradiol*. (2016) 26:309–15. doi: 10.1007/s00062-014-0359-6

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Endovascular and Clinical Outcomes of Vertebrobasilar Intracranial Atherosclerosis-Related Large Vessel Occlusion

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Background and Purpose: Endovascular treatment (EVT) for acute vertebrobasilar intracranial atherosclerosis-related large vessel occlusion (ICAS-LVO) and its outcomes are not well known. We aimed to evaluate endovascular and clinical outcomes of vertebrobasilar ICAS-LVO patients who underwent EVT.

Methods: Consecutive acute stroke patients who underwent EVT for vertebrobasilar LVO were retrospectively reviewed. Patients were assigned to the ICAS (+) or the ICAS (–) group based on angiographical findings. Procedural details and clinical outcomes were compared between the ICAS (+) and ICAS (–) groups.

Results: This study included 77 patients with acute vertebrobasilar LVO who underwent EVT. Among the study subjects, 24 (31.2%) had an ICAS-LVO. Recanalization was achieved in 19 patients in the ICAS (+) group (79.2%), which was comparable with the ICAS (–) group (84.9%; $p = 0.529$). However, recanalization using conventional endovascular modalities (stent retriever thrombectomy, contact aspiration thrombectomy, or intra-arterial urokinase infusion) was less successful in the ICAS (+) group (36.8%) than the ICAS (–) group (100.0%; $p < 0.001$). All the remaining patients in the ICAS (+) group required specific rescue treatments appropriate for ICAS, including balloon angioplasty, stenting, or intra-arterial glycoprotein IIb/IIIa inhibitor infusion to obtain a successful recanalization. Procedural time was not significantly longer in the ICAS (+) group. The rates of favorable outcomes (37.5% vs. 41.5%; $p = 0.740$), death, and symptomatic intracerebral hemorrhage were not significantly different between the groups.

Conclusion: ICAS-LVO was common in patients who underwent EVT for acute vertebrobasilar LVO. Although conventional modalities were often ineffective for vertebrobasilar ICAS-LVO, a comparable recanalization rate could be obtained with ICAS-specific modalities. Recanalization rate and procedural time were comparable, and clinical outcomes did not differ between patients with or without ICAS-LVO.

Keywords: endovascular treatment, intracranial atherosclerosis, vertebrobasilar occlusion, occlusion type, clinical outcome

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INTRODUCTION

Due to the significant improvement of recanalization rate in modern endovascular treatment (EVT) of large vessel occlusion (LVO), we are now focusing on types of intractable cases (1–4). An LVO caused by *in situ* thrombo-occlusion from underlying intracranial atherosclerosis (intracranial atherosclerosis-related LVO, ICAS-LVO) is considered one of the intractable cases. Subsequently, devising an optimal endovascular strategy for management of ICAS-LVO is important. Then, for an optimal endovascular strategy, reliable information is required such as prediction, procedural details, and endovascular and clinical outcomes of ICAS-LVO.

Because ICAS-LVO is more frequent in posterior circulation (5–7), an endovascular strategy for ICAS-LVO might be more important in procedures for vertebrobasilar LVO than LVO in anterior circulation. Moreover, patients with vertebrobasilar LVO have higher morbidity and mortality compared with LVO in anterior circulation (8, 9). Although there are several nonspecific factors affecting the prognosis of acute vertebrobasilar LVO (10), they have not been actively utilized when selecting patients eligible for EVT (11–13). In fact, all recent randomized controlled trials were performed only with LVO in anterior circulation, and substantial criteria were established to minimize futile recanalization of LVO in anterior circulation. In contrast to LVO in anterior circulation, greater focus has been on the recanalization procedure in vertebrobasilar LVO rather than patient selection factors. Therefore, efficient recanalization of ICAS-LVO might be a more important issue especially in vertebrobasilar LVO. In addition, EVT of the vertebrobasilar ICAS-LVO should be understood in the context of patient clinical outcomes.

Information regarding vertebrobasilar ICAS-LVO is lacking. The procedural details and endovascular and clinical outcomes of vertebrobasilar ICAS-LVO have been reported in only a few studies (6, 7). Accordingly, we evaluated the procedural details and clinical outcomes of vertebrobasilar ICAS-LVO patients treated with EVT.

METHODS

We retrospectively reviewed consecutive acute stroke patients who underwent EVT for intracranial LVO in posterior circulation in a tertiary stroke center from September 2010 to June 2018. The intracranial LVO was restricted to occlusion of a basilar artery or intracranial segment of a vertebral artery (vertebrobasilar artery). The Institutional Review Board approved this study and waived the requirement of informed consent for this study due to its retrospective design. For patients eligible for intravenous tissue-type plasminogen activator (tPA) treatment, a full dose (0.9 mg/kg) of tPA was administered. EVT was considered for patients with a computed tomography angiography (CTA)-determined endovascularly accessible LVO relevant to neurological symptoms, initial National Institutes of Health Stroke Scale score $\geq$ 4, and stroke onset within 12 h.

Endovascular Treatment

According to the predetermined protocol, a stent retriever (Solitaire; Medtronic, Minneapolis, MN or Trevo; Stryker, Kalamazoo, MI) was used as the first endovascular modality in most procedures. A balloon-guiding catheter was not used in endovascular procedures. All procedures were performed under local anesthesia.

In patients with LVO who did not respond to several trials of stent retriever or who showed significant stenosis on the occlusion segment, rescue EVTs were considered. Endovascular modalities for rescue were contact aspiration thrombectomy with Penumbra Reperfusion Catheter (Penumbra, Alameda, CA) or Sofia (Microvention, Tustin, CA), intra-arterial urokinase infusion, balloon angioplasty, intracranial stenting, and/or intra-arterial glycoprotein IIb/IIIa inhibitor (GPI) infusion. Decision for optimal rescue endovascular modalities was based on the operator's best judgment. In most patients who underwent intracranial stenting, intra-arterial GPI was administered to resolve or prevent in-stent thrombosis. We performed the flat-panel CT before GPI infusion in most cases of patients. Although we did not have a specific criterion of unfavorable condition for GPI infusion, large contrast enhancement was the most common reason not to use GPI or to lessen the total dose of GPI. Typically, 5–10 mg of abciximab (typically 1–2 mg/min) or 0.5–2.0 mg of tirofiban (0.05 mg/ml concentration with 0.1 mg/min) was infused intra-arterially. To secure the stability of arterial patency after balloon angioplasty, intracranial stenting, or intra-arterial GPI infusion, serial delay angiograms were collected for at least 20 min after recanalization. The procedure was finished only when significant angiographic worsening was not observed in arterial patency or perfusion status. Intravenous maintenance of GPI after the EVT was also considered if necessary. Oral dual antiplatelet medication was started from the day after the EVT procedure if there was no significant intracranial hemorrhage or other hemorrhagic complication.

Successful recanalization was defined as a modified Thrombolysis Cerebral Ischemia grade 2b or 3, which should not accompany reocclusion events on delay angiograms. Reocclusion event was defined as a complete or incomplete occlusion event after sufficient recanalization. To identify the reocclusion events, follow-up angiography was performed for at least 20 min after recanalization in all patients.

Determination of ICAS-LVO

ICAS-LVO was determined based on occlusion type. All occlusions were classified as either branching site or truncal type primarily based on digital subtraction angiography (DSA) findings (14). Briefly, if arterial bifurcation and all its distal branches beyond the occlusion segment were saved, it was considered a truncal-type occlusion. Based on the principal theory, the truncal-type occlusion can be regarded as an ICAS-LVO (**Figures 1**,**2**).

The occlusion type was assessed by 2 independent neurointerventionalists. The kappa value for the inter-rater reliability of DSA-determined occlusion type was 0.92. Discrepant cases were decided by consensus among reviewers. For cases whose occlusion type could not be determined based

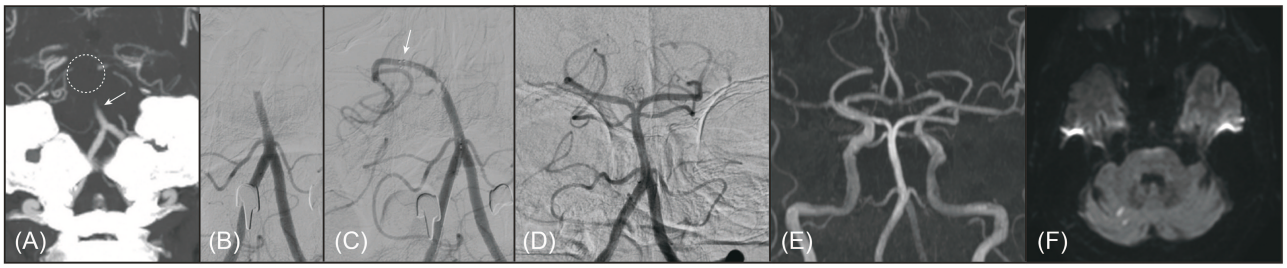

FIGURE 1 | A representative example of 67-year old male patient with branching-site occlusion. **(A,B)** Basilar artery (BA) occlusion was noted on preprocedural computed tomography angiography (**A**, coronal view of maximal intensity projection image; arrow) and digital subtraction angiography (**B**, anteroposterior view). BA bifurcation site was not clearly seen on preprocedural computed tomography angiography (dotted circle). **(C)** Post-deployment angiogram showed only unilateral posterior cerebral artery was observed, which could be considered as a finding of branching-site occlusion (branch-missing sign). Distal marker of the stent retriever was seen on the angiogram (arrow). **(D)** With 1 stent retriever thrombectomy, the BA was completely recanalized. **(E)** On follow-up magnetic resonance angiography (time-of-flight image) performed 1 day after procedure, the recanalized BA was patent. **(F)** Only multiple tiny acute infarctions were noted in bilateral cerebellum and occipital lobe on diffusion-weighted magnetic resonance images. The patient discharged without any neurologic deficits, whose modified Rankin Scale score was 0 at 3 months after stroke.

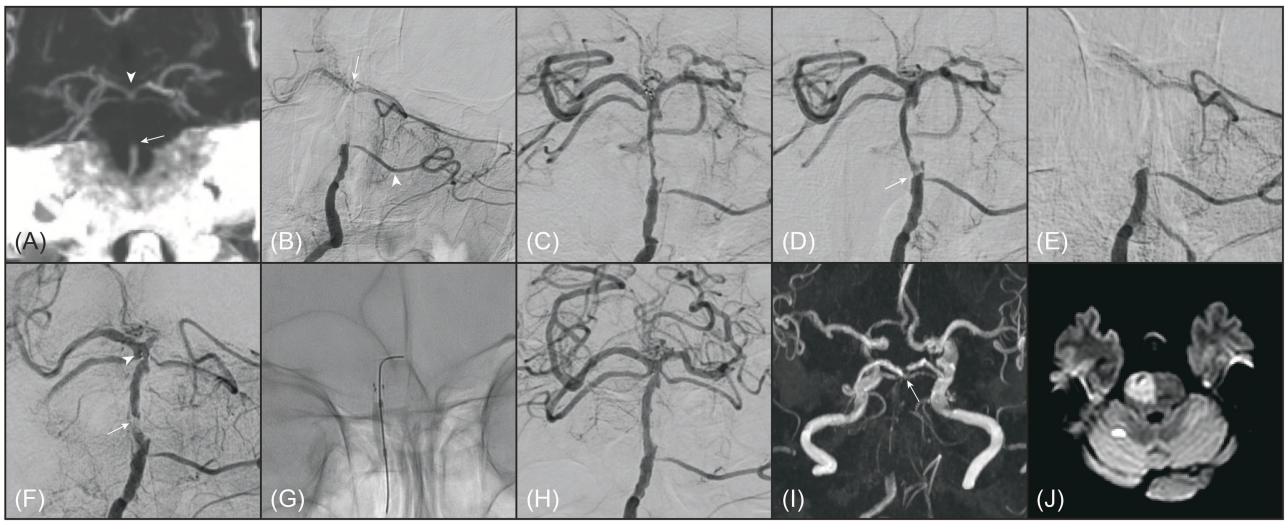

FIGURE 2 | A representative example of 80-year old female patient with truncal-type occlusion. **(A)** On preprocedural computed tomography angiography (coronal view of maximal intensity projection image), occlusion of basilar artery (BA) was noted (arrow). On the computed tomography angiography, BA bifurcation was clearly seen (arrowhead). **(B)** On digital subtraction angiography (anteroposterior view), BA occlusion was also noted. BA bifurcation (arrow) and bilateral posterior cerebral arteries were seen by collateral flows through left anterior inferior cerebellar artery (arrowhead). **(C)** BA bifurcation and bilateral posterior cerebral arteries were definitely verified by stent-through flow. **(D)** By 1 stent retriever thrombectomy, BA occlusion was recanalized, however, focal stenosis with angiographical haziness was noted at the original occlusion site (arrow). **(E)** The recanalized BA was immediately reoccluded. Even with intra-arterial administration of tirofiban 0.5 mg, BA was not recanalized. **(F)** Intracranial stenting with Solitaire (Medtronic, Minneapolis, MN) was performed across the occlusion segment. Distal marker of Solitaire was observed at distal BA (arrowhead). Despite intracranial stenting, arterial patency was not well maintained, which suggested an impending occlusion (arrow). **(G)** Balloon angioplasty with Gateway (Stryker, Kalamazoo, MI) was performed. **(H)** BA was successfully recanalized with mild stenosis and did not show reocclusion event. **(I)** On follow-up magnetic resonance angiography (time-of-flight image) performed 1 day after procedure, distal BA flow was well maintained. (arrow) **(J)** Acute infarction was noted in most of right pons on diffusion-weighted magnetic resonance images. Her modified Rankin Scale score was 5 at 3 months after stroke.

on DSA, mostly due to poor image quality or invalid distal confirmation, the occlusion type was determined using CTA (15). Inter-rater reliability of the CTA-determined occlusion type was excellent (kappa, 0.98).

Clinical Outcomes

Clinical outcomes included functional outcome, death, and symptomatic intracerebral hemorrhage (SICH). Functional outcome and death were assessed using the modified Rankin Scale (mRS) score at 3 months after stroke onset. Favorable outcome was defined as mRS score 0–2. The functional outcome was primarily evaluated by stroke neurologists during the patient's routine clinic follow-up at 3 months ± 2 weeks. If a patient could not come to the clinic, a stroke neurologist or trained nurse interviewed the patient or their family via telephone to determine the mRS score.

ICH was evaluated on follow-up CT or magnetic resonance (gradient echo) images obtained 24 ± 6 h after EVT. The ICH was finally determined by consensus among stroke neurologists, neurointerventionalists, and neuroradiologists during regular stroke conferences. The determination of ICH was immediately entered into the prospective registry. ICH was regarded as symptomatic if National Institutes of Health Stroke Scale score increased ≥4.

Statistical Analysis

Based on the occlusion type determined, patients were assigned to either the ICAS (+) group or the ICAS (–) group. Patients with a truncal-type occlusion were assigned to the ICAS (+) group. Demographics, common risk factors for stroke, procedural details and outcomes, and clinical outcomes were compared between ICAS (+) and ICAS (–) groups. Mann-Whitney U test, χ^2 test, and Fisher exact test were used for comparison. Also, multivariable logistic regression analysis was also performed to independent factors for favorable outcome. For this analysis, age, variables with P-value < 0.1, time profiles including onset-to-puncture and puncture-to-recanalization time, and ICAS-LVO were adjusted. A P-value < 0.05 was considered statistically significant with a 95% confidence interval (CI). Statistical analyses were performed using software (version 3.4.2; r-project.org).

RESULTS

Among 604 patients who underwent EVT for an intracranial LVO, 77 (mean age, 73.2 ± 12.8 years; male, 53.2%) were finally included (**Figure 3**). Patients with distal artery occlusion (n = 16) and etiology of arterial dissection (n = 2) were also excluded. In the study population, 69 patients (89.6%) had a basilar artery occlusion and 8 (10.4%) had an intracranial vertebral artery occlusion. Occlusion type was determined based on DSA in 67 patients (87.0%) and CTA in 10 patients (13.0%). Among the included patients, 24 (31.2%) had an ICAS-LVO. Atrial fibrillation was less frequent in the ICAS (+) group, whereas intravenous tPA was more frequent in the ICAS (+) group (**Table 1**). Stroke severity was not significantly different between groups—median initial NIHSS score in the ICAS (+) group was 14.5 and 12.0 in the ICAS (–) group (P = 0.624; **Supplemental Figure 1**).

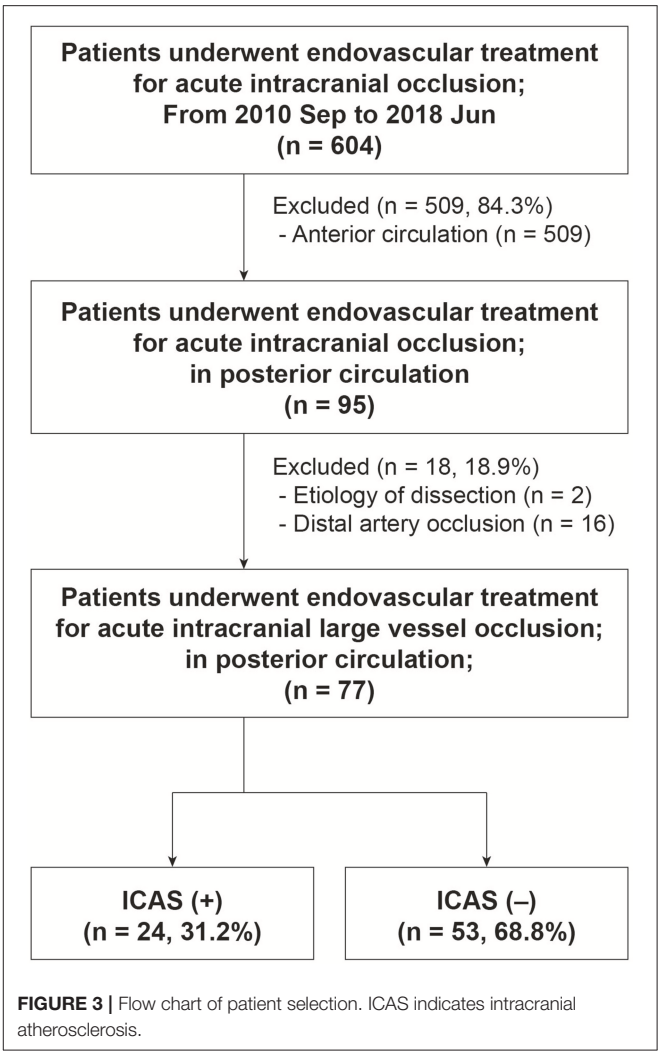

FIGURE 3 | Flow chart of patient selection. ICAS indicates intracranial atherosclerosis.

Procedural Details and Outcomes

Successful recanalization was achieved in 64 patients (83.1%). Successful recanalization rate in the ICAS (+) group was similar to that in the ICAS (–) group (79.2% vs. 84.9%; P = 0.529; **Table 2**). All patients in the ICAS (–) group obtained a successful recanalization with conventional endovascular modalities, of which most (93.3%) were mechanical thrombectomy devices. Conversely, only 36.8% of patients in the ICAS (+) group achieved a successful recanalization with conventional endovascular modalities (P < 0.001). The remaining patients in the ICAS (+) group (63.2%; n = 12) eventually required ICAS-specific modalities to achieve a successful recanalization, including intra-arterial GPI infusion, balloon angioplasty, and intracranial stenting. Among the 12 patients treated with ICAS-specific modalities, 8 obtained a successful recanalization only with GPI infusion (66.7%), and 3 (25.0%) eventually required rescue stenting. For intracranial stenting, Solitaire was used in all cases. In patients in the ICAS (+) group treated with GPI (n = 11), abciximab was infused in 6 (54.5%; mean dose, 9.2 ± 3.4 mg) and tirofiban in 5 patients (45.5%; 0.7 ± 0.2 mg).

Reocclusion events after initial recanalization using conventional endovascular modalities were observed more frequently in the ICAS (+) group than in the ICAS (–) group (62.5% vs. 5.7%; P < 0.001; **Table 2**). In 15 patients with reocclusion events in the ICAS (+) group, GPI was used in 13 (86.7%). Reocclusion events were resolved only with GPI infusion in 8 patients (61.5%; 8 of 13). For patients in whom GPI infusion was unsuccessful, additional consecutive intracranial stenting with balloon angioplasty provided more recanalization in 3 patients (23.1%; 3 of 13). Altogether, 84.6% (11 of 13) of patients with reocclusion events were successfully recanalized with GPI infusion and/or consecutive intracranial stenting with balloon angioplasty.

TABLE 1 | Comparison of variables between patients with and without vertebrobasilar intracranial atherosclerosis-related acute large vessel occlusion (ICAS-LVO).

	Total patients ($n = 77$)	ICAS (+) ($n = 24$)	ICAS (–) ($n = 53$)	*P*-value	Odds ratio* (95% CI)
Age, years	73.2 (±12.8)	72.7 (±13.8)	73.5 (±12.5)	0.800	0.99 (0.96–1.03)
Sex, male	41 (53.2)	14 (58.3)	27 (50.9)	0.547	1.34 (0.51–3.57)
Hypertension	62 (80.5)	21 (87.5)	41 (77.4)	0.366	2.05 (0.52–8.06)
Diabetes	30 (39.0)	6 (25.0)	24 (45.3)	0.091	0.40 (0.14–1.17)
Dyslipidemia	19 (24.7)	6 (25.0)	13 (24.5)	0.965	1.03 (0.34–3.13)
Smoking	10 (13.0)	7 (29.2)	3 (5.7)	0.008	6.86 (1.59–29.6)
Coronary artery disease	24 (31.2)	5 (20.8)	19 (35.8)	0.188	0.47 (0.15–1.46)
Atrial fibrillation	36 (46.8)	7 (29.2)	29 (54.7)	0.037	0.34 (0.12–0.96)
Initial NIHSS score	13.0 [7.0; 24.0]	14.5 [9.0; 21.5]	12.0 [7.0; 25.0]	0.624	1.00 (0.95–1.05)
Basilar artery occlusion	69 (89.6)	16 (66.7)	53 (100.0)	<0.001	N/A
Use of IV tPA	18 (23.4)	10 (41.7)	8 (15.1)	0.011	4.02 (1.33–12.1)
Onset-to-puncture, min	262.0 [146.0; 435.0]	207.0 [158.0; 307.8]	285.0 [140.0; 475.0]	0.253	0.94 (0.87–1.02)†

CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; IV tPA, intravenous tissue plasminogen activator; N/A, not applicable.
Values in parentheses represent the standard deviation, number of patients (%), or median; brackets represent first and third quartiles.
**Odds ratio for ICAS (+)*
†Odds ratio per 30 min of time.

TABLE 2 | Procedural and clinical outcomes of patients with and without vertebrobasilar intracranial atherosclerosis-related acute large vessel occlusion (ICAS-LVO).

	Total patients ($n = 77$)	ICAS (+) ($n = 24$)	ICAS (–) ($n = 53$)	*P*-value	Odds ratio* (95% CI)
ENDOVASCULAR OUTCOMES					
Successful recanalization	64 (83.1)	19 (79.2)	45 (84.9)	0.529	0.68 (0.20–2.33)
Conventional modalities	52 (81.2)	7 (36.8)	45 (100.0)	<0.001	N/A
Stent retriever	38 (59.4)	5 (26.2)	33 (73.3)		
Contact aspiration thrombectomy	10 (15.6)	1 (5.3)	9 (20.0)		
Urokinase	4 (6.2)	1 (5.3)	3 (6.7)		
ICAS-specific modalities	12 (18.8)	12 (63.2)	0 (0.0)		
GPI	8 (12.5)	8 (42.1)	0 (0.0)		
PTA	1 (1.6)	1 (5.3)	0 (0.0)		
Stenting + PTA + GPI	3 (4.7)	3 (15.8)	0 (0.0)		
Procedural Events					
Reocclusion during the procedure	18 (23.4)	15 (62.5)	3 (5.7)	<0.001	27.8 (6.66–115.9)
Puncture-to-recanalization, min	46.5 [27.8; 93.2]	52.0 [25.5; 117.5]	45.0 [28.0; 77.0]	0.837	1.07 (0.80–1.44)†
Onset-to-recanalization, min	351.0 [207.5; 497.2]	325.0 [243.0; 437.5]	383.0 [201.0; 529.0]	0.791	0.97 (0.90–1.06)†
CLINICAL OUTCOMES					
Favorable outcome	31 (40.3)	9 (37.5)	22 (41.5)	0.740	0.85 (0.32–2.28)
Death	16 (20.8)	4 (16.7)	12 (22.6)	0.763	0.68 (0.20–2.39)
Symptomatic ICH	4 (5.2)	3 (12.5)	1 (1.9)	0.087	7.43 (0.73–75.5)

CI, confidence interval; GPI, glycoprotein IIb/IIIa inhibitor; PTA, percutaneous transluminal angioplasty; ICH, intracerebral hemorrhage; N/A, not applicable.
Values in parentheses represent the number of patients (%) or median; brackets represent first and third quartiles.
**Odds ratio for ICAS (+).*
†Odds ratio per 30 min of time.

Median puncture-to-recanalization time was 46.5 min (interquartile range, 27.8–93.2; range, 9.0–273.0; **Supplemental Figure 2**) and median onset-to-recanalization time was 351.0 min (interquartile range, 207.5–497.2; range, 99.0–1020.0; **Supplemental Figure 3**). Puncture-to-recanalization time was not significantly different between the ICAS (+) and the ICAS (–) groups (52.0 vs. 45.0 min; $P = 0.837$). Onset-to-recanalization time was not significantly different between the groups, either (325.0 vs. 383.0 min; $P = 0.791$).

Clinical Outcomes

Favorable outcome (37.5% vs. 41.5%; $P = 0.740$) and death (16.7% vs. 22.6%; $P = 0.763$) were not significantly different between the ICAS (+) and ICAS (–) groups (**Table 2**, **Figure 4**). SICH developed in 4 patients (5.2%) in the study population. SICH was higher in the ICAS (+) group than the ICAS (–) group; however, the difference was not statistically significant (12.5% vs. 1.9%; $P = 0.087$). SICH developed in 12.5% of patients who underwent intra-arterial GPI infusion, which was not significantly higher than in patients who did not receive intra-arterial GPI infusion (3.3%; $P = 0.189$). In addition, use of intravenous tPA was not associated with development of SICH ($P = 0.999$). For patients with basilar artery occlusion ($n = 69$), clinical outcomes were not significantly different between the ICAS (+) and ICAS (–) groups (**Supplemental Table**).

In multivariable analysis, initial NIHSS score (odds ratio 0.82 with 95% confidence interval 0.74–0.91; $P < 0.001$; **Table 3**) and puncture-to-recanalization time (odds ratio 0.81 per 10 min with 0.65–0.99; $P = 0.046$) were independent factors for favorable outcome.

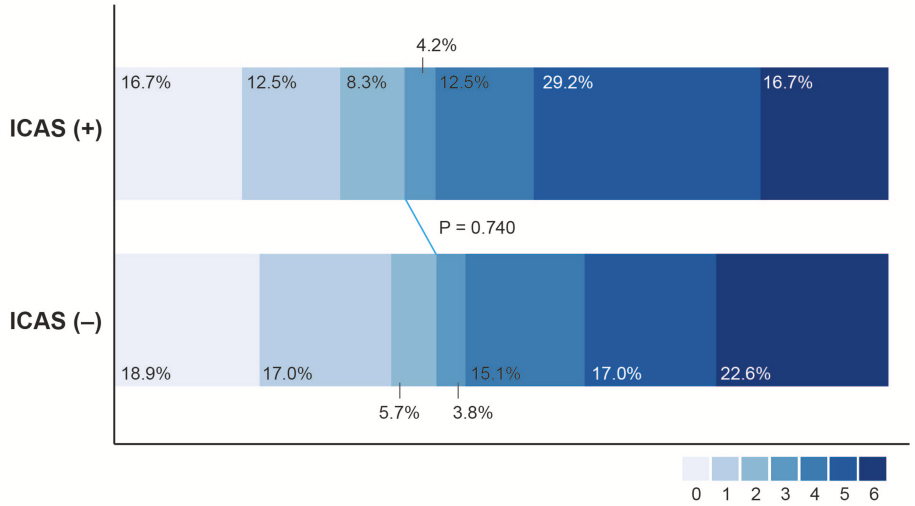

FIGURE 4 | Distribution of modified Rankin Scale score at 3 months after treatment in patients with intracranial atherosclerosis-related large vessel occlusion (ICAS [+]) and without (ICAS [–]).

DISCUSSION

In this study, ICAS-LVO comprised approximately 31% of all vertebrobasilar LVOs eligible for EVT. Patients with ICAS-LVO required specific rescue treatments appropriate for underlying ICAS, which resulted in a successful recanalization rate similar to that of patients without ICAS-LVO, and clinical outcomes in patients with or without ICAS-LVO were not significantly different.

ICAS-LVO is more frequent in patients with acute vertebrobasilar occlusion eligible for EVT (6, 7). Kim et al. reported that approximately 37% of ICAS-LVO in acute vertebrobasilar artery occlusion has been observed in the Korean population (6). The reported frequency of ICAS-LVO did not differ from our study. Lee et al. also reported the frequency of ICAS-LVO in acute basilar artery occlusion as approximately 24%, similar to our study (23.2%; 16 of 69 basilar artery occlusions) (7). Because most ICAS-LVO studies included LVOs in both anterior and posterior circulation, comparing frequencies of ICAS-LVO between anterior and posterior circulation is difficult (5, 16–18). The frequency of ICAS-LVO in both circulations was approximately 8–23%, far less than posterior circulation studies (6, 7). In addition, posterior circulation involvement was an independent factor associated with ICAS-LVO (5). The reason ICAS-LVO is more prevalent in posterior circulation is unclear. However, an optimal endovascular strategy for ICAS-LVO might be more important in posterior than anterior circulation cases due to higher frequency.

Clinical outcomes of patients with vertebrobasilar ICAS-LVO who underwent EVT were not consistent in previous studies. Lee et al. showed that patients with vertebrobasilar ICAS-LVO had comparable clinical outcomes to those without vertebrobasilar ICAS-LVO (7). Conversely, in another study, patients with vertebrobasilar ICAS-LVO had a less favorable outcome despite similar recanalization rates (6). Furthermore, vertebrobasilar ICAS-LVO was an independent factor for poor prognosis. One potential reason for the difference of clinical outcome was procedural time. Based on those studies, longer procedural time was associated with poor clinical outcomes (7). In this study, time profiles including onset-to-recanalization time and puncture-to-recanalization time were not significantly longer in patients with vertebrobasilar ICAS-LVO. In addition, clinical outcomes were also comparable to those of patients without vertebrobasilar ICAS-LVO. However, even in this study, puncture-to-recanalization time was an independent factor for favorable outcome. Considering the findings from previous and current studies, procedural time could be an important factor that influences clinical outcome in acute vertebrobasilar ICAS-LVO. Conversely, recanalization success might be an important factor affecting clinical outcomes of patients with ICAS-LVO of anterior circulation because their clinical outcomes were proportional to successful recanalization rate (16, 18–20).

Occlusion location might affect the stroke severity in LVO of posterior circulation. In BA occlusion, patients with proximal or middle clot had higher mortality than distal (21). Clinical outcome was not favorable in proximal or middle clot, either. Another study also showed a higher mortality in BA occlusion with atherothrombosis, which were represented as a proximal and middle BA occlusion (22). One possible explanation for the more severe stroke severity in the ICAS-LVO group is the involvement of pons perforator. In our study, an initial NIHSS score was higher in the ICAS-LVO group. This might be come from that branching-site occlusion absolutely involves distal BA based on its original theory, while the truncal-type occlusion might be possible at all segments of BA including its proximal and middle part.

Procedural details to treat vertebrobasilar ICAS-LVO are not well known. The feasibility of intracranial stenting,

TABLE 3 | Univariable and multivariable analyses of variables affecting favorable outcome.

	Univariable analysis			Multivariable analysis	
	Favorable outcome (*n* = 31)	**Unfavorable outcome (*n* = 46)**	***P*-value**	**Odds ratio (95% CI)**	***P*-value**
Age, years	70.9 (±15.3)	74.8 (±10.8)	0.216	0.97 (0.92–1.04)	0.397
Sex, male	18 (58.1)	23 (50.0)	0.487		
Hypertension	24 (77.4)	38 (82.6)	0.573		
Diabetes	10 (32.3)	20 (43.5)	0.322		
Dyslipidemia	6 (19.4)	13 (28.3)	0.374		
Smoking	5 (16.1)	5 (10.9)	0.512		
Coronary artery disease	9 (29.0)	15 (32.6)	0.740		
Atrial fibrillation	17 (54.8)	19 (41.3)	0.243		
Initial NIHSS score	7.0 [5.5; 11.5]	22.0 [12.2; 28.0]	<0.001	0.82 (0.74–0.91)	<0.001
Basilar artery occlusion	29 (93.5)	40 (87.0)	0.463		
Use of IV tPA	8 (25.8)	10 (21.7)	0.679		
Onset-to-puncture, min	210.0 [123.0; 415.5]	265.5 [169.2; 440.2]	0.347	0.96 (0.86–1.06)*	0.414
Puncture-to-recanalization, min	35.0 [19.0; 58.0]	56.0 [38.0; 130.5]	0.001	0.81 (0.65–0.99)†	0.046
Onset-to-recanalization, min	264.0 [182.0; 443.0]	390.0 [294.0; 497.5]	0.180		
Successful recanalization	29 (93.5)	35 (76.1)	0.063		
Reocclusion during the procedure	4 (12.9)	14 (30.4)	0.075	0.43 (0.04–5.07)	0.504
Use of GPI during procedure	5 (16.1)	11 (23.9)	0.409		
Symptomatic ICH	0 (0.0)	4 (8.7)	0.143		
ICAS-related large vessel occlusion	9 (29.0)	15 (32.6)	0.740	1.10 (0.15–8.21)	0.924

CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; IV tPA, intravenous tissue plasminogen activator; GPI, glycoprotein IIb/IIIa inhibitor; ICH, intracerebral hemorrhage; ICAS, intracranial atherosclerosis.

Values in parentheses represent the standard deviation, number of patients (%), or median; brackets represent first and third quartiles.

** Odds ratio per 30 min of time.*

† Odds ratio per 10 min of time.

balloon angioplasty, and intra-arterial GPI infusion, termed ICAS-specific endovascular modalities in vertebrobasilar ICAS-LVO, have been reported only in a few case series (23, 24). Kim et al. only reported the use of ICAS-specific modalities based on the presence of vertebrobasilar ICAS-LVO (6). More ICAS-specific modalities were used in patients with vertebrobasilar ICAS-LVO for rescue treatment. However, the study did not offer detailed information regarding the success rate of modern conventional modalities (e.g., stent retriever or contact aspiration thrombectomy) or effectiveness of each ICAS-specific modality in vertebrobasilar ICAS-LVO. Procedural details of the current study were similar to those of other studies on ICAS-LVO (18, 19, 23–26). To obtain a successful recanalization, ICAS-LVO required significantly more rescue treatments, which were all ICAS-specific modalities. Apparently, ICAS-specific modalities were feasible and necessary in most patients with vertebrobasilar ICAS-LVO. Interestingly, among them, intra-arterial GPI infusion could be considered as the first ICAS-specific modality. In this study, 66.7% of patients who were treated by ICAS-specific modalities could get a successful recanalization by intra-arterial GPI alone. In anterior circulation ICAS-LVOs, intra-arterial GPI was effective in about 40% of patients without the use of other ICAS-specific modalities (20). According to the response to the first intra-arterial GPI infusion, one might consider intracranial stenting or balloon angioplasty.

In summary, the expected successful recanalization rate in vertebrobasilar ICAS-LVO using modern conventional modalities is not high, possibly less than 40%. In addition, ICAS-specific endovascular modalities were quite feasible and effective. Furthermore, shorter procedural time appears more important in vertebrobasilar ICAS-LVO for better clinical outcome. Rapid and active introduction of ICAS-specific modalities should be considered as an optimal endovascular strategy in vertebrobasilar ICAS-LVO.

SICH was not statistically different between patients with or without ICAS-LVO; however, frequency of SICH in the ICAS (+) group was higher than in the ICAS (–) group. Most likely, the number of SICH cases was too small to reach statistical significance in this study. Although the number of cases was too small, none were associated with development of SICH among variables used in this study, including use of intra-arterial GPI or intravenous tPA. Further studies are necessary to verify this issue.

This study had several strengths and limitations. First, this study was retrospective; thus, types and specific timing of introduction of rescue endovascular modalities were not protocolized. Although treatment protocol was fundamentally predetermined, many stages during the endovascular procedures were dependent on operator discretion. However, because a reliable method to identify and treatment protocol to manage ICAS-LVO do not exist, the results from this retrospective study might help in the understanding of procedural details for managing vertebrobasilar ICAS-LVO and devising an optimal treatment protocol.

Second, occlusion type was used to identify ICAS-LVO. This is the first study of vertebrobasilar ICAS-LVO that used occlusion type for its identification. Occlusion type is considered a reliable angiographical surrogate marker for ICAS-LVO during or before an endovascular procedure (14, 15). Occlusion type could be determined even in cases with persistent occlusion and had excellent inter-rater reliability. More importantly, endovascular strategy, which is devised from endovascular and clinical results based on the occlusion type, might also be practical for daily

EVT procedure. In our center, we actively use occlusion type in identifying the ICAS-LVO in real practice. It might contribute to the comparable procedural time for vertebrobasilar ICAS-LVOs in this study, although it should be verified prospectively. In spite of the clinical advantages, occlusion type might be imperfect in identifying occlusion etiology in some situations. For example, an occlusion by a large size of embolus might be erroneously classified as a truncal-type occlusion. Although occlusion types in this study were mostly determined by DSA, CTA-determined occlusion type considerably depends on collateral adequacy (15). Thus, it seems necessary to compare the occlusion type with another angiographical definition of ICAS-LVO for more reliability (1, 5).

Third, results from this study were derived from a single stroke center in Asia, where ICAS is more prevalent. Thus, generalizability might be limited to a specific population. However, management of ICAS-LVO is challenging in modern EVT, and its importance has been increasing in intractable cases irrespective of ethnicity. Furthermore, in situations where only minimal information regarding procedural and clinical outcomes is available, the current study provides important baseline data for vertebrobasilar ICAS-LVO.

CONCLUSIONS

ICAS-LVO was common in patients who underwent EVT for acute vertebrobasilar LVO. Patients with a vertebrobasilar ICAS-LVO achieved a comparably successful recanalization rate with similar procedural time; however, those patients required more rescue endovascular modalities specific to ICAS-LVO for successful recanalization. The clinical outcomes were comparable in patients with or without vertebrobasilar ICAS-LVO.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

J-HB established the study idea, designed the manuscript structure, acquired and analyzed the data, and wrote the manuscript. BMK established the study idea, designed the manuscript structure, acquired data, and made critical revisions to the manuscript with substantive intellectual content. DJK, JHH, HSN, and YDK acquired data and made critical revisions to the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00215/full#supplementary-material

REFERENCES

1. Lee JS, Hong JM, Kim JS. Diagnostic and therapeutic strategies for acute intracranial atherosclerosis-related occlusions. *J Stroke.* (2017) 19:143–51. doi: 10.5853/jos.2017.00626
2. Kim BM. Causes and solutions of endovascular treatment failure. *J Stroke.* (2017) 19:131–42. doi: 10.5853/jos.2017.00283
3. Bang OY. Considerations when subtyping ischemic stroke in asian patients. *J Clin Neurol.* (2016) 12:129–36. doi: 10.3988/jcn.2016.12.2.129
4. Chang Y, Kim BM, Bang OY, Baek JH, Heo JH, Nam HS, et al. Rescue stenting for failed mechanical thrombectomy in acute ischemic stroke: a multicenter experience. *Stroke.* (2018) 49:958–64. doi: 10.1161/STROKEAHA.117.020072
5. Lee JS, Hong JM, Lee KS, Suh HI, Demchuk AM, Hwang YH, et al. Endovascular therapy of cerebral arterial occlusions: intracranial atherosclerosis versus embolism. *J Stroke Cerebrovasc Dis.* (2015) 24:2074–80. doi: 10.1016/j.jstrokecerebrovasdis.2015.05.003
6. Kim YW, Hong JM, Park DG, Choi JW, Kang DH, Kim YS, et al. Effect of intracranial atherosclerotic disease on endovascular treatment for patients with acute vertebrobasilar occlusion. *AJNR Am J Neuroradiol.* (2016) 37:2072–8. doi: 10.3174/ajnr.A4844
7. Lee YY, Yoon W, Kim SK, Baek BH, Kim GS, Kim JT, et al. Acute basilar artery occlusion: differences in characteristics and outcomes after endovascular therapy between patients with and without underlying severe atherosclerotic stenosis. *AJNR Am J Neuroradiol.* (2017) 38:1600–4. doi: 10.3174/ajnr.A5233
8. Mattle HP, Arnold M, Lindsberg PJ, Schonewille WJ, Schroth G. Basilar artery occlusion. *Lancet Neurol.* (2011) 10:1002–14. doi: 10.1016/S1474-4422(11)70229-0
9. Singer OC, Berkefeld J, Nolte CH, Bohner G, Haring HP, Trenkler J, et al. Mechanical recanalization in basilar artery occlusion: the ENDOSTROKE study. *Ann Neurol.* (2015) 77:415–24. doi: 10.1002/ana.24336
10. Kang DH, Jung C, Yoon W, Kim SK, Baek BH, Kim JT, et al. Endovascular thrombectomy for acute basilar artery occlusion: a multicenter retrospective observational study. *J Am Heart Ass.* (2018) 7:e009419. doi: 10.1161/JAHA.118.009419
11. Powers WJ, Derdeyn CP, Biller J, Coffey CS, Hoh BL, Jauch EC, et al. (2015) American heart association/american stroke association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke.* (2015) 46:3020–35. doi: 10.1161/STR.0000000000000074
12. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. (2018) Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke.* (2018) 49:e46–110. doi: 10.1161/STR.0000000000000158
13. Song D, Cho AH. Previous and recent evidence of endovascular therapy in acute ischemic stroke. *Neurointervention.* (2015) 10:51–9. doi: 10.5469/neuroint.2015.10.2.51
14. Baek JH, Kim BM, Kim DJ, Heo JH, Nam HS, Song D, et al. Importance of truncal-type occlusion in stentriever-based thrombectomy for acute stroke. *Neurology.* (2016) 87:1542–50. doi: 10.1212/WNL.0000000000003202
15. Baek JH, Kim BM, Yoo J, Nam HS, Kim YD, Kim DJ, et al. Predictive value of computed tomography angiography-determined occlusion type in stent retriever thrombectomy. *Stroke.* (2017) 48:2746–52. doi: 10.1161/STROKEAHA.117.018096

16. Al Kasab S, Almadidy Z, Spiotta AM, Turk AS, Chaudry MI, Hungerford JP, et al. Endovascular treatment for AIS with underlying ICAD. *J Neurointerv Surg.* (2017) 9:948–51. doi: 10.1136/neurintsurg-2016-012529
17. Matias-Guiu JA, Serna-Candel C, Matias-Guiu J. Stroke etiology determines effectiveness of retrievable stents. *J Neurointerv Surg.* (2014) 6:e11. doi: 10.1136/neurintsurg-2012-010395
18. Yoon W, Kim SK, Park MS, Kim BC, Kang HK. Endovascular treatment and the outcomes of atherosclerotic intracranial stenosis in patients with hyperacute stroke. *Neurosurgery.* (2015) 76:680–6. doi: 10.1227/NEU.0000000000000694
19. Jia B, Feng L, Liebeskind DS, Huo X, Gao F, Ma N, et al. Mechanical thrombectomy and rescue therapy for intracranial large artery occlusion with underlying atherosclerosis. *J Neurointerv Surg.* (2018) 10:746–50. doi: 10.1136/neurintsurg-2017-013489
20. Baek JH, Kim BM, Heo JH, Kim DJ, Kim YD, Nam HS. Outcomes of endovascular treatment for acute intracranial atherosclerosis–related large vessel occlusion. *Stroke.* (2018) 49:2699–705. doi: 10.1161/STROKEAHA.118.022327
21. Cross DT 3rd, Moran CJ, Akins PT, Angtuaco EE, Diringer MN. Relationship between clot location and outcome after basilar artery thrombolysis. *AJNR Am J Neuroradiol.* (1997) 18:1221–8.
22. Eckert B, Kucinski T, Pfeiffer G, Groden C, Zeumer H. Endovascular therapy of acute vertebrobasilar occlusion: early treatment onset as the most important factor. *Cerebrovasc Dis.* (2002) 14:42–50. doi: 10.1159/000063722
23. Behme D, Weber W, Mpotsaris A. Acute basilar artery occlusion with underlying high-grade basilar artery stenosis: multimodal endovascular therapy in a series of seven patients. *Clin Neuroradiol.* (2015) 25:267–74. doi: 10.1007/s00062-014-0303-9
24. Gao F, Lo WT, Sun X, Mo DP, Ma N, Miao ZR. Combined use of mechanical thrombectomy with angioplasty and stenting for acute basilar occlusions with underlying severe intracranial vertebrobasilar stenosis: preliminary experience from a single chinese center. *AJNR Am J Neuroradiol.* (2015) 36:1947–52. doi: 10.3174/ajnr.A4364
25. Kang DH, Kim YW, Hwang YH, Park SP, Kim YS, Baik SK. Instant reocclusion following mechanical thrombectomy of in situ thromboocclusion and the role of low-dose intra-arterial tirofiban. *Cerebrovasc Dis.* (2014) 37:350–5. doi: 10.1159/000362435
26. Lee JS, Hong JM, Lee KS, Suh HI, Choi JW, Kim SY. Primary stent retrieval for acute intracranial large artery occlusion due to atherosclerotic disease. *J Stroke.* (2016) 18:96–101. doi: 10.5853/jos.2015.01347

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW
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Endovascular Therapy for Acute Ischemic Stroke of Intracranial Atherosclerotic Origin—Neuroimaging Perspectives

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Large vessel occlusion (LVO) due to intracranial atherosclerosis (ICAS) is a common cause of acute ischemic stroke (AIS) in Asians. Endovascular therapy (EVT) has been established as the mainstay of treatment in patients with AIS and LVO. However, only a few patients of Asian descent with ICAS-related LVO (ICAS-LVO) were included in recent randomized controlled trials of EVT for AIS. Therefore, the findings of these trials cannot be directly applied to Asian patients with ICAS-LVO. In embolic LVO due to thrombus from the heart or a more proximal vessel, rapid, and complete recanalization can be achieved in more than 70–80% of patients, and it is important to exclude patients with large cores. In contrast, patients with ICAS-LVO usually have favorable hemodynamic profiles (good collateral status, small core, and less severe perfusion deficit), but poor response to EVT (more rescue treatments and longer procedure times are required for successful recanalization due to higher rates of reocclusion). Patients with ICAS-LVO may have different anatomic (plaque, angioarchitecture), hemodynamic (collateral status), and pathophysiologic (thrombus composition) features on neuroimaging compared to patients with embolic LVO. In this review, we discuss these neuroimaging features, their clinical implications with respect to determination of EVT responses, and the need for development of specific EVT devices and procedures for patients with ICAS-LVO.

Keywords: atherosclerosis, neuroimage, endovascular therapy, acute ischemic stroke, intracranial

INTRODUCTION

Large vessel occlusion (LVO), thought to originate from intracranial atherosclerosis (ICAS), is a common cause of acute ischemic stroke (AIS) in Asians (1). Embolic LVO due to thrombus from the heart or a more proximal vessel and ICAS-related LVO (ICAS-LVO) both show similar luminal changes and are treated with endovascular therapy (EVT) in acute settings. However, recent clinical studies suggest that treatment responses may differ between these two types of LVO (2–10). Patients with ICAS-LVO may have different anatomic (plaque, angioarchitecture), hemodynamic (collateral status), and pathophysiologic (thrombus composition) features on neuroimaging compared to patients with embolic LVO.

In this review, we discuss these features, their clinical implications with respect to determination of EVT responses, and the need for development of specific EVT devices and procedures for patients with ICAS-LVO.

SEARCH STRATEGY AND SELECTION CRITERIA

We searched PubMed and ClinicalTrials.gov for articles published in English up to September 2018 using the following search terms: stroke, cerebrovascular disease, endovascular therapy, and intracranial stenosis. We also searched references from relevant articles and reviews. The final reference list was generated based on originality and relevance to this topic. We did not discuss individual imaging techniques or etiologies of non-atherosclerotic intracranial arterial disease in depth, since these topics are reviewed elsewhere (11–18).

ICAS-LVO IN RECENT RANDOMIZED CONTROLLED TRIALS OF EVT FOR AIS

Phase III, randomized controlled trials (RCTs) conducted in 2015 demonstrated overwhelming evidence of the benefit of early window EVT for treatment of AIS with small core and LVO (19–23). More recently, the results of phase III RCTs of EVT in extended time windows showed significant and remarkable functional recovery after EVT compared to medical treatment in carefully selected patients (24, 25). In individual patient data meta-analyses of RCTs, the benefits of EVT were consistent in all prespecified subgroups of age, sex, initial stroke severity score, site of vessel occlusion, presence of tandem occlusion, extent of initial early ischemic changes on computed tomography (CT), intravenous tissue plasminogen activation (tPA), and onset-to-randomization time (26, 27). However, the type of LVO was not considered in the RCTs, and the number of patients with ICAS-LVO was small considering that only few Asian patients were enrolled in the 2 RCTs (20, 22).

The results of EVT in patients with ICAS-LVO are shown in **Table 1**. Recanalization failure, residual stenosis, and reocclusion were more frequently observed than embolic occlusion and rescue therapy with permanent stent placement or adjuvant antithrombotics are often required after EVT in ICAS-LVO patients (2–4, 9). Consequently, longer procedure times were required and higher complication rates and poorer long-term outcomes were reported after EVT in patients with ICAS-LVO than in those with embolic occlusion (5, 6, 8). Therefore, the results of the phase III RCTs of EVT cannot be directly applied to patients with ICAS-LVO.

DIAGNOSIS OF SUSPECTED ICAS-LVO

Differentiation of ICAS-LVO from embolic LVO is often challenging, especially in cases without known ICAS and in the setting of EVT for AIS when workups for potential sources of cardioembolism cannot be performed (**Figure 1**). Several clinical features may be helpful for differentiating ICAS-LVO from embolic LVO (28). Although advanced magnetic resonance imaging (MRI) techniques may provide information on the ischemic zone, thrombus, blood-brain barrier, and vessel wall pathology (29), only non-contrast brain CT and conventional angiographic techniques are available to differentiate these two types of LVOs in most centers.

As shown in **Table 1**, most investigators used angiographic features for the diagnosis of ICAS-LVO. Baek et al. defined ICAS-LVO as truncal-type occlusion when all major branches and their bifurcation sites are clearly visible beyond the occlusion segment (2, 3). Other investigators considered angiographic findings of residual or fixed stenosis to be ICAS-LVO (4–8).

The prevalence of ICAS-LVO was reported to range from 5.5 to 25%. The prevalence of ICAS in EVT candidates varied depending on the diagnostic methods for ICAS-LVO and race or ethnicity (1, 9).

FEATURES OF ICAS-LVO

ICAS-LVO has more differentiating features than embolic LVO, which are discussed below (**Table 2**).

Intracranial Plaque

The presence of intracranial plaques can influence endovascular procedures and affect outcome. EVT for ICAS-LVO is associated with residual stenosis or reocclusion, insufficient expansion of devices, inadvertent detachment, arterial dissection, and vasospasm (4, 5, 30). Therefore, repeat procedures and long procedure times are often necessary for successful reperfusion. They are also associated with poor clinical outcomes (2, 6). Repeated stent retrieval attempts, especially in the presence of a plaque at the LVO site, can further damage the fibrous cap and lead to aggravation of *in situ* thrombosis. In western trials, ICAS was less prevalent and early reocclusion after successful reperfusion with EVT was rare (31).

Perforator

In preventive intervention for ICAS, the incidence of symptomatic complications was high after intracranial stenting for perforator-bearing segments or in patients with branch occlusive disease (BOD) with subcortical infarcts caused by occluding the perforator orifice (32–34). The involved segment was more diffuse and positive remodeling was less frequently observed in BOD-type ICAS than in non-BOD-type ICAS (35, 36). The complication rates of EVT may also be increased in patients with AIS and LVO in the perforator-bearing segments, especially when permanent stent placement is required. Therefore, increased complication rate with the permanent placement of stent in the perforator bearing segment should be considered, especially in the setting of EVT for LVO when appropriate antiplatelet premedication before the procedure is not possible. Further studies are needed because a higher peri-procedural ischemic stroke rate was reported in the treatment of perforator-bearing arteries, and there was no difference between angioplasty alone and balloon mounted/self-expandable stenting (33).

TABLE 1 | Summary of literature on angiographic features suggesting large vessel occlusion of suspected intracranial atherosclerotic origin and outcomes after endovascular therapy.

References	Vascular territory	Diagnosis of ICAS-LVO	Main findings	Implications
Baek et al. (2)	Any	Truncal-type occlusion	Reocclusion 77% of ICAS ($n = 22$) 5% of Embolic ($n = 202$)	Reocclusion was common and additional modalities are needed in ICAS
Baek et al. (3)	Carotid	Truncal-type occlusion	mTICI 2b-3 (with stentriever) 29% of ICAS ($n = 56$) 94% of Embolic ($n = 262$)	ICAS showed a low recanalization rate with strentriever and a similar rate with rescue therapy
Hwang et al. (4)	Any	Residual stenosis and tandem occlusion	Residual stenosis 100% of ICAS ($n = 40$) 28% Embolic ($n = 123$)	54% of patients with residual stenosis had ICAS
Al Kasab et al. (5)	Any	Fixed stenosis	Procedure time 99 min in ICAS ($n = 36$) 37 min in Embolic ($n = 165$)	Longer procedure time and poorer outcome in ICAS
Kim et al. (6)	V-B	Residual stenosis or reocclusion	Procedure time 96 min in ICAS ($n = 19$) 61 min in Embolic ($n = 32$)	Longer procedure time and poorer outcome in ICAS
Kang et al. (7)	Any	Fixed stenosis or aggravation after IA injection of vasodilator	mTICI 2b-3 in ICAS ($n = 140$) 96% in angioplasty/stent 94% in IA GP inhibitor	Both angioplasty/stenting and IA GP inhibitor are effective
Lee et al. (8)	Carotid	Residual stenosis >70%, or stenosis ≤70% with a tendency toward reocclusion and/or flow impairment during the procedure	mTICI 2b-3 76.8% in ICAS ($n = 99$) 79.6% in Embolic ($n = 421$)	ICAS showed similarly successful reperfusion rates but poorer functional outcome with EVT than embolic occlusion
Gascou et al. (9)	Any	Not specified	ICAS in 8 Embolic in 136	ICAS was associated with recanalization failure and higher rates of complication and mortality
Yang et al. (10)	Carotid	Fixed stenosis or retrospective analysis of the TOAST classification	Favorable outcome at 90 days in ICAS ($n = 302$) 48% in stentriever group 70% in angioplasty and/or stenting group	Angioplasty and/or stenting as first-line therapy may be superior to thrombectomy in ICAS

ICAS, intracranial atherosclerosis; V-B, vertebrobasilar; mTICI, modified treatment in cerebral ischemia score; IA, intra-arterial; GP, glycoprotein IIb/IIIa; EVT, endovascular therapy; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

Arterial Diameter

ICAS-LVO often involves smaller-sized vessels than clots that originated from the heart (such as red clots in atrial fibrillation occluding the distal internal carotid artery). Moreover, the *ring finger protein 213* (*RNF213*) gene variant, the most susceptible gene for moyamoya in Asians, was found in 1 in 4 Japanese and Korean patients with non-moyamoya intracranial stenosis (37, 38). Hongo et al. reported that patients with ICAS and *RNF213* variants had middle cerebral arteries with relatively smaller outer diameter (2.09 ± 0.32 mm) (39). The results of the RCT of the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Arterial Stenosis showed that treating very small vessels (<2.5–2.75 mm diameter) was associated with higher complication rates, because small vessels are more likely to have restenosis or acute thrombosis and they may also be more prone to injury with stenting (32).

Calcification And Tortuosity

Patients with ICAS may have stiff, calcified, and tortuous vessels. In these patients, a longer time may be required to reach the target site and incomplete recanalization and poor functional outcomes were reported (40). A *post-hoc* analysis of a RCT showed that the type of intracranial arterial calcification determined the effect of EVT for AIS (41).

Thrombus

Blood flow affects thrombus composition, with "red clots" or erythrocyte-rich thrombi found in low-pressure systems (heart or venous system), and "white clots" or platelet-rich thrombi found in high pressure systems (e.g., arteries) (42). The composition and burden of clot correlate with revascularization rate in EVT. Fibrin-rich thrombi have higher coefficients of static friction with the vessel walls, and larger thrombi have larger surface areas of thrombus-vessel interaction (43). Treatment response to medical treatment (such as tPA and glycoprotein IIb/IIIa inhibitors) and EVT may vary for ICAS-LVO and embolic occlusion. The thrombus size is usually smaller in ICAS-LVO than in embolic LVO, but the recanalization rates with EVT or tPA were lower in the former than in the latter (43–46). A histopathologic analysis of retrieved thrombi showed that atheromatous gruel (cholesterol

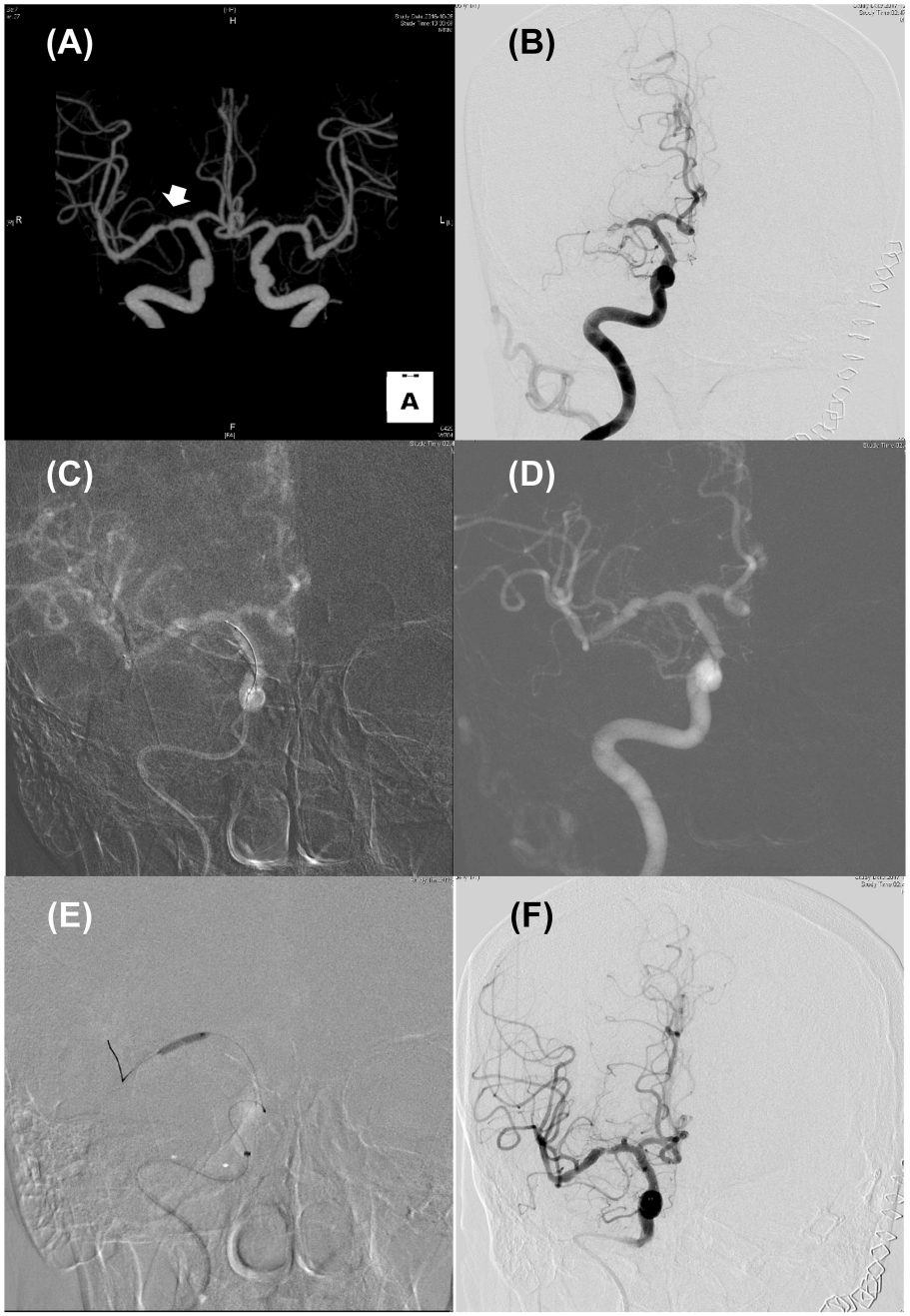

FIGURE 1 | Illustrated case for the management of acute stroke due to intracranial atherosclerosis. **(A)** CT angiography performed 2 years ago revealed focal stenosis on right mid-MCA (Arrow). **(B)** Initial internal carotid angiography showed truncal-type occlusive lesion on right mid-MCA with minimal blood flow across the occlusive lesion. **(C,D)** Roadmap images during solitaire stent (4 × 20 mm) placement **(C)** and after retrieval **(D)**. Pre-existing stenotic lesion still be seen. **(E)** Balloon angioplasty using Gateway TPA balloon (2 × 15 mm; Boston scientific) was performed. **(F)** Delayed carotid angiography 30 min after permanent solitaire stent placement. Despite residual stenosis, improved distal flow can be seen.

clefts, form cells, or fibrous caps) was associated with failed recanalization, and erythrocyte-rich thrombi were associated with successful recanalization (45). In ICAS-LVO cases, adjuvant glycoprotein IIb/IIIa inhibitors for *in situ* thrombosis or angioplasty with/without permanent stent placement may be helpful (2, 3). However, beside stroke subtypes, other factors also influence the characteristics of thrombi, such as collaterals and angioarchitecture (44, 47). In addition, in patients with coronary atherosclerotic plaques, growing thrombi consist of both platelet-rich and erythrocyte-rich

TABLE 2 | Neuroimaging features and specific considerations in endovascular therapy for large vessel occlusions of intracranial atherosclerotic origin.

Differential neuroimaging features in ICAS (vs. embolic)	Impacts on efficacy and strategies in EVT	Specific requirements for ICAS-LVO EVT equipment	Assessment tools
1. Intracranial plaque	Residual stenosis/reocclusion, insufficient expansion of devices, intimal damage, arterial dissection, and vasospasm Long procedure time	Permanent stenting Avoid repeat procedures	HR-MRI Catheter-based imaging (IVUS, OCT)
2. Erythrocyte-poor thrombus	Low recanalization rate with EVT in the presence of fibrin-rich clots Lower recanalization rate with intravenous thrombolysis in ICAS than in embolic stroke Lower recanalization rate with EVT due to reocclusion than red clot	Adjuvant antithrombotics Antiplatelet strategy other than fibrinolytics for *in situ* thrombosis	Thrombus images Pathology of retrieved clot
3. Angioarchitecture			
Calcification and tortuosity	Long procedure time Incomplete recanalization and poor functional outcome	Intermediate catheter*	Luminal images Non-contrast CT
Perforator-bearing segment	A higher stroke rate after preventive ICAS intervention	Not available	HR-MRI DWI lesion pattern
Diameter of artery	Increased hemorrhagic complications after preventive ICAS intervention	Intermediate catheter Appropriately sized devices and Solumbra technique*	Luminal images
4. Preexisting collaterals	Slower growing and less severe hypoperfusion Higher recanalization rates Better outcome	A longer time window for EVT	Collateral images DWI and PWI pattern
5. Non-atherosclerotic diseases	High restenosis rates in MMD Stent placement may be the preferred treatment in ICAD	Stent placement should be avoided in MMD, but may be considered in ICAD	Detailed clinical and luminal images HR-MRI Catheter-based images

ICAS, intracranial atherosclerosis; EVT, endovascular therapy; LVO, large vessel occlusion; HR-MRI, high-resolution magnetic resonance imaging; IVUS, intravascular ultrasound; OCT, optical coherence tomography; CT, computed tomography; DWI, diffusion-weighted image; PWI, perfusion-weighted image; MMD, moyamoya disease; ICAD, intracranial arterial dissection.

**Theoretical suggestion, not based on the results of clinical studies.*

clots, and thrombus stability also determines the response to revascularization therapy (48).

Collaterals

The importance of collateral status has been reported in preventive RCTs of ICAS patients and in acute interventional RCTs (49–52). Although the individual patient data meta-analysis of RCTs of LVO for AIS showed that early treatment with EVT was associated with improved outcomes (53), a recent meta-analysis showed that good collateral status is associated with better clinical responses to EVT even in later time windows, suggesting that collateral status can extend the time window for EVT (54). A retrospective multicenter study of 720 patients showed that while the probability of good outcomes in patients with embolic occlusion declined as onset-to-puncture time increased, the probability of good outcomes in patients with ICAS-LVO did not decline but tended to increase with increase in onset-to-puncture time (8). The incidence of slow progressors may be <30% of patients with anterior circulation LVO in large referral centers (55), but may be higher in ICAS-LVO because collateral circulation in patients with ICAS was better than in those with other stroke subtypes (56).

Non-atherosclerotic Origin

In addition to ICAS, non-atherosclerotic intracranial arterial diseases, such as moyamoya disease or intracranial arterial dissection, may also cause LVO. Careful evaluation of clinical and luminal studies (such as healthy risk factor profiles and no tandem stenosis or calcification in intracranial arterial dissection, and the presence of family history and basal collaterals in moyamoya disease) may provide clues for the diagnosis of these non-atherosclerotic diseases. However, it is often difficult to differentiate them in clinical practice. Prospective observational high-resolution MRI (HR-MRI) studies of non-stroke subjects (57), young stroke patients (58), and acute stroke patients (59) showed that non-atherosclerotic intracranial large artery disease is prevalent across a wide range of atherosclerosis risk groups. Therapeutic strategies used in intracranial atherosclerosis may not be helpful or may even be detrimental in some patients with non-atherosclerotic LVO (18). For example, stent placement should be avoided in moyamoya disease (60–62), but stent placement (especially, closed cell-type stent) may be considered in intracranial arterial dissection. A recent study showed that endovascular thrombectomy is an effective in selected patients with acute ischemic stroke associated with cervical artery dissection (63), but further studies are needed in patients with acute infarcts due to intracranial non-atherosclerotic occlusion.

SPECIFIC DIAGNOSTIC AND THERAPEUTIC CONSIDERATIONS IN EVT FOR ICAS-LVO

Assessment Tools for Underlying Features of ICAS

Plaque Images

HR-MRI may provide information on arterial wall pathology, such as plaque characteristics and arterial remodeling. Recently, the imaging findings of intracranial plaques were verified with histopathology (64, 65). A HR-MRI study showed that EVT causes post-recanalization changes of affected arterial segments, which correlated with thrombectomy procedural factors such as number of procedures and type of device used, and was associated with poor outcomes (66, 67). HR-MRI studies conducted after various modes of EVT demonstrated vessel damage related to stentriever process and may be useful for the development of optimal endovascular therapeutic strategies or devices with minimal intimal injury (66, 67). HR-MRI can also provide information on angioarchitecture. Data on the presence and location of perforators in relation to the plaque, in patients with ICAS-LVO, can be useful when considering stent placement in perforator-bearing segments. Lastly, HR-MRI can be used to differentiate non-atherosclerotic intracranial large vessel disease from ICAS in patients. Although concerted efforts have been made to increase signal-to-noise and contrast-to-noise characteristics and to shorten the scanning time, routine use of HR-MRI is not feasible in clinical practice. Like in coronary heart disease, catheter-based imaging can be an alternative modality for use in EVT settings. Intravascular ultrasound (IVUS) and optical coherence tomography (OCT, the light analog of IVUS) are intravascular imaging techniques used in interventional cardiology (68). A meta-analysis of RCTs comparing IVUS- and angiographic-guided percutaneous coronary interventions showed that IVUS guidance was associated with significantly lower rates of angiographic restenosis, repeat revascularization, and overall occurrence of major cardiac events (69). The results of several case reports suggest that these techniques may provide useful information for the selection of patients with ICAS who may benefit from stent placement therapy (16). In addition, IVUS can be used during the EVT procedure to differentiate ICAS-LVO from embolic LVO by visualization of calcified plaque in ICAS. IVUS may help differentiation of intracranial arterial dissection from ICAS and identification of the most distal and proximal extent of arterial dissection, so that the entire length of the dissection could be covered with stent (70). These techniques can also provide virtual histology to characterize plaques in large intracranial vessels. An *in vitro* study of intracranial arterial segments with atherosclerotic plaques demonstrated a strong correlation between virtual histology using IVUS and 7T MRI and histopathologic analysis (71). Gounis et al. recently introduced the high-frequency OCT device for the highly tortuous cerebrovasculature that provides good quality imaging of vessel wall layers, the ostium of small branches/perforators, and the relationship between neurovascular devices and vessel wall (17).

Thrombus Images

Identifying the characteristics of a thrombus in AIS may provide vital information for the determination of the optimal strategy for revascularization therapy and for the choice of antithrombotics for the secondary prevention of stroke. The characteristics of a thrombus (size and composition) may determine the recanalization rate, time required for re-opening, and the response to acute and preventive treatment in patients with AIS. Therefore, it is extremely useful to know the thrombus characteristics before initiating recanalization therapy. A thrombus can be detected on a non-contrast CT image as a hyperdense artery sign or a blooming artifact on T2*-weighted gradient-recalled image. Details on the methods to measure thrombus size and burden are presented elsewhere (14). Thrombus size determines the response to revascularization. Although thrombus length is strongly associated with successful recanalization with intravenous tPA therapy, the predictive power of thrombus size in determining successful reperfusion in EVT appears to be diminished (14). The results of recent RCTs showed that there was no correlation between the clot burden score (using clot volume and length) and the effects of EVT (72, 73). Thrombus composition and its associated pathogenesis can be visualized by CT or MRI. The density on CT may reflect the thrombus composition. Erythrocytes in thrombi increase attenuation on CT, and the hyperdense artery sign is more commonly seen in erythrocyte-dominant thrombi than in fibrin-rich thrombi. For example, thrombus permeability, as measured by thrombus density on thin-slice non-contrast CT imaging, was found to correlate with the histological components of retrieved thrombi and permeable thrombi were associated with cardioembolic occlusion in patients with AIS (74). However, a recent systematic analysis showed a lack of association between a CT-based clot image (e.g., Hounsfield units) and histopathology of thrombi or stroke etiology (75). Similarly, an erythrocyte component in thrombi induces ferromagnetic field distortion, which results in a blooming artifact on gradient-recalled echo or susceptibility-weighted imaging. The presence of a blooming artifact on MRI is associated with cardioembolic stroke (76, 77). Pathological studies of thrombi retrieved via EVT showed that the presence and absence of blooming artifacts were found to be due to erythrocyte- and fibrin-predominant occlusive thrombi, respectively, and erythrocyte-rich thrombi were associated with successful recanalization of EVT and cardioembolic stroke (78, 79). Lastly, direct thrombus imaging targeting fibrinogen can determine the initial burden and location of thrombi and may also help visualize residual thrombi or distal thromboembolism. Kim et al. investigated hyperacute direct thrombus imaging techniques and monitored the therapeutic efficacy of thrombolysis using fibrin-targeted gold nanoparticles and CT imaging (80). Various MRI probes, such as fibrin-binding gadolinium-labeled peptides, have been used for the evaluation of acute thrombosis after plaque rupture in animal models (81–83).

Collateral Images

Conventional angiographic evaluation is the gold standard for collateral assessment (84). However, more time is needed to

include the venous phase and contralateral or vertebrobasilar views. In using EVT in clinical settings, most interventionalists perform angiography of the affected territory and open the occluded vessel without performing angiography of unaffected territories in a bid to shorten the puncture-to-reperfusion time. Both multiphase CT angiography and perfusion MRI-based collateral maps can be performed in acute settings (85–87), and they showed a good correlation with conventional angiography for leptomeningeal collateral grading in AIS (87–89). These non-invasive collateral assessments are particularly important in ICAS-LVO, because pre-procedure CT or MRI data can be used for selecting slower infarct progressors presented at a later time. CT angiography shows the anatomical configuration of collateral vessels and its use is becoming more routine. However, there is no consensus on the best method for evaluating and grading collaterals and various CT angiography techniques and grading systems are used (90–92). Other imaging techniques, such as CT perfusion and arterial spin labeling MRI, may also provide information on collateral status (15).

EVT Devices and Techniques for ICAS-LVO

Stentrievers were the main devices described for use in EVT in the RCTs, and the current guidelines recommend mechanical thrombectomy with a strentriever in conjunction with intravenous tPA as the standard of care in anterior circulation stroke caused by LVOs (93). Owing to the aforementioned characteristics of ICAS-LVO, better tools and techniques are needed for smaller and/or tortuous arteries, the minimization of vessel damage, and the facilitation of rescue therapies. For these purposes, detachable stents with radio-opaque markers for visualizing residual stenosis are required. Stents with radiopaque design can provide better visualization of stent-thrombus interaction during stentrieval process, and also provide additional information on the nature of thrombus as atherosclerotic lesion may appear as an area of strut compression or waist. Permanent stent placement may be required in case of residual stenosis or re-occlusion. In this situation, radiopaque stent strip is informative in stent placement and detachability is essential. However, no radiopaque detachable stentriever is available until now; radiopaque trevo stent is not detachable while solitaire AB is not radiopaque.

In cases in which the relevant artery is tortuous, a large bore balloon guide catheter is preferred, and the stenotic segment of the intracranial artery is crossed with microwire as distally as possible to ensure maximal support while allowing tracking of the balloon guide catheter. To overcome vascular tortuosity, coaxial double-guiding catheter technique, or double-wire technique could be considered (94–96).

In addition, distal access catheters (such as intermediate catheter) provide support and stability for microcatheters and are also suitable for aspiration. The ability to deliver intermediate catheters to the vicinity of the thrombus ensures the generation of greater effective retrieval force by the device especially in cases with significant vessel tortuosity. It also provides a strong enough suction force to remove soft thrombi without using a stent retriever (ADAPT, a direct aspiration first pass technique) (43). Theoretically, this approach is ideal as it results in lesser damage to vessels and underlying plaques, and it may prevent the distal migration of clots to a greater extent than possible with stentrievers. However, the contact aspiration technique requires optimal contact between the aspiration catheter tip and the thrombus, which depends on the location of the thrombus and the tortuosity of the vessel (97). In some cases, the contact aspiration technique may not be effective due to imprecise positioning of the aspiration catheter tip relative to the thrombus. The results of a recent RCT showed no significant differences in the primary outcome of final successful recanalization rates between ADAPT and stentrievers (98). Stentrievers can also be used in conjunction with direct aspiration at the face of a thrombus during thrombectomy (Solumbra technique) (99, 100).

Rescue treatments, including balloon angioplasty, rescue stenting, and intra-arterial glycoprotein IIb/IIIa inhibitor infusion, can be considered for ICAS-LVO refractory to stentriever (3). On the contrary, Yang and the ACUAL investigators studied 302 patients with ICAS-LVO and reported that patients who received angioplasty and/or stenting as first-line therapy showed favorable outcome and lower rate of intracranial bleeding than those received stentriever (10). Further studies are needed in patients with ICAS-LVO to determine the first-line device and technique for thrombectomy (stentriever, ADAPT, or Solumbra), pharmacological adjunct (intravenous tPA or intra-arterial antithrombotics), and cessation time for procedures in cases of repetitive reocclusion.

CONCLUSIONS

Despite the recent success of EVT, there are still numerous challenges with respect to management of ICAS-LVO. Studies discussed herein suggest that there are more diverse neuroimaging features in ICAS-LVO than in embolic occlusion. While recent RCTs of EVT showed that appropriate selection is important in AIS, selection of appropriate EVT procedures may be more important in patients with ICAS-LVO. Patients with ICAS-LVO usually have favorable hemodynamic profiles but demonstrate poor response to EVT. Though ICAS-LVO requires more complex and technically demanding recanalization strategies than embolic occlusion, good outcomes are attainable with the application of appropriate therapeutic strategies.

Future studies should focus on investigating reliable imaging predictors related to response to EVT in ICAS-LVO patients, and on developing and evaluating thrombectomy approaches to overcome the characteristic drawback of reocclusion in ICAS-LVO. Advanced neuroimaging of plaques, thrombi, and collaterals could not be performed in the EVT setting. However, post-EVT analysis may be useful for the characterization of patients with ICAS-LVO, clearer understanding of the pathophysiology of ICAS-LVO, and future guidance for optimal therapeutic strategies for ICAS-LVO. For clinical use of advanced neuroimaging techniques for patients with AIS, fast, and safe assessment tools that can visualize individual features of ICAS, automated software that allows fast post-processing is mandatory, and is increasingly being used in clinical trials (17, 29). In addition, optimal tools and techniques for ICAS-LVO are not settled yet. Most of the studies presented here were retrospective studies conducted

in East Asian countries. It is necessary to conduct RCTs of acute interventions for ICAS-LVO in diversified populations to reach recommendations.

AUTHOR CONTRIBUTIONS

OB study concept and design, acquisition of data, analysis and interpretation of data, drafting/revising the manuscript for content. BK, W-KS, and PJ drafting/revising the manuscript for content.

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REFERENCES

1. Gorelick PB, Wong KS, Bae HJ, Pandey DK. Large artery intracranial occlusive disease: a large worldwide burden but a relatively neglected frontier. *Stroke.* (2008) 39:2396–9. doi: 10.1161/STROKEAHA.107.505776
2. Baek JH, Kim BM, Kim DJ, Heo JH, Nam HS, Song D, et al. Importance of truncal-type occlusion in stentriever-based thrombectomy for acute stroke. *Neurology.* (2016) 87:1542–50. doi: 10.1212/WNL.0000000000003202
3. Baek JH, Kim BM, Heo JH, Kim DJ, Nam HS, Kim YD. Outcomes of endovascular treatment for acute intracranial atherosclerosis-related large vessel occlusion. *Stroke.* (2018) 49:2699–705. doi: 10.1161/STROKEAHA.118.022327
4. Hwang YH, Kim YW, Kang DH, Kim YS, Liebeskind DS. Impact of target arterial residual stenosis on outcome after endovascular revascularization. *Stroke.* (2016) 47:1850–7. doi: 10.1161/STROKEAHA.116.013046
5. Al Kasab S, Almadidy Z, Spiotta AM, Turk AS, Chaudry MI, Hungerford JP, et al. Endovascular treatment for AIS with underlying ICAD. *J Neurointerv Surg.* (2017) 9:948–51. doi: 10.1136/neurintsurg-2016-012529
6. Kim YW, Hong JM, Park DG, Choi JW, Kang DH, Kim YS, et al. Effect of intracranial atherosclerotic disease on endovascular treatment for patients with acute vertebrobasilar occlusion. *AJNR Am J Neuroradiol.* (2016) 37:2072–8. doi: 10.3174/ajnr.A4844
7. Kang DH, Yoon W, Kim SK, Baek BH, Lee YY, Kim YW, et al. Endovascular treatment for emergent large vessel occlusion due to severe intracranial atherosclerotic stenosis. *J Neurosurg.* (2018). doi: 10.3171/2018.1.JNS172350. [Epub ahead of print].
8. Lee JS, Lee SJ, Yoo JS, Hong JH, Kim CH, Kim YW, et al. Prognosis of acute intracranial atherosclerosis-related occlusion after endovascular treatment. *J Stroke.* (2018) 20:394–403. doi: 10.5853/jos.2018.01627
9. Gascou G, Lobotesis K, Machi P, Maldonado I, Vendrell JF, Riquelme C, et al. Stent retrievers in acute ischemic stroke: complications and failures during the perioperative period. *AJNR Am J Neuroradiol.* (2014) 35:734–40. doi: 10.3174/ajnr.A3746
10. Yang D, Lin M, Wang S, Wang H, Hao Y, Zi W, et al. Primary angioplasty and stenting may be superior to thrombectomy for acute atherosclerotic large-artery occlusion. *Interv Neuroradiol.* (2018) 24:412–20. doi: 10.1177/1591019918763380
11. Bodle JD, Feldmann E, Swartz RH, Rumboldt Z, Brown T, Turan TN. High-resolution magnetic resonance imaging: an emerging tool for evaluating intracranial arterial disease. *Stroke.* (2013) 44:287–92. doi: 10.1161/STROKEAHA.112.664680
12. Alexander MD, Yuan C, Rutman A, Tirschwell DL, Palagallo G, Gandhi D, et al. High-resolution intracranial vessel wall imaging: imaging beyond the lumen. *J Neurol Neurosurg Psychiatry.* (2016) 87:589–97. doi: 10.1136/jnnp-2015-312020
13. Kim J, Park JE, Nahrendorf M, Kim DE. Direct thrombus imaging in stroke. *J Stroke.* (2016) 18:286–96. doi: 10.5853/jos.2016.00906
14. Heo JH, Kim K, Yoo J, Kim YD, Nam HS, Kim EY. Computed tomography-based thrombus imaging for the prediction of recanalization after reperfusion therapy in stroke. *J Stroke.* (2017) 19:40–9. doi: 10.5853/jos.2016.01522
15. Bang OY, Goyal M, Liebeskind DS. Collateral circulation in ischemic stroke: assessment tools and therapeutic strategies. *Stroke.* (2015) 46:3302–9. doi: 10.1161/STROKEAHA.115.010508
16. Pavlin-Premrl D, Sharma R, Campbell BCV, Mocco J, Opie NL, Oxley TJ. Advanced imaging of intracranial atherosclerosis: lessons from interventional cardiology. *Front Neurol.* (2017) 8:387. doi: 10.3389/fneur.2017.00387
17. Gounis MJ, Ughi GJ, Marosfoi M, Lopes DK, Fiorella D, Bezerra HG, et al. Intravascular optical coherence tomography for neurointerventional surgery. *Stroke.* (2018). doi: 10.1161/STROKEAHA.118.022315. [Epub ahead of print].
18. Bang OY, Toyoda K, Arenillas JF, Liu L, Kim JS. Intracranial large artery disease of non-atherosclerotic origin: recent progress and clinical implications. *J Stroke.* (2018) 20:208–17. doi: 10.5853/jos.2018.00150
19. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med.* (2015) 372:11–20. doi: 10.1056/NEJMoa1411587
20. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med.* (2015) 372:1019–30. doi: 10.1056/NEJMoa1414905
21. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med.* (2015) 372:1009–18. doi: 10.1056/NEJMoa1414792
22. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med.* (2015) 372:2285–95. doi: 10.1056/NEJMoa1415061
23. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med.* (2015) 372:2296–306. doi: 10.1056/NEJMoa1503780
24. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med.* (2018) 378:11–21. doi: 10.1056/NEJMoa1706442
25. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med.* (2018) 378:708–18. doi: 10.1056/NEJMoa1713973
26. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet.* (2016) 387:1723–31. doi: 10.1016/S0140-6736(16)00163-X
27. Campbell BC, Hill MD, Rubiera M, Menon BK, Demchuk A, Donnan GA, et al. Safety and efficacy of solitaire stent thrombectomy: individual patient data meta-analysis of randomized trials. *Stroke.* (2016) 47:798–806. doi: 10.1161/STROKEAHA.115.012360
28. Lee JS, Hong JM, Lee KS, Suh HI, Demchuk AM, Hwang YH, et al. Endovascular therapy of cerebral arterial occlusions: intracranial atherosclerosis versus embolism. *J Stroke Cerebrovasc Dis.* (2015) 24:2074–80. doi: 10.1016/j.jstrokecerebrovasdis.2015.05.003
29. Bang OY, Chung JW, Son JP, Ryu WS, Kim DE, Seo WK, et al. Multimodal MRI-based triage for acute stroke therapy: challenges and progress. *Front Neurol.* (2018) 9:586. doi: 10.3389/fneur.2018.00586
30. Toyoda K, Koga M, Hayakawa M, Yamagami H. Acute reperfusion therapy and stroke care in Asia after successful endovascular trials. *Stroke.* (2015) 46:1474–81. doi: 10.1161/STROKEAHA.115.008781
31. Mosimann PJ, Kaesmacher J, Gautschi D, Bellwald S, Panos L, Piechowiak E, et al. Predictors of unexpected early reocclusion after successful mechanical thrombectomy in acute ischemic stroke patients. *Stroke.* (2018) 49:2643–51. doi: 10.1161/STROKEAHA.118.021685

32. Abou-Chebl A, Steinmetz H. Critique of "Stenting versus aggressive medical therapy for intracranial arterial stenosis" by Chimowitz et al in the new England Journal of Medicine. *Stroke.* (2012) 43:616–20. doi: 10.1161/STROKEAHA.111.641563
33. Nordmeyer H, Chapot R, Aycil A, Stracke CP, Wallocha M, Hadisurya MJ, et al. Angioplasty and stenting of intracranial arterial stenosis in perforator-bearing segments: a comparison between the anterior and the posterior circulation. *Front Neurol.* (2018) 9:533. doi: 10.3389/fneur.2018.00533
34. Park KY, Kim BM, Kim DJ, Kim DI, Heo JH, Nam HS, et al. Incidence and risk factors for diffusion-weighted imaging (+) lesions after intracranial stenting and its relationship with symptomatic ischemic complications. *Stroke.* (2014) 45:3298–303. doi: 10.1161/STROKEAHA.114.006182
35. Ryoo S, Park JH, Kim SJ, Kim GM, Chung CS, Lee KH, et al. Branch occlusive disease: clinical and magnetic resonance angiography findings. *Neurology.* (2012) 78:888–96. doi: 10.1212/WNL.0b013e31824c4699
36. Ryoo S, Lee MJ, Cha J, Jeon P, Bang OY. Differential vascular pathophysiologic types of intracranial atherosclerotic stroke: a high-resolution wall magnetic resonance imaging study. *Stroke.* (2015) 46:2815–21. doi: 10.1161/STROKEAHA.115.010894
37. Miyawaki S, Imai H, Shimizu M, Yagi S, Ono H, Mukasa A, et al. Genetic variant RNF213 c.14576G>A in various phenotypes of intracranial major artery stenosis/occlusion. *Stroke.* (2013) 44:2894–7. doi: 10.1161/STROKEAHA.113.002477
38. Bang OY, Chung JW, Cha J, Lee MJ, Yeon JY, Ki CS, et al. A polymorphism in RNF213 is a susceptibility gene for intracranial atherosclerosis. *PLoS ONE.* (2016) 11:e0156607. doi: 10.1371/journal.pone.0156607
39. Hongo H, Miyawaki S, Imai H, Shinya Y, Ono H, Mori H, et al. Smaller outer diameter of atherosclerotic middle cerebral artery associated with RNF213 c.14576G>A Variant (rs112735431). *Surg Neurol Int.* (2017) 8:104. doi: 10.4103/sni.sni_59_17
40. Hernandez-Perez M, Bos D, Dorado L, Pellikaan K, Vernooij MW, Lopez-Cancio E, et al. Intracranial carotid artery calcification relates to recanalization and clinical outcome after mechanical thrombectomy. *Stroke.* (2017) 48:342–7. doi: 10.1161/STROKEAHA.116.015166
41. Compagne KCJ, Clephas PRD, Majoie C, Roos Y, Berkhemer OA, van Oostenbrugge RJ, et al. Intracranial carotid artery calcification and effect of endovascular stroke treatment. *Stroke.* (2018) 49:2961–8. doi: 10.1161/STROKEAHA.118.022400
42. Mackman N. Triggers, targets and treatments for thrombosis. *Nature.* (2008) 451:914–8. doi: 10.1038/nature06797
43. Yoo AJ, Andersson T. Thrombectomy in acute ischemic stroke: challenges to procedural success. *J Stroke.* (2017) 19:121–30. doi: 10.5853/jos.2017.00752
44. Qazi EM, Sohn SI, Mishra S, Almekhlafi MA, Eesa M, d'Esterre CD, et al. Thrombus characteristics are related to collaterals and angioarchitecture in acute stroke. *Can J Neurol Sci.* (2015) 42:381–8. doi: 10.1017/cjn.2015.291
45. Hashimoto T, Hayakawa M, Funatsu N, Yamagami H, Satow T, Takahashi JC, et al. Histopathologic analysis of retrieved thrombi associated with successful reperfusion after acute stroke thrombectomy. *Stroke.* (2016) 47:3035–7. doi: 10.1161/STROKEAHA.116.015228
46. Choi MH, Park GH, Lee JS, Lee SE, Lee SJ, Kim JH, et al. Erythrocyte fraction within retrieved thrombi contributes to thrombolytic response in acute ischemic stroke. *Stroke.* (2018) 49:652–9. doi: 10.1161/STROKEAHA.117.019138
47. Alves HC, Treurniet KM, Dutra BG, Jansen IGH, Boers AMM, Santos EMM, et al. Associations between collateral status and thrombus characteristics and their impact in anterior circulation stroke. *Stroke.* (2018) 49:391–6. doi: 10.1161/STROKEAHA.117.019509
48. Gorog DA, Fayad ZA, Fuster V. Arterial thrombus stability: does it matter and can we detect it? *J Am Coll Cardiol.* (2017) 70:2036–47. doi: 10.1016/j.jacc.2017.08.065
49. Liebeskind DS, Cotsonis GA, Saver JL, Lynn MJ, Turan TN, Cloft HJ, et al. Collaterals dramatically alter stroke risk in intracranial atherosclerosis. *Ann Neurol.* (2011) 69:963–74. doi: 10.1002/ana.22354
50. Liebeskind DS, Tomsick TA, Foster LD, Yeatts SD, Carrozzella J, Demchuk AM, et al. Collaterals at angiography and outcomes in the Interventional Management of Stroke (IMS) III trial. *Stroke.* (2014) 45:759–64. doi: 10.1161/STROKEAHA.113.004072
51. Liebeskind DS, Jahan R, Nogueira RG, Zaidat OO, Saver JL, SWIFT Investigators. Impact of collaterals on successful revascularization in Solitaire FR with the intention for thrombectomy. *Stroke.* (2014) 45:2036–40. doi: 10.1161/STROKEAHA.114.004781
52. Berkhemer OA, Jansen IG, Beumer D, Fransen PS, van den Berg LA, Yoo AJ, et al. Collateral status on baseline computed tomographic angiography and intra-arterial treatment effect in patients with proximal anterior circulation stroke. *Stroke.* (2016) 47:768–76. doi: 10.1161/STROKEAHA.115.011788
53. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA.* (2016) 316:1279–88. doi: 10.1001/jama.2016.13647
54. Leng X, Fang H, Leung TW, Mao C, Miao Z, Liu L, et al. Impact of collaterals on the efficacy and safety of endovascular treatment in acute ischaemic stroke: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry.* (2016) 87:537–44. doi: 10.1136/jnnp-2015-310965
55. Copen WA, Rezai Gharai L, Barak ER, Schwamm LH, Wu O, Kamalian S, et al. Existence of the diffusion-perfusion mismatch within 24 hours after onset of acute stroke: dependence on proximal arterial occlusion. *Radiology.* (2009) 250:878–86. doi: 10.1148/radiol.2503080811
56. Kim SJ, Seok JM, Bang OY, Kim GM, Kim KH, Jeon P, et al. MR mismatch profiles in patients with intracranial atherosclerotic stroke: a comprehensive approach comparing stroke subtypes. *J Cereb Blood Flow Metab.* (2009) 29:1138–45. doi: 10.1038/jcbfm.2009.38
57. Ahn SH, Lee J, Kim YJ, Kwon SU, Lee D, Jung SC, et al. Isolated MCA disease in patients without significant atherosclerotic risk factors: a high-resolution magnetic resonance imaging study. *Stroke.* (2015) 46:697–703. doi: 10.1161/STROKEAHA.114.008181
58. Kim YJ, Lee JK, Ahn SH, Kim BJ, Kang DW, Kim JS, et al. Nonatheroscleotic isolated middle cerebral artery disease may be early manifestation of Moyamoya disease. *Stroke.* (2016) 47:2229–35. doi: 10.1161/STROKEAHA.116.012751
59. Park MS, Cha J, Chung JW, Seo WK, Kim GM, Bang OY. Arterial dissection as a cause of intracranial stenosis in East Asians. *J Am Coll Cardiol.* (2017) 70:2205–6. doi: 10.1016/j.jacc.2017.08.048
60. Natarajan SK, Karmon Y, Tawk RG, Hauck EF, Hopkins LN, Siddiqui AH, et al. Endovascular treatment of patients with intracranial stenosis with moyamoya-type collaterals. *J Neurointerv Surg.* (2011) 3:369–74. doi: 10.1136/jnis.2011.004754
61. Drazin D, Calayag M, Gifford E, Dalfino J, Yamamoto J, Boulos AS. Endovascular treatment for moyamoya disease in a Caucasian twin with angioplasty and Wingspan stent. *Clin Neurol Neurosurg.* (2009) 111:913–7. doi: 10.1016/j.clineuro.2009.08.012
62. Khan N, Dodd R, Marks MP, Bell-Stephens T, Vavao J, Steinberg GK. Failure of primary percutaneous angioplasty and stenting in the prevention of ischemia in Moyamoya angiopathy. *Cerebrovasc Dis.* (2011) 31:147–53. doi: 10.1159/000320253
63. Li S, Zi W, Chen J, Zhang S, Bai Y, Guo Y, et al. Feasibility of thrombectomy in treating acute ischemic stroke because of cervical artery dissection. *Stroke.* (2018) 49:3075–7. doi: 10.1161/STROKEAHA.118.023186
64. van der Kolk AG, Zwanenburg JJ, Brundel M, Biessels GJ, Visser F, Luijten PR, et al. Intracranial vessel wall imaging at 7.0-T MRI. *Stroke.* (2011) 42:2478–84. doi: 10.1161/STROKEAHA.111.620443
65. Harteveld AA, Denswil NP, Siero JC, Zwanenburg JJ, Vink A, Pouran B, et al. Quantitative intracranial atherosclerotic plaque characterization at 7T MRI: an *ex vivo* study with histologic validation. *AJNR Am J Neuroradiol.* (2016) 37:802–10. doi: 10.3174/ajnr.A4628
66. Seo WK, Oh K, Suh SI, Seol HY. Clinical significance of wall changes after recanalization therapy in acute stroke: high-resolution vessel wall imaging. *Stroke.* (2017) 48:1077–80. doi: 10.1161/STROKEAHA.116.015429
67. Renu A, Laredo C, Lopez-Rueda A, Llull L, Tudela R, San-Roman L, et al. Vessel wall enhancement and blood-cerebrospinal fluid barrier disruption after mechanical thrombectomy in acute ischemic stroke. *Stroke.* (2017) 48:651–7. doi: 10.1161/STROKEAHA.116.015648
68. Sanidas E, Dangas G. Evolution of intravascular assessment of coronary anatomy and physiology: from ultrasound imaging to optical and flow assessment. *Eur J Clin Invest.* (2013) 43:996–1008. doi: 10.1111/eci.12119

69. Parise H, Maehara A, Stone GW, Leon MB, Mintz GS. Meta-analysis of randomized studies comparing intravascular ultrasound versus angiographic guidance of percutaneous coronary intervention in pre-drug-eluting stent era. *Am J Cardiol.* (2011) 107:374–82. doi: 10.1016/j.amjcard.2010.09.030
70. Wehman JC, Holmes DR Jr, Hanel RA, Levy EI, Hopkins LN. Intravascular ultrasound for intracranial angioplasty and stent placement: technical case report. *Neurosurgery.* (2006) 59:ONSE481-3; discussion ONSE3. doi: 10.1227/01.NEU.0000222825.92929.0C
71. Majidi S, Sein J, Watanabe M, Hassan AE, Van de Moortele PF, Suri MF, et al. Intracranial-derived atherosclerosis assessment: an *in vitro* comparison between virtual histology by intravascular ultrasonography, 7T MRI, and histopathologic findings. *AJNR Am J Neuroradiol.* (2013) 34:2259–64. doi: 10.3174/ajnr.A3631
72. Mokin M, Levy EI, Siddiqui AH, Goyal M, Nogueira RG, Yavagal DR, et al. Association of clot burden score with radiographic and clinical outcomes following Solitaire stent retriever thrombectomy: analysis of the SWIFT PRIME trial. *J Neurointerv Surg.* (2017) 9:929–32. doi: 10.1136/neurintsurg-2016-012631
73. Treurniet KM, Yoo AJ, Berkhemer OA, Lingsma HF, Boers AM, Fransen PS, et al. Clot burden score on baseline computerized tomographic angiography and intra-arterial treatment effect in acute ischemic stroke. *Stroke.* (2016) 47:2972–8. doi: 10.1161/STROKEAHA.116.014565
74. Berndt M, Friedrich B, Maegerlein C, Moench S, Hedderich D, Lehm M, et al. Thrombus permeability in admission computed tomographic imaging indicates stroke pathogenesis based on thrombus histology. *Stroke.* (2018) 49:2674–82. doi: 10.1161/STROKEAHA.118.021873
75. Brinjikji W, Duffy S, Burrows A, Hacke W, Liebeskind D, Majoie CB, et al. Correlation of imaging and histopathology of thrombi in acute ischemic stroke with etiology and outcome: a systematic review. *J Neurointerv Surg.* (2016) doi: 10.1136/neurintsurg-2016-012589.53
76. Kang DW, Jeong HG, Kim DY, Yang W, Lee SH. Prediction of stroke subtype and recanalization using susceptibility vessel sign on susceptibility-weighted magnetic resonance imaging. *Stroke.* (2017) 48:1554–9. doi: 10.1161/STROKEAHA.116.016217
77. Zhang R, Zhou Y, Liu C, Zhang M, Yan S, Liebeskind DS, et al. Overestimation of susceptibility vessel sign: a predictive marker of stroke cause. *Stroke.* (2017) 48:1993–6. doi: 10.1161/STROKEAHA.117.016727
78. Liebeskind DS, Sanossian N, Yong WH, Starkman S, Tsang MP, Moya AL, et al. CT and MRI early vessel signs reflect clot composition in acute stroke. *Stroke.* (2011) 42:1237–43. doi: 10.1161/STROKEAHA.110.605576
79. Shin JW, Jeong HS, Kwon HJ, Song KS, Kim J. High red blood cell composition in clots is associated with successful recanalization during intra-arterial thrombectomy. *PLoS ONE.* (2018) 13:e0197492. doi: 10.1371/journal.pone.0197492
80. Kim DE, Kim JY, Sun IC, Schellingerhout D, Lee SK, Ahn CH, et al. Hyperacute direct thrombus imaging using computed tomography and gold nanoparticles. *Ann Neurol.* (2013) 73:617–25. doi: 10.1002/ana.23849
81. Botnar RM, Perez AS, Witte S, Wiethoff AJ, Laredo J, Hamilton J, et al. *In vivo* molecular imaging of acute and subacute thrombosis using a fibrin-binding magnetic resonance imaging contrast agent. *Circulation.* (2004) 109:2023–9. doi: 10.1161/01.CIR.0000127034.50006.C0
82. Sirol M, Fuster V, Badimon JJ, Fallon JT, Moreno PR, Toussaint JF, et al. Chronic thrombus detection with *in vivo* magnetic resonance imaging and a fibrin-targeted contrast agent. *Circulation.* (2005) 112:1594–600. doi: 10.1161/CIRCULATIONAHA.104.522110
83. Uppal R, Ay I, Dai G, Kim YR, Sorensen AG, Caravan P. Molecular MRI of intracranial thrombus in a rat ischemic stroke model. *Stroke.* (2010) 41:1271–7. doi: 10.1161/STROKEAHA.109.575662
84. Zaidat OO, Yoo AJ, Khatri P, Tomsick TA, von Kummer R, Saver JL, et al. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. *Stroke.* (2013) 44:2650–63. doi: 10.1161/STROKEAHA.113.001972
85. Menon BK, d'Esterre CD, Qazi EM, Almekhlafi M, Hahn L, Demchuk AM, et al. Multiphase CT angiography: a new tool for the imaging triage of patients with acute ischemic stroke. *Radiology.* (2015) 275:510–20. doi: 10.1148/radiol.15142256
86. Campbell BC, Christensen S, Tress BM, Churilov L, Desmond PM, Parsons MW, et al. Failure of collateral blood flow is associated with infarct growth in ischemic stroke. *J Cereb Blood Flow Metab.* (2013) 33:1168–72. doi: 10.1038/jcbfm.2013.77
87. Kim SJ, Son JP, Ryoo S, Lee MJ, Cha J, Kim KH, et al. A novel magnetic resonance imaging approach to collateral flow imaging in ischemic stroke. *Ann Neurol.* (2014) 76:356–69. doi: 10.1002/ana.24211
88. Lee KH, Cho SJ, Byun HS, Na DG, Choi NC, Lee SJ, et al. Triphasic perfusion computed tomography in acute middle cerebral artery stroke: a correlation with angiographic findings. *Arch Neurol.* (2000) 57:990–9. doi: 10.1001/archneur.57.7.990
89. Maier IL, Scalzo F, Leyhe JR, Schregel K, Behme D, Tsogkas I, et al. Validation of collateral scoring on flat-detector multiphase CT angiography in patients with acute ischemic stroke. *PLoS ONE.* (2018) 13:e0202592. doi: 10.1371/journal.pone.0202592
90. Shuaib A, Butcher K, Mohammad AA, Saqqur M, Liebeskind DS. Collateral blood vessels in acute ischaemic stroke: a potential therapeutic target. *Lancet Neurol.* (2011) 10:909–21. doi: 10.1016/S1474-4422(11)70195-8
91. van den Wijngaard IR, Holswilder G, Wermer MJ, Boiten J, Algra A, Dippel DW, et al. Assessment of collateral status by dynamic CT angiography in acute MCA stroke: timing of acquisition and relationship with final infarct volume. *AJNR Am J Neuroradiol.* (2016) 37:1231–6. doi: 10.3174/ajnr.A4746
92. Yeo LL, Paliwal P, Teoh HL, Seet RC, Chan BP, Ting E, et al. Assessment of intracranial collaterals on CT angiography in anterior circulation acute ischemic stroke. *AJNR Am J Neuroradiol.* (2015) 36:289–94. doi: 10.3174/ajnr.A4117
93. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American heart association/American stroke association. *Stroke.* (2018) 49:e46–110. doi: 10.1161/STR.0000000000000158
94. Kim BM. Causes and solutions of endovascular treatment failure. *J Stroke.* (2017) 19:131–42. doi: 10.5853/jos.2017.00283
95. Nakahara T, Sakamoto S, Hamasaki O, Sakoda K. Double wire technique for intracranial stent navigation. *J Vasc Interv Radiol.* (2003) 14:667–8. doi: 10.1097/01.RVI.0000071092.76348.2E
96. Lee TH, Choi CH, Park KP, Sung SM, Lee SW, Lee BH, et al. Techniques for intracranial stent navigation in patients with tortuous vessels. *AJNR Am J Neuroradiol.* (2005) 26:1375–80.
97. Kim YW, Son S, Kang DH, Hwang YH, Kim YS. Endovascular thrombectomy for M2 occlusions: comparison between forced arterial suction thrombectomy and stent retriever thrombectomy. *J Neurointerv Surg.* (2017) 9:626–30. doi: 10.1136/neurintsurg-2016-012466
98. Lapergue B, Blanc R, Gory B, Labreuche J, Duhamel A, Marnat G, et al. Effect of endovascular contact aspiration vs stent retriever on revascularization in patients with acute ischemic stroke and large vessel occlusion: the ASTER randomized clinical trial. *JAMA.* (2017) 318:443–52. doi: 10.1001/jama.2017.9644
99. Lee JS, Hong JM, Lee SJ, Joo IS, Lim YC, Kim SY. The combined use of mechanical thrombectomy devices is feasible for treating acute carotid terminus occlusion. *Acta Neurochir.* (2013) 155:635–41. doi: 10.1007/s00701-013-1649-5
100. Humphries W, Hoit D, Doss VT, Elijovich L, Frei D, Loy D, et al. Distal aspiration with retrievable stent assisted thrombectomy for the treatment of acute ischemic stroke. *J Neurointerv Surg.* (2015) 7:90–4. doi: 10.1136/neurintsurg-2013-010986

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REVIEW
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Endovascular Treatment of Acute Stroke Due to Intracranial Atherosclerotic Stenosis–Related Large Vessel Occlusion

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Endovascular treatment (EVT) has become a standard treatment for acute ischemic stroke due to large vessel occlusion (LVO) in the anterior circulation. However, whether EVT tools used for intracranial atherosclerotic stenosis (ICAS)-related LVO are as safe and effective as for use in embolic LVO remains unclear. There have been only a few studies about EVT for ICAS-related LVO, and these studies revealed that mechanical thrombectomy with a stent retriever or contact aspiration was less effective and more time consuming in ICAS-related LVO than in embolic LVO. Because fast and successful recanalization (defined as modified Thrombolysis in Cerebral Ischemia grade, 2b or 3) is the most critical factor influencing favorable outcomes, it is important to determine the appropriate EVT strategy for fast recanalization of ICAS-related LVO. In this report, we review the results of mechanical thrombectomy using stent retriever or contact aspiration and rescue treatments after failure of mechanical thrombectomy for ICAS-related LVO. Finally, we propose the EVT strategy appropriate for ICAS-related LVO based on a literature review and our experience.

Keywords: acute stroke, large vessel occlusion, intracranial atherosclerosis, endovascular treatment, stenosis and cerebrovascular occlusion

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INTRODUCTION

Endovascular treatment (EVT) for acute stroke due to emergent large vessel occlusion (LVO) has been successful, and EVT has become a standard treatment for LVO (1). The rate of recanalization, defined as modified Thrombolysis In Cerebral Ischemia (mTICI) grade 2b or 3, has been improving since the first 5 successful EVT trials, which demonstrated that higher recanalization rates are associated with better clinical outcomes (2–5). For mechanical thrombectomy, the two mainstay modalities are stent retriever (SR) and contact aspiration (CA) thrombectomies. Both methods were primarily invented for removal of the embolic clots occluding the large vessel. The pathomechanism of intracranial atherosclerosis (ICAS)-related LVO is likely due to *in-situ* thromboocclusion rather than embolic occlusion (6–8). The efficacy of both methods for recanalization of *in-situ* thromboocclusion in ICAS-related LVO has not been well elucidated. ICAS is one of the main causes of acute stroke in Asian, Hispanic, and African populations (9–11) and furthermore recent studies have documented that ICAS-related LVO is responsible for

approximately 12–30% of all causes of LVO in East Asia (7, 8, 12–16). Therefore, it is worthwhile to investigate the efficacy of SR or CA thrombectomy and the most appropriate EVT strategy for ICAS-related LVO. This review aims to investigate on what are the problems in EVT and to find out the appropriate treatment strategy for ICAS-related LVO.

OUTCOMES OF ENDOVASCULAR TREATMENT FOR ICAS-RELATED LVO

Until recently, there have been only a few retrospective studies in which the clinical outcomes of EVT for ICAS-related LVO have been evaluated, and the results were inconsistent. In a study, patients with ICAS-related LVO had more favorable outcomes than patients with embolic LVO (15). In contrast, other researchers showed less favorable outcomes or no significant difference between the two groups (8, 14, 16–18). Notably, the rate of favorable outcomes was proportionate to the recanalization success rate. Successful recanalization and favorable outcome rates were observed more frequently in patients with ICAS-related LVO in a few reports, but the opposite was observed in a different study. In another study with similar recanalization rates, clinical outcomes were similar between the two groups (**Table 1**).

In a recent study, ICAS-related LVO was a worse prognostic factor in multivariate analysis although recanalization rates were similar between embolic and ICAS-related LVO groups. A significant interaction of underlying etiology (ICAS verse embolic) on patient outcome was observed with procedure (puncture-o-recanalization) time. Therefore, they suggested that "the relatively poor outcome in the ICAS-related LVO is mainly attributable to longer procedure time, reflecting the procedure complexity and the higher rate of reocclusion" (19).

From the results of the previous studies, we can infer that recanalization status and procedural time (puncture-to-recanalization time) are more relevant factors affecting patient outcomes than occlusion etiology itself (ICAS vs. embolic). In other words, if successful recanalization in the ICAS-related LVO was achieved as fast and with high rate as in the embolic LVO, functional outcome of ICAS-related LVO would be comparable to that of embolic LVO.

ENDOVASCULAR TREATMENT FOR ICAS-RELATED LVO

Stent Retriever Thrombectomy for ICAS-Related Large Vessel Occlusion

SR thrombectomy is recommended as the first-line EVT modality for acute stroke due to anterior circulation LVO (1). SR thrombectomy for obtaining initial recanalization appeared to be as effective in ICAS-related LVO as in embolic LVO (6, 7, 12–16, 19). However, reocclusion during EVT is very frequent after an initial recanalization with SR thrombectomy in ICAS-related LVO, with reported ranges from 57.1 to 77.3% (6, 7, 12–16). For SR thrombectomy, a microwire should be passed through the occlusion site followed by a microcatheter with an inner diameter $\geq$0.021-inch. Although physicians may be concerned that passage of a microwire followed by a microcatheter is potentially dangerous, the initial SR attempt was successful in most ICAS-related LVO cases, and has not been reported to be difficult (6, 7, 13–15). However, once reocclusion occurs, repeated SR thrombectomy attempt seemed to be ineffective and prone to procedural complications because it may cause vessel injury, resulting in repeat reocclusion, spasm, and dissection (6, 7, 13–16, 20, 22, 23).

Although it has not yet been well known why reocclusion is so frequent in ICAS-related LVO, it can be explained by its pathomechanism and thrombectomy procedure itself. The pathomechanism of ICAS-related LVO, similar to that of coronary artery disease, is likely *in-situ* thromboocclusion due to unstable plaque rupture (6–8). An acute *in-situ* clot formed on an ICAS plaque is platelet-rich one (22). Repeat passages of a microwire, a microcatheter and SR may further damage the inflamed plaque and thus provoke more platelet activation and even arterial dissection (**Figure 1**) (6, 7, 21). Therefore, repeat attempts of SR thrombectomy should be avoided so far as possible once reocclusion has occurred in ICAS-related LVO (6, 7, 13, 14).

Contact Aspiration Thrombectomy for ICAS-Related Large Vessel Occlusion

Although first-line CA thrombectomy is as effective as SR thrombectomy in embolic LVO, it seemed less effective for recanalization of ICAS-related LVO. In a study that compared the efficacy of SR vs. CA thrombectomy in 146 ICAS-related LVO, the rate of switching to alternative thrombectomy technique (SR to CA thrombectomy or vice versa) after the frontline modality failed was significantly higher in the CA group (40%) than in the SR group (4.7%, $p < 0.001$) (21). Theoretically, a successful CA thrombectomy requires firm engagement of a large-bore catheter distal tip with the occluding clot. In ICAS-related LVO, the parent artery is likely to be tortuous in form and tapered to the occlusion site.

Therefore, the distal tip of a large-bore catheter is likely to less firmly engage the occluding clot in ICAS-related LVO than the embolic clot in a normal parent artery (**Figure 1**). Furthermore, the reocclusion rate of CA thrombectomy was similar to that of SR thrombectomy (8). In CA thrombectomy, a microcatheter and a microwire were navigated through the occlusion site and then a large-bore catheter is advanced over the wire and microcatheter to the occluding clot. Thus, the preceding passage of a microwire and a microcatheter may also irritate the inflamed plaque and eventually provoke more platelet activation in ICAS-related LVO.

Rescue Treatments

As in the embolic LVO, fast and successful recanalization is the most important factor for achieving good outcomes in ICAS-related LVO. Therefore, if the primary thrombectomy failed to achieve recanalization, rescue treatments should be performed as soon as possible. Rescue treatments after failure of frontline thrombectomy for LVO include switching to another tool (SR to CA thrombectomy or vice versa), simultaneous use of both SR and CA thrombectomies, intraarterial thrombolytic infusion,

TABLE 1 | Comparison of outcomes between intracranial atherosclerotic stenosis-related and embolic large vessel occlusion.

References	Group	Recanalization	mRS, 0–2	Symptomatic ICH	Mortality
Kang et al. (8)	ICAS-related	80.0%	65.0%	2.5%	NA
	Embolic	83.7%	67.5%	5.4%	NA
Lee et al. (16)	ICAS-related	62.5%	41.7%	NA	8.3%
	Embolic	63.6%	31.3%	NA	24.6%
Jia et al. (18)	ICAS-related	95.7%	63.8%	4.3%	12.8%
	Embolic	96.8%	51.6%	4.3%	12.9%
Al Kasab et al. (17)	ICAS-related	*64.7%	*42.4%	11.1%	39.4%
	Embolic	*95.3%	*55.8%	9.8%	20.7%
Yoon et al. (15)	ICAS-related	*95.0%	*62.5%	7.5%	15.0%
	Embolic	*81.8%	*38.6%	3.0%	9.1%
Baek et al. (14)	ICAS-related	80.4%	46.4%	5.4%	19.6%
	Embolic	88.5%	46.9%	5.0%	15.3%
Lee et al. (19)	ICAS-related	76.8%	45.5%	7.1	NA
	Embolic	79.6%	54.5%	10.7	NA

*ICAS, intracranial atherosclerotic stenosis; mRS, modified Rankin Scale score; ICH, intracranial hemorrhage; *, statistically significant.*

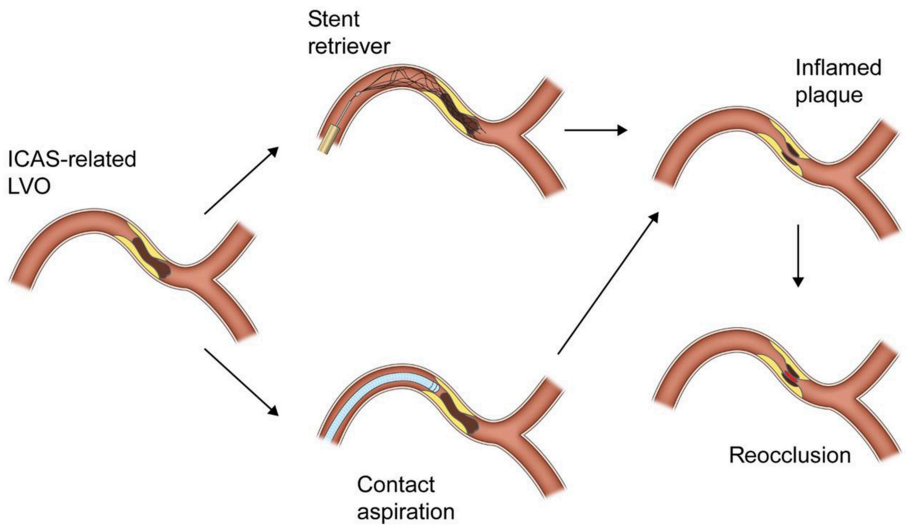

FIGURE 1 | A schematic drawing of reocclusion mechanism after stent retriever or contact aspiration thrombectomy for intracranial atherosclerotic stenosis-related large vessel occlusion.

intraarterial, or intravenous glycoprotein IIb/IIIa inhibitor (GPI) infusion and stenting with or without balloon angioplasty (6–8, 13–15, 18, 23–26). Because reocclusion in ICAS-related LVO is very frequent and most likely due to platelet activation, a severe degree of residual stenosis, or combined contribution of both, rescue treatment should be focused on platelet inhibition and alleviating the degree of residual stenosis. GPI has been suggested for platelet inhibition in the several previous reports. Intraarterial or intravenous infusion of low dose of GPI (Tirofiban, 0.5–1.5 mg or Reopro, 3–10 mg) was effective for resolution or prevention of re-occlusion of ICAS-related LVO (7, 8, 14) (**Figure 2**). GPI could make the endothelium more stable, which could reverse the *in-situ* thrombotic reocclusion tendency (6, 7, 14, 22). In our center, intra-procedural administration method of GPI is typically as follows; angiogram is obtained every 10 min at least 2 times after administration of 0.3–0.5 mg of Tirofiban (or Reopro, 3–5 mg). If reocclusion (tendency) is not resolved, additional 0.3–0.5 mg of Tirofiban (or Reopro, 3–5 mg) is administered up to 1.5 mg (or Reopro, 10 mg) until reocclusion (tendency) is resolved (or improved antegrade flow velocity) on angiogram obtained every 10 min. The dose of GPI did not depend on whether or not to use intravenous tPA administration.

Rescue stenting and/or angioplasty is an another (or additional) option for resolving reocclusion. As well known, a severe degree of focal stenosis is an important factor that provokes clot formation. Therefore, by alleviating the underlying severe degree of stenosis, rescue stenting and/or balloon angioplasty is likely to play a role in preventing reocclusion or in recanalization for such cases that are never opened with mechanical thrombectomy (24, 25) (**Figure 3**).

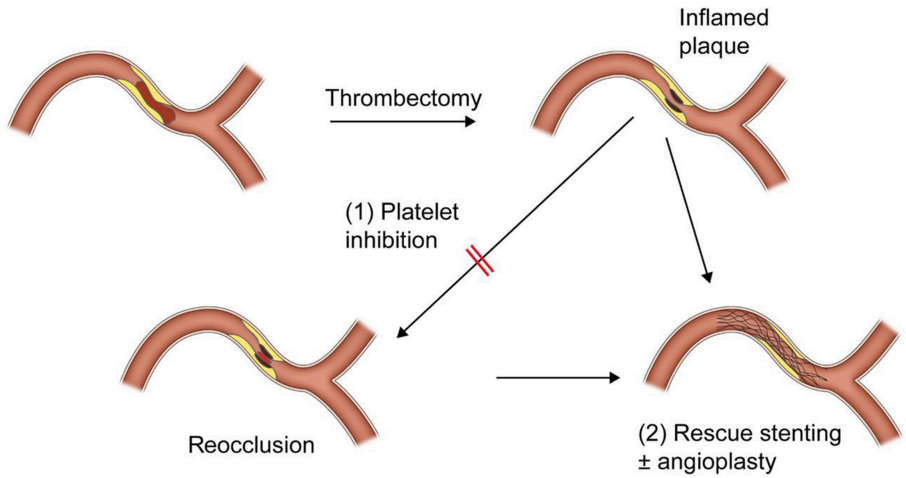

FIGURE 2 | A schematic drawing of rescue treatment for reocclusion after initial recanalization of intracranial atherosclerotic stenosis-related large vessel occlusion.

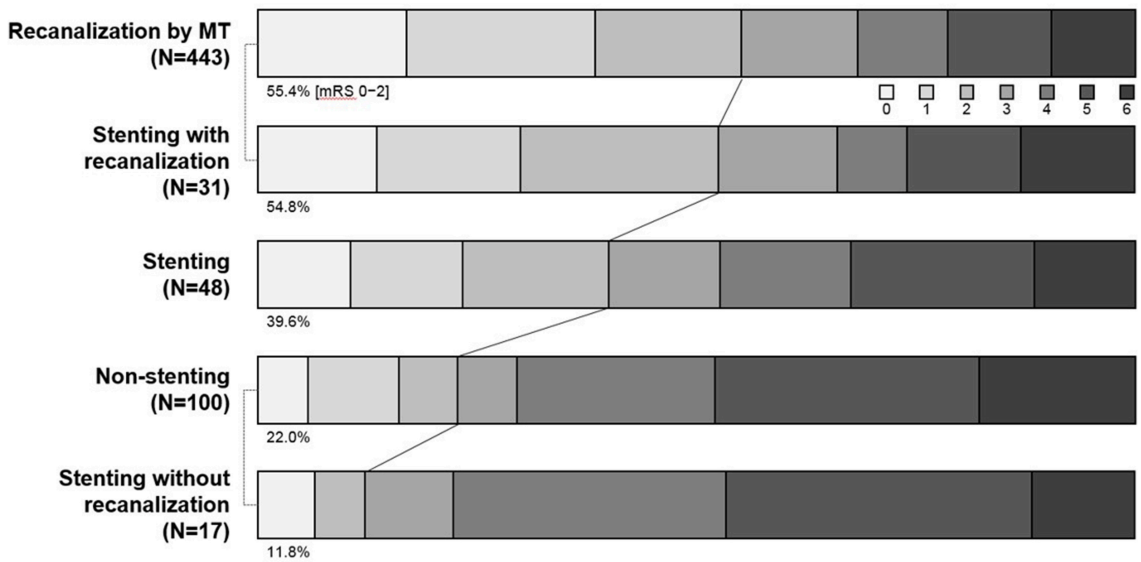

FIGURE 3 | Comparison of modified Rankin scale score among mechanical thrombectomy success, rescue stenting, and non-stenting groups. MT, mechanical thrombectomy.

In literature, it seemed to depend on operators' preference whether to do stent alone, stent with pre- or post-stent balloon angioplasty, or balloon angioplasty alone (6, 17–19, 24, 25). It also depended on operators' preference to use what kind of stent. However, self-expanding stent seemed to be favored rather than balloon-expandable stent. In addition, of the self-expanding stent, Solitaire-FR stent rather than Wingspan stent seemed to be favored for rescue stenting. It is likely because Wingspan stent requires additional preparation time and more technical demands for delivery, whereas it seems simple to detach a Solitaire-FR that was already in using for thrombectomy (6, 24, 25).

Recent two studies compared patients who received rescue stenting with those who was left without further treatment after mechanical thrombectomy failure. Rescue stenting group showed better functional outcome than non-stenting group (24, 25). Patients with recanalization success showed a similar distribution of mRS at 3 months, regardless of recanalization methods (mechanical thrombectomy or rescue stenting) (**Figure 3**). In those studies, the majority of patients with rescue stenting had ICAS-related LVO. Therefore, rescue stenting may be a rescue method in ICAS-related LVO. Another recent study also have demonstrated that both GPI and rescue stenting are similarly effective and safe in ICAS-related LVO (23).

Postprocedural delayed reocclusion also worsen patients' functional outcome (25, 26). Timing and maintenance of postprocedural antiplatelet medication is important to prevent postprocedural reocclusion. Although there has not been controlled study, intravenous infusion of GPI with maintenance dose for a 6–12 h after completion of EVT and then change

to oral antiplatelet medication has been proposed (14). The degree of residual stenosis may be an another factor for post-procedural reocclusion. It has not yet been studied whether rescue stenting and/or angioplasty is needed to prevent postprocedural delayed reocclusion. However, if the degree of stenosis is very severe, alleviating the stenosis by rescue stenting and/or angioplasty may be helpful in both instant and delayed reocclusion. It should be addressed if rescue stenting and/or angioplasty is helpful for preventing postprocedural delayed reocclusion.

It has yet remained unclear whether stenting combined with anti-thrombotic drug is safe in acute stroke setting. In recent reports, however, intracranial or cervical carotid artery stenting with use of antithrombotic medication in acute stroke setting did not increase the development of symptomatic intracranial hemorrhage, while significantly improved functional outcome (24, 25, 27). Because of retrospective nature of these studies, the type and mode of antithrombotic medication combined with stenting varied depending on centers; (1) intra-arterial or intravenous loading of GPI followed by maintenance of 6–12 h, then changed to oral dual antiplatelets, (2) loading dose of oral dual antiplatelets just before or after rescue stenting (aspirin 85–500 mg and clopidogrel 300 mg), (3) oral mono antiplatelet (clopidogrel, 75–300 mg), and (4) no antiplatelet medication until follow-up CT or MR on the next day (24, 27). When GPI and rescue stenting which requires antithrombotic medication is applied in acute stroke setting, the most feared concern is possibly increased risk of intracranial hemorrhage. In recent multicenter studies, however, intracranial or cervical carotid stenting combined with use of antithromboics drugs in acute stroke setting did not increase the development of symptomatic intracranial hemorrhage whereas significantly improved functional outcome (24, 25, 27). In our experience, it seems very helpful in decision making to obtain flat-panel CT before GPI infusion and/or rescue stenting. Although a specific criterion of unfavorable candidate for GPI and/or rescue stenting has not yet been recommended, we have not done further treatment for cases that have large area of contrast material enhancement on flat-panel CT. In this strategy, the rate of symptomatic intracranial hemorrhage was not higher in patients with GPI and/or rescue stenting than in patients without (7, 14, 24, 25).

ENDOVASCULAR STRATEGY APPROPRIATE FOR ICAS-RELATED LVO

Recanalization status and procedural time are more relevant factors affecting patient outcomes than occlusion etiology. For faster and more successful recanalization, identifying underlying ICAS as the cause of LVO and setting an optimal strategy for ICAS-related LVO are key factors leading to better clinical outcomes in ICAS-related LVO patients. Before starting EVT, the following markers may suggest ICAS-related LVO from embolic LVO: (1) the absence of atrial fibrillation on echocardiogram and (2) absence of hyperdense artery sign on CT or susceptibility (blooming) artifact sign on MR gradient echo image, and (3) truncal-type occlusion on CTA. During the EVT, (1) a truncal-type occlusion and (2) a remnant (fixed focal) stenosis after initial recanalization at the occlusion site are suggested as useful surrogate markers of ICAS-related LVO (**Table 2**). It is critical to determine when to introduce what kind of rescue treatment after failure of mechanical thrombectomy in ICAS-related LVO. Procedural time in the ICAS-related LVO was consistently longer than in the embolic group across the all previous studies (7, 8, 12–16, 20, 21), and this can be explained by repeat SR or CA thrombectomy attempts before applying the appropriate rescue treatment for ICAS-related LVO (7, 12, 14, 19). If the appropriate EVT strategy for ICAS-related LVO can be set early (before starting EVT, if possible), operators can shorten the puncture–to-recanalization (procedural) time as well as increase recanalization rate, thus providing a better clinical outcome (6, 7, 14, 19). Rescue stenting and/or balloon angioplasty, intra-arterial or intravenous GPI infusion, or combination of those have been reported as appropriate treatments for ICAS thrombo-occlusion (7, 8, 14, 15, 18, 23, 23–25). The stepwise approach in using such modalities in addition to mechanical thrombectomy is likely helpful in faster and more successful recanalization of ICAS-related LVO.

From practical point of view, a microcatheter with inner diameter 0.021-inch may be less difficult in delivery to the target lesion of ICAS-related LVO than a large-bore aspiration catheter because the relevant parent artery is likely more tortuous in ICAS-related LVO than in embolic LVO. Furthermore, SR

TABLE 2 | Surrogate markers suggested of intracranial atherosclerosis-related large vessel occlusion.

	Surrogate markers	ICAS-related	Embolic
Before starting EVT	Atrial fibrillation, 2017 (13)	+*	+++
	Susceptibility artifact on MR gradient echo image, 2015 (28)	+	+++
	Hyperdense artery sign on NECT, 2017 (29)	+	++
	Truncal-type occlusion on CT angiography, 2017 (13), 2016 (14)	+++	+
During the EVT	Truncal-type occlusion, 2016 (7), 2017 (13), 2016 (14)	++++	+
	Residual stenosis, 2014 (8), 2015 (16), 2018 (23)	++++	+

EVT, endovascular treatment; ICAS, intracranial atherosclerotic stenosis; MR, magnetic resonance; NECT, non-enhanced computed tomography; CT, computed tomography.
** The number of + sign indicates to have more probability to have ICAS-related or embolic surrogate markers.*

TABLE 3 | Comparison between stent retriever and contact aspiration thrombectomy in practice.

	Stent retriever	Contact aspiration
Delivery to the target lesion	Not difficult	Occasionally difficult
Help in differentiation in ICAS-related from embolic LVO during the procedure (7, 13)*	Yes	No
First-pass recanalization success (23)	Higher	Lower

**, by disclosing occlusion type (truncal-type or branching-site occlusion). Truncal-type is suggestive of intracranial atherosclerosis related large vessel occlusion.*

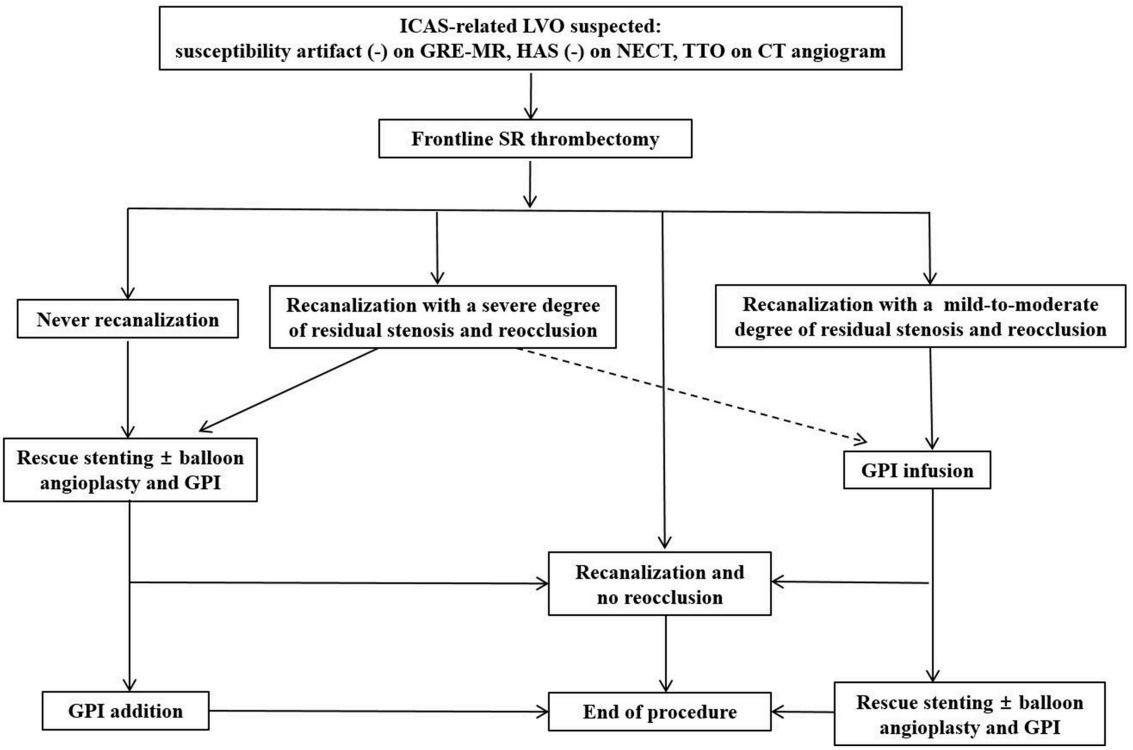

FIGURE 4 | The stepwise endovascular strategy appropriate for intracranial atherosclerotic stenosis-related large vessel occlusion. ICAS, intracranial atherosclerotic stenosis; LVO, large vessel occlusion; GRE-MR, gradient echo magnetic resonance imaging; HAS, hyperdense artery sign; NECT, non-enhanced computed tomography; TTO, truncal type occlusion; CT, computed tomography; SR, stent retriever; GPI, glycoprotein IIb/IIIa inhibitor.

is better to detect ICAS-related LVO by showing occlusion type (truncal or branching-site) as well as to obtain first-pass recanalization (**Table 3**). Therefore, SR thrombectomy is recommended as frontline modality if ICAS-related LVO is suspected. After achieving initial recanalization, a follow-up angiogram should be obtained every 10 min at least up to 30 min for detecting reocclusion (tendency). If reocclusion occurs with mild-to-moderate degree of residual stenosis after initial recanalization, GPI should be first recommended for avoiding acute stenting so far as possible. Whereas, if recanalization is never obtained or if reocclusion appears due to a severe degree of residual stenosis, rescue stenting and/or balloon angioplasty may be considered (**Figure 4**).

Although there has been no well-controlled study yet, rescue stenting and/or GPI use may be recommended as a rescue endovascular strategy appropriate for ICAS-LVO with never recanalization or repeat reocclusion. A prospective study is needed to find most appropriate endovascular strategy for ICAS-related LVO.

CONCLUSIONS

Recanalization success and puncture-to-recanalization (procedure) time are two important procedural prognostic factors in ICAS-related LVO. With similar recanalization rate and procedure time, clinical outcome of ICAS-related LVO would be comparable to that of embolic LVO. For obtaining successful recanalization in ICAS-related LVO as fast and with high rate as in embolic LVO, the specific EVT strategy appropriate for ICAS is needed.

AUTHOR CONTRIBUTIONS

BK established the study idea, designed the manuscript structure, acquired and analyzed the data, and wrote the manuscript. J-HB and HP established the study idea, designed the manuscript structure, and made critical revisions to the manuscript with substantive intellectual content.

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REFERENCES

1. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. (2018) 49:e46–110. doi: 10.1161/STR.0000000000000158
2. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischemic stroke: a meta-analysis of individual patient data from five randomized trials. *Lancet*. (2016) 387:1723–31. doi: 10.1016/S0140-6736(16)00163-X
3. Lapergue B, Blanc R, Gory B, Labreuche J, Duhamel A, Marnat G, et al. Effect of endovascular contact aspiration vs stent retriever on revascularization in patients with acute ischemic stroke and large vessel occlusion: the ASTER randomized clinical trial. *JAMA*. (2017) 318:443–52. doi: 10.1001/jama.2017.9644
4. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. (2018) 378:11–21. doi: 10.1056/NEJMoa1706442
5. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. (2018) 22:708–18. doi: 10.1056/NEJMoa1713973
6. Kim BM. Causes and solutions of endovascular treatment failure. *J Stroke*. (2017) 19:131–42. doi: 10.5853/jos.2017.00283
7. Baek JH, Kim BM, Kim DJ, Heo JH, Nam HS, Song D, et al. Importance of truncal-type occlusion in stentriever-based thrombectomy for acute stroke. *Neurology*. (2016) 87:1542–50. doi: 10.1212/WNL.0000000000003202
8. Kang DH, Kim YW, Hwang YH, Park SP, Kim YS, Baik SK. Instant reocclusion following mechanical thrombectomy of in situ thromboocclusion and the role of low-dose intra-arterial tirofiban. *Cerebrovasc Dis*. (2014) 37:350–5. doi: 10.1159/000362435
9. Wong LK. Global burden of intracranial atherosclerosis. *Int J Stroke*. (2006) 1:158–9. doi: 10.1111/j.1747-4949.2006.00045.x
10. Bang OY. Intracranial atherosclerosis: current understanding and perspectives. *J Stroke*. (2014) 16:27–35. doi: 10.5853/jos.2014.16.1.27
11. Toyoda K, Koga M, Hayakawa M, Yamagami H. Acute reperfusion therapy and stroke care in Asia after successful endovascular trials. *Stroke*. (2015) 46:1474–81. doi: 10.1161/STROKEAHA.115.008781
12. Lee JS, Hong JM, Lee KS, Suh HI, Choi JW, Kim SY. Primary stent retrieval for acute intracranial large artery occlusion due to atherosclerotic disease. *J Stroke*. (2016) 18:96–101. doi: 10.5853/jos.2015.01347
13. Baek JH, Kim BM, Yoo J, Nam HS, Kim YD, Kim DJ, et al. Predictive value of computed tomography angiography-determined occlusion type in stent retriever thrombectomy. *Stroke*. (2017) 48:2746–52. doi: 10.1161/STROKEAHA.117.018096
14. Baek J-H, Kim BM, Heo JH, Kim DJ, Nam HS, Kim YD. Outcomes of endovascular treatment for acute intracranial atherosclerosis-related large vessel occlusion. *Stroke*. (2018) 49:2699–705. doi: 10.1161/STROKEAHA.118.022327
15. Yoon W, Kim SK, Park MS, Kim BC, Kang HK. Endovascular treatment and the outcomes of atherosclerotic intracranial stenosis in patients with hyperacute stroke. *Neurosurgery*. (2015) 76:680–6. doi: 10.1227/NEU.0000000000000694
16. Lee JS, Hong JM, Lee KS, Suh HI, Demchuk AM, Hwang YH, et al. Endovascular therapy of cerebral arterial occlusions: intracranial atherosclerosis versus embolism. *J Stroke Cerebrovasc Dis*. (2015) 24:2074–80. doi: 10.1016/j.jstrokecerebrovasdis.2015.05.003
17. Al Kasab S, Almadidy Z, Spiotta AM, Turk AS, Chaudry MI, Hungerford JP, et al. Endovascular treatment for AIS with underlying ICAD. *J Neurointerv Surg*. (2017) 9:948–51. doi: 10.1136/neurintsurg-2016-012529
18. Jia B, Feng L, Liebeskind DS, Huo X, Gao F, Ma N, et al. Mechanical thrombectomy and rescue therapy for intracranial large artery occlusion with underlying atherosclerosis. *J Neurointerv Surg*. (2018) 10:746–50. doi: 10.1136/neurintsurg-2017-013489
19. Lee JS, Lee S-J, Yoo JS, Hong J-H, Kim C-H, Kim Y-W, et al. Prognosis of acute intracranial atherosclerosis-related occlusion after endovascular treatment. *J Stroke*. (2018) 20:394–403. doi: 10.5853/jos.2018.01627
20. Matias-Guiu JA, Serna-Candel C, Matias-Guiu J. Stroke etiology determines effectiveness of retrievable stents. *J Neurointerv Surg*. (2014) 6:e11. doi: 10.1136/neurintsurg-2012-010395
21. Gascou G, Lobotesis K, Machi P, , Maldonado I, Vendrell JF, Riquelme C, et al. Stent retrievers in acute ischemic stroke: complications and failures during the perioperative period. *AJNR Am J Neuroradiol*. (2014) 35:734–40. doi: 10.3174/ajnr.A3746
22. Libby P. Inflammation in atherosclerosis. *Nature*. (2002) 420:868–74. doi: 10.1038/nature01323
23. Kang DH, Yoon W, Kim SK, Baek BH, Lee YY, Kim YW, et al. Endovascular treatment for emergent large vessel occlusion due to severe intracranial atherosclerotic stenosis. *J Neurosurg*. (2018) 1:1–8. doi: 10.3171/2018.1.JNS172350
24. Baek JH, Kim BM, Kim DJ, Heo JH, Nam HS, Yoo J. Stenting as a rescue treatment after failure of mechanical thrombectomy for anterior circulation large artery occlusion. *Stroke*. (2016) 47:2360–3. doi: 10.1161/STROKEAHA.116.014073
25. Chang Y, Kim BM, Bang OY, Baek JH, Heo JH, Nam HS, et al. Rescue stenting for failed mechanical thrombectomy in acute ischemic stroke: a multicenter experience. *Stroke*. (2018) 49:958–64. doi: 10.1161/STROKEAHA.117.020072
26. Hwang Y-H, Kim Y-W, Kang D-H, Kim Y-S, Liebeskind DS. Impact of target residual stenosis on outcome after endovascular revascularization. *Stroke*. (2016) 47:1850–7. doi: 10.1161/STROKEAHA.116.013046
27. Papanagiotou P, Haussen DC, Turjman F, Labreuche J, Piotin M, Kastrup A, et al. Carotid stenting with antithrombotic agents and intracranial thrombectomy leads to the highest recanalization rate in patients with acute stroke with tandem lesions. *JACC Cardiovas Intervent*. (2018) 11:1290–9. doi: 10.1016/j.jcin.2018.05.036
28. Kim SK, Yoon W, Kim TS, Heo TW, Park MS. Histologic analysis of retrieved clots in acute ischemic stroke: correlation with stroke etiology and gradient-echo MRI. *AJNR Am J Neuroradiol*. (2015) 36:1756–62. doi: 10.3174/ajnr.A4402
29. Kim SK, Baek BH, Lee YY, Yoon W. Clinical implications of CT hyperdense artery sign in patients with acute middle cerebral artery occlusion in the era of modern mechanical thrombectomy. *J Neurol*. (2017) 264:2350–456. doi: 10.1007/s00415-017-8655-0

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW
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Angiographical Identification of Intracranial, Atherosclerosis-Related, Large Vessel Occlusion in Endovascular Treatment

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Identification of intracranial, atherosclerosis-related, large vessel occlusion (ICAS-LVO) is important to set up an optimal endovascular treatment strategy, as most ICAS-LVOs require specific endovascular modalities for efficient recanalization. However, there is currently no decisive way to identify ICAS-LVO for endovascular treatment. Instead of the few, non-specific, clinical and imaging findings that operators have depended on, this review focused on the occlusion type, one of angiographical methods to identify the ICAS-LVO. Occlusion type was originally devised for predicting procedural details and endovascular outcomes of ICAS-LVO. Among occlusion types, truncal-type occlusion is regarded as a surrogate marker for ICAS-LVO. Although rare, false positives or negatives in truncal-type occlusion are possible. Nonetheless, occlusion type was easy to apply and reliably predictive of procedural outcomes. Furthermore, occlusion type can be determined prior to the procedure, which could allow it to be more helpful in setting up an optimal strategy before starting endovascular treatment.

Keywords: intracranial atherosclerosis, angiography, occlusion type, endovascular treatment, acute stroke

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INTRODUCTION

Mechanical thrombectomy has become a standard treatment for acute, intracranial, large vessel occlusion (LVO) (1–3). Clinical outcomes of patients with an intracranial LVO have been remarkably improved by mechanical thrombectomy, and an improved recanalization rate was one of most important factors for these favorable outcomes (4). With modern endovascular devices (e.g., stent retriever, contact aspiration thrombectomy), 70–90% successful recanalization rates have been reported (5–9). Nevertheless, there are still a few problems with these devices. In spite of high recanalization rates, 40% futile recanalization rates—patients whose functional status is not independent—have been reported after endovascular treatment (EVT) (3, 10, 11). This might be because patient outcome is also affected by many other clinical and procedural factors, including time to recanalization, system of stroke care, and post-procedural management (12–14). In this regard, one of the most important modifiable factors is to set up an optimal endovascular strategy, because LVO can be effectively recanalized within a shorter timeframe using the optimal endovascular strategy (9).

Acute, intracranial, atherosclerosis-related LVO (ICAS-LVO) is not rare (15). The reported frequency of ICAS-LVO in EVT-eligible patients varies across studies, ranging from 5 to 36% (16–28). More exactly, the frequency of ICAS-LVO depends on the definition used and the patients' ethnicities, locations of occlusions, and eligible criteria for EVT (**Table 1**). In several studies from Korea, ICAS-LVO was found in 12–30% of study patients. Under the definition of significant fixed focal stenosis (FFS), the frequency was about 15–20%, although the precise definition was slightly variable across studies. Occlusion type, one of the major definitions used for ICAS-LVOs, also showed a similar range of frequencies, at about 12–18% (17, 18). ICAS-LVO is known to be more frequent in the posterior circulation (24, 32). In fact, one study reported that about 37% of ICAS-LVOs were in the posterior circulation (22). Based on angiographical determination, ICAS-LVOs seem to be less frequent in Western studies, at about 5–8% of EVT-eligible patients (19, 29).

Importantly, ICAS-LVO is considered a principal reason for failure of modern endovascular thrombectomy (17, 21, 23, 29). With modern endovascular modalities (e.g., stent retriever, contact aspiration thrombectomy), successful recanalization was possible in <30% of cases of ICAS-LVO (17, 23). Thus, the feasibility and safety of rescue endovascular modalities appropriate to ICAS-LVO (e.g., balloon angioplasty, stenting, intra-arterial glycoprotein IIb/IIIa inhibitor infusion) are constant points of discussion (17, 20, 23, 26, 28, 30–36). Although there is a lack of prospective studies regarding treatment of ICAS-LVO, most reports have indicated that ICAS-specific endovascular modalities are feasible in an acute setting. With optimal use of ICAS-specific endovascular modalities, patient outcome was also comparable to that of embolic occlusion (16, 23, 28). Finally, the rapid introduction of ICAS-specific endovascular modalities can be very important for timely and successful recanalization.

Therefore, determination of ICAS-LVO seems essential and critical for selecting an optimal endovascular treatment strategy. However, disappointingly, there is no corroborant method to identify ICAS-LVO. Such an identification method should be reliable and show acceptable sensitivity and specificity. It should be predictive of procedural details and applicable during or before EVT to help operators establish an optimal endovascular strategy. Some demographics, clinical risk factors, and imaging findings have been reported to be associated with ICAS-LVO (24, 32, 37–39). However, these demographics and clinical risk factors might not be specific to ICAS-LVO. Only atrial fibrillation proved to be fairly predictive for endovascular outcomes and is a clinically used risk factor (18, 24, 40). Although atrial fibrillation is associated with a higher probability of embolic occlusion, this association might be circumstantial (32). Certain imaging findings, such as a hyperdense artery sign or blooming artifact, might be helpful but are still controversial regarding role in the etiology of acute LVO (37, 41).

Unlike those less-specific identification methods, ICAS-LVO can be precisely identified angiographically (17, 32). Because angiographical determination has been most widely used in studies of ICAS-LVO, it is necessary to understand this method in depth to develop optimal endovascular treatment strategies. Among them, this review will discuss about the occlusion type—one of methods to identify the ICAS-LVO based exclusively on angiographical findings.

OCCLUSION TYPE

Occlusion type is one of the most reliable angiographical surrogate markers for ICAS-LVO. Occlusion type was originally devised to differentiate ICAS-LVO from an embolic occlusion and was aimed for practical use in clinical settings (17). Before the introduction of occlusion type, clinical, and radiological findings (e.g., atrial fibrillation and hyperdense artery sign) were considered to presume an embolic occlusion. Although the concept of FFS was considered for similar purposes, it was used as merely an operational definition for ICAS-LVO and was not easy to apply during the procedure. More importantly, the predictive value of FFS for modern mechanical thrombectomy outcome has not been systemically evaluated (23). In contrast, occlusion type on computed tomography angiography (CTA) or digital subtraction angiography (DSA) was well correlated with procedural outcomes, especially in stent retriever thrombectomy (17, 18).

Significance of Occlusion Type

The theoretical background of occlusion type for identification of ICAS-LVO is intuitive. For embolic occlusion, it is not likely for an embolus to be spontaneously halted in the middle of a normal artery. Instead, the embolus would likely become lodged at the site of an arterial bifurcation (i.e., a branching-site occlusion, BSO). In another words, an arterial occlusion found at the middle of an artery (i.e., truncal-type occlusion, TTO) is likely not caused by an embolus. In the narrow spectrum of occlusion etiologies of LVO, the TTO might be from an *in situ* thromboocclusion caused by an underlying ICAS.

According to a study that evaluated this hypothesis, TTO was significantly associated with stent retriever failure (odds ratio (OR): 32.2; 95% confidence interval (CI): 7.78–133.0) and with none of the embolic sources, such as cardioembolism and artery-to-artery embolism (OR: 9.07; 95% CI: 3.74–22.0) (17). Impressively, patients with a TTO showed a much higher rate of reocclusion events than those with a BSO (77.3 vs. 5.0%; $p < 0.001$). Furthermore, most patients (78.9%) eventually needed rescue modalities to achieve a successful recanalization. It seems evident that the clinical and endovascular details of TTOs are comparable to those of ICAS-LVO (16, 21, 23, 28, 29). Thus, in situations where no confirmative identification method for ICAS-LVO is feasible during the procedure, occlusion type could be a helpful surrogate marker to identify ICAS-LVO.

The ultimate goal in determining occlusion type was to help set up an optimal endovascular treatment strategy for ICAS-LVO. Therefore, the previous study originally focused on the predictive value of occlusion type for success of stent retrievers and the necessity of rescue modalities specific to ICAS-LVO.

TABLE 1 | Frequencies of intracranial atherosclerosis-related large vessel occlusion (ICAS-LVO) in endovascular treatment-eligible patients.

Study	Definition of ICAS-LVO	Nation of study population	Anterior or posterior circulation	Total number of patients included	ICAS-LVO%
Matias-Guiu et al. (29)	TOAST classification	Spain	Both	88	17.0
Kang et al. (30)	Fixed focal stenosis[a]	Korea	Both	132	30.3
Gascou et al. (19)	Intracranial stenosis	France	Both	144[b]	5.5
Al Kasab et al. (16)	Significant fixed focal stenosis	US	Both	435	8.3
Lee et al. (24)	Significant fixed focal stenosis	Korea	Both	158	15.2
Lee et al. (23)	Significant fixed focal stenosis	Korea	Both	53[c]	17.0
Yi et al. (26)	Significant fixed focal stenosis	China	Both	55	21.8
Yoon et al. (28)	Significant fixed focal stenosis	Korea	Both	172	22.9
Jia et al. (20)	Significant fixed focal stenosis	China	Anterior	140	34.0
Kim et al. (22)	Significant fixed focal stenosis	Korea	Posterior	51[d]	37.3
Baek et al. (31)	Truncal-type occlusion (by DSA)	Korea	Both	259	12.4
Baek et al. (18)	Truncal-type occlusion (by CTA)	Korea	Both	238	18.1

[a] *ICAS-LVO was identified by follow-up vascular imaging at 5–7 days.*
[b] *This study included only patients treated with stent retrievers.*
[c] *This study included only patients treated with stent retrievers as the first-line treatment modality.*
[d] *This study included only patients treated primarily with mechanical thrombectomy.*
TOAST, Trial of ORG 10172 in Acute Stroke Treatment; DSA, digital subtraction angiography; CTA, computed tomography angiography.

TABLE 2 | Angiographical findings suggestive of branching-site and truncal-type occlusions on catheter or digital subtraction angiography (DSA) and computed tomography angiography (CTA).

	Branching-site occlusion	Truncal-type occlusion
Principle	Involvement of the bifurcation site	Intact bifurcation site and all distal major branches beyond occlusion
DSA	(1) Failure of advancement of ACOM collateral flow to ipsilateral MCA[a] (T-occlusion) (2) Direct visualization of Y- or T-shaped filling defect[b,c,d] (Y- or T-shaped clot) (3) Absence or partial visualization of another branch[d] (branch-missing sign)	(1) Advancement of ACOM collateral flow to ipsilateral MCA[a] (below T-occlusion) (2) Clearly-visible distal major branches and bifurcation site beyond occlusion[b,c,d]
CTA	Vague or invisible major distal branches and bifurcation site beyond occlusion	Clearly-visible distal major branches and bifurcation site beyond occlusion

[a] *By contralateral ICA angiogram.*
[b] *By any angiography, including microcatheter angiography.*
[c] *By minimal or partial recanalization using a thrombectomy procedure.*
[d] *By post-deployment angiogram with stent-through flow.*
ICA, internal carotid artery; ACOM, anterior communicating artery; MCA, middle cerebral artery.

Based on the predictability of stent retriever successfulness in occlusion type, one could change endovascular modality from stent retriever to other modalities specific to ICAS-LVO earlier if TTO is observed. This strategy might avoid unnecessary trials of stent retriever and shorten procedural time. As for its practical application, occlusion type can be easily determined during endovascular procedures. Especially, in stent retriever thrombectomy, the occlusion type can be determined by a single stent retriever deployment across the occluded segment, as described in detail in the next section. Furthermore, occlusion type can be reliably determined before the endovascular procedure using preprocedural CTA (18). Early determination of occlusion type might be helpful in setting up the optimal endovascular treatment strategy. In addition, the predictive value of CTA-determined occlusion type was superior to atrial fibrillation or presence of a hyperdense artery sign, which have previously been the most widely considered pre-procedural identification methods, to presume occlusion etiology.

Clinical outcomes according to occlusion type was reported (42). In the single center report of 318 patients, the TTO group showed a comparable recanalization rate with the BSO group (80.4 vs. 88.5%; $p = 0.097$), although procedural details were completely different. With the comparable recanalization rate, clinical outcomes including favorable outcome (modified Rankin Scale score at 3 months 0–2; 46.4 vs. 46.9%; $p = 0.944$), symptomatic intracranial hemorrhage, and mortality were not significantly different between the TTO and the BSO groups.

Determination of Occlusion Type During or Before Endovascular Procedures

Occlusion type can be classified as either BSO or TTO during endovascular procedures. For angiographical determination of

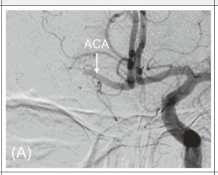
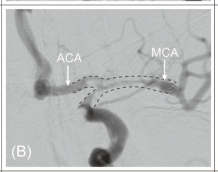
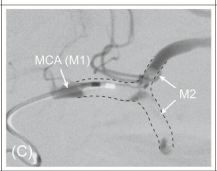
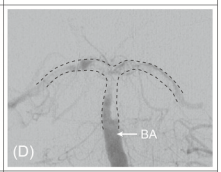
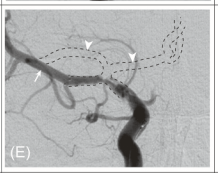
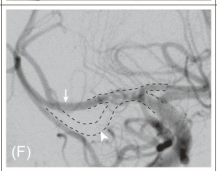
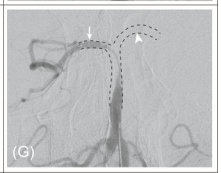
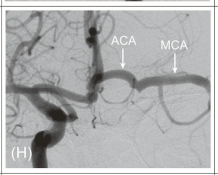
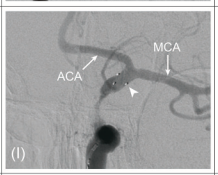
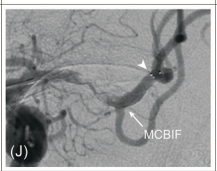
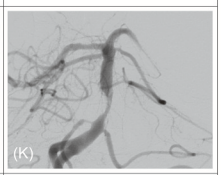
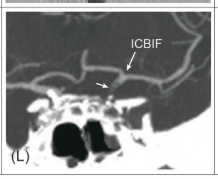
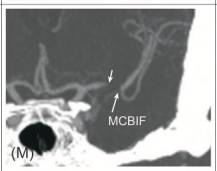
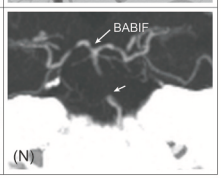
Occlusion type	Findings	Internal carotid artery	Middle cerebral artery	Basilar artery
Braching-site occlusion	Failure of advancement of collateral flow through ACOM on contralateral ICA angiogram			
	Y- or T-shaped filling defect *on stent retriever deployment, on microcatheter angiogram, or after minimal recanalization*			
	Branch-missing sign *on stent retriever deployment*			
Truncal-type occlusion	Advancement of collateral flow through ACOM on contralateral ICA angiogram			
	Clearly-visible all major branches and its birufcation site *on stent retriever deployment, on microcatheter angiogram, or after minimal recanalization*			
	Clearly-visible all major branches and its birufcation site *on CTA images*			

FIGURE 1 | Determination of occlusion type by digital subtraction angiography (DSA) and computed tomography angiography (CTA). On contralateral internal carotid artery (ICA) angiogram, collateral flow cannot advance to ipsilateral middle cerebral artery (MCA) through anterior communicating artery (ACOM) because ipsilateral ICA bifurcation (ICBIF) site is involved in branching-site occlusion **(A)**. On the contrary, collateral flow can progress to ipsilateral MCA in truncal-type occlusion **(H)**. In branching-site occlusion, Y- or T-shaped filling defect (clot) involving arterial bifurcation site can be observed on stent retriever deployment **(B)**, on microcatheter angiogram **(C)**, or after minimal recanalization **(D)**. In addition, owing to the involvement of arterial bifurcation site, only one branch that stent retriever is deployed to can be seen on post-deployment angiogram in branching-site occlusion [arrow in **(E–G)**], while another branch is not seen [missing branch sign; arrowhead in **(E–G)**]. In truncal-type occlusion, all major branches and its bifurcation site can be clearly observed by stent retriever deployment [**(I,J)**; arrowhead, distal markers of stent retriever], on microcatheter angiogram beyond occlusion, or after minimal recanalization **(K)**. Those can also be observed on CTA images [**(L–N)**; arrow, original occlusion point]. ACA, anterior cerebral artery; M2, superior and inferior divisions of middle cerebral artery; MCBIF, middle cerebral artery bifurcation site; BABIF, basilar artery bifurcation site.

BSO, the following findings can be considered (**Table 2**). First, on contralateral internal carotid artery (ICA) angiography, collateral flow through the anterior communicating artery (ACOM) cannot advance to the ipsilateral middle cerebral artery (MCA) if the ipsilateral ICA bifurcation site is involved, a so-called ICA T-occlusion (BSO; **Figure 1A**). In contrast to that, the collateral flow can advance further to the ipsilateral MCA through the ACOM system if an occlusion is located below the bifurcation site (TTO; **Figure 1H**). This finding has been commonly observed at the start of endovascular procedures during collateral evaluation. However, with the recent push to shorten the time to recanalization, the target vessel is treated without collateral assessment in most current endovascular procedures.

Second, Y- or T-shaped filling defects involving the bifurcation site can be directly observed during endovascular procedures by microcatheter angiogram, after partial recanalization by minimal thrombectomy procedure, or by angiogram performed with stent retriever in deployment (**Figures 1B–D**). Without doubt, these findings should be considered BSOs.

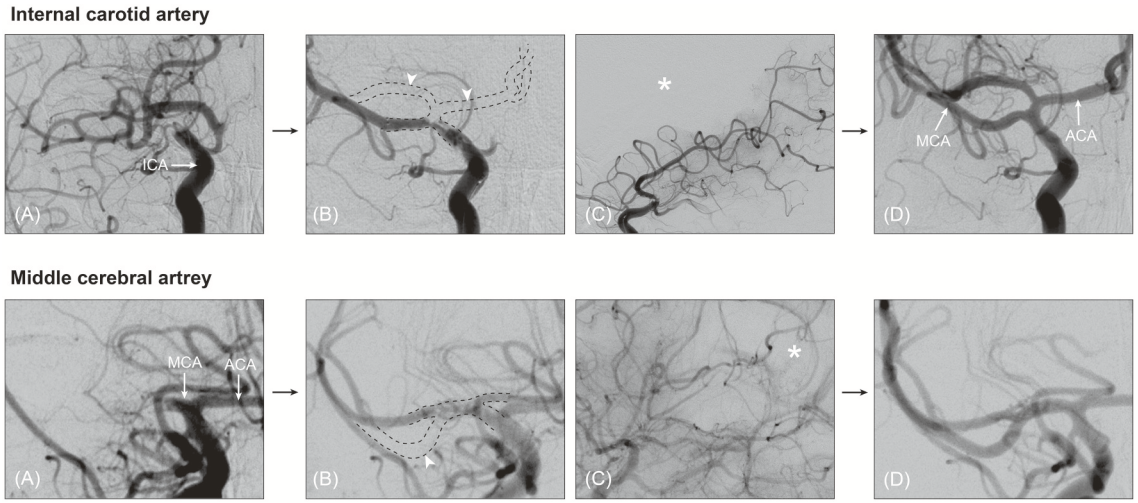


FIGURE 2 | Angiographical territorial filling defect, suggestive of branching-site occlusion. On post-deployment angiogram during stent retriever thrombectomy, branch-missing sign can be observed (**A,B**, arrowhead). In patients whose missing branch is vague, angiographical filling defect could be helpful to guess the presence of the missing branch. On lateral view of post-deployment angiogram, corresponding territorial filling defect is seen (asterisk in **C**). On final angiogram, the missing branch is obviously observed **(D)**. ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery.

TABLE 3 | Consistency of CTA- and DSA-determined occlusion type.

	CTA-determined occlusion type	
	Branching-site occlusion	**Truncal-type occlusion**
DSA-determined occlusion type		
Branching-site occlusion	182 (96.8%)	10 (24.4%)
Truncal-type occlusion	6 (3.2%)	31 (75.6%)
Total	188	41

This table was remade using the same study population in Baek et al. (18).
CTA, computed tomography angiography; DSA, catheter or digital subtraction angiography.

Third, post-deployment angiography during stent retriever thrombectomy could give useful hints as to the occlusion type. For embolic occlusions in which an embolus might locate at the bifurcation site, the stent-through blood might only flow into the one branch where the stent retriever is deployed. Consequently, post-deployment angiography shows only one of all of the major branches (i.e., branch-missing sign, implicating BSO; **Figures 1E–G**). An angiographical territorial filling defect could be an indirect finding for the absence of the other major branches (**Figure 2**). If an occlusion is located at the arterial trunk, all major distal branches can be clearly seen by stent-through blood flow (TTO; **Figures 1I,J**).

To define the TTO, one should confirm that a bifurcation site and all its major distal branches are intact (distal confirmation). This distal confirmation can be performed by evaluating collateral flow through the ACOM system, microcatheter angiography beyond the occlusion site, stent-through blood flow across the occlusion site, or achievement of minimal recanalization (**Figure 1K**). More importantly, distal confirmation is also possible by CTA, which is more intuitive and easier than using catheter angiography or DSA (**Table 2** and **Figures 1L–N**). In fact, its interrater agreement for classifying occlusion type was higher than that of DSA (kappa value 0.96 vs. 0.89) (18).

Concerns With Regard to Occlusion Type

Disadvantages and Advantages in Determining Occlusion Type by DSA

Occlusion type is practically significant, is informative to set up an endovascular strategy, and is simpler to apply than FFS. In spite of these advantages, using DSA-determined occlusion type for identifying ICAS-LVOs has a few limitations. Above all, some additional manipulations are required for determination of occlusion type—for example, contralateral ICA angiography, microcatheter angiography beyond the occlusion, or post-deployment angiography. Among them, most determination practically depends on stent-through blood flow. Therefore, occlusion type often cannot be determined by DSA in patients who undergo non-stent retriever thrombectomy (e.g., contact aspiration thrombectomy), who did not have post-deployment angiography, or in whom stent-through blood flow was not achieved. In practice, occlusion type could not be determined by DSA in about 3.8% of patients (18). However, CTA findings are still helpful in those cases whose occlusion type cannot be determined by DSA.

One of most important advantages of occlusion type is that it is not affected by treatment results. In contrast with FFS, occlusion type can be determined even in cases of persistent occlusion or incomplete recanalization. Furthermore, occlusion type is obviously unaffected by the remnants of emboli, vasospasm, and iatrogenic artery dissection.

TABLE 4 | Summary of 10 patients who had CTA-determined truncal-type occlusion and DSA-determined branching-site occlusion (CTA-TTO with DSA-BSO).

	Occlusion site	AF	Reocclusion	mTICI	AOL	Recanalization modality	DSA findings suggestive of initial TTO
1	ICA	+	−	2a	3	Stent retriever	None
2	MCA	−	−	2b	3	Stent retriever	None
3	ICA	+	−	2b	3	Stent retriever	Huge clot halted in cervical ICA
4	ICA	+	−	3	3	Stent retriever	Huge clot halted in cervical ICA
5	ICA	+	−	0	0	N/A	Huge clot halted in cervical ICA
6	ICA	+	−	0	0	N/A	None
7	ICA	−	−	2b	3	Stent retriever	Huge clot halted in cervical ICA
8	ICA	+	−	3	3	Stent retriever	Huge clot halted in cervical ICA
9	BA	−	+	3	3	Stent retriever for distal BA; PTA with stenting and GPI for BA trunk	Fixed focal stenosis in the BA trunk (as a tandem lesion)
10	ICA	+	−	2b	3	Stent retriever	None

CTA, computed tomography angiography; DSA, catheter or digital subtraction angiography; AF, atrial fibrillation; mTICI, modified thrombolysis in cerebral infarction; AOL, arterial occlusive lesion; ICA, internal carotid artery; MCA, middle cerebral artery; BA, basilar artery; PTA, percutaneous transluminal angioplasty; GPI, glycoprotein IIb/IIIa inhibitor.

False Positives in TTO Determination by CTA (CTA-TTO With DSA-BSO)

Although CTA can be useful for identifying occlusion type, there is still the problem of false classification. DSA- and CTA-determined occlusion types can contradict each other. CTA-determined occlusion type was not in agreement with DSA-determined occlusion type in about 7.0% of patients (**Table 3**) (18). Among them, quite a few cases (62.5%, 10 of 16) had a DSA-determined BSO that was originally classified as a TTO on preprocedural CTA. One possible mechanism for this change in occlusion type is that distal migration of the clot which halted in the arterial trunk. In fact, half of these patients had a huge clot in the arterial trunk on DSA, which was observed as an angiographical filling defect (**Table 4**). Their original occlusion might have been a TTO in which the clot halted in the arterial trunk. However, on DSA, in addition to these clots in the arterial trunk, a distal BSO was also newly found. This finding is suggestive of distal migration of a proximal clot that halted in the arterial trunk to its distal bifurcation site, which finally led to the formation of a new, distal BSO that was not seen on preprocedural CTA. Similarly, in patient with BA occlusion, a new distal BSO might develop as a result of an artery-to-artery embolism from an ICAS-related lesion in the BA trunk. New distal BSOs were completely recanalized by stent retriever without residual stenosis in almost all cases. Although a few patients did not have a "truncal embolus" on DSA, complete distal migration of a proximal clot is a possible mechanism, in the same manner as described above.

It remains unclear why an embolus would halt in the middle of an artery. In those patients, the arteries did not show any morphological abnormalities that would explain why an embolus could be caught. Instead, we hypothesize that it might relate to the size of the embolus—a very large embolus might become compacted and ultimately lodged in the tortuous but not stenotic middle trunk of an artery (e.g., cavernous segment of internal carotid artery). Also, hemodynamic flow competition forces can affect the migration of emboli. For example, if a patient had sufficiently strong collateral flow through the ACOM to elicit effective retrograde flow, it might be possible for an embolus to not advance to its bifurcation site. In fact, in these patients, most truncal emboli were found in the cervical or petro-cavernous segment of ICA, in whom ACOM is quite thick and therefore cross collateral flows are sufficiently strong (**Table 4**).

False Negatives in TTO Determination by CTA (CTA-BSO With DSA-TTO)

Distal confirmation in CTA is dependent on visualization of a distal part of the artery beyond the occlusion. Because contrast media should reach the distal part of the artery beyond the occlusion, collateral flow is important in determining occlusion type by CTA. Collateral flow through the communicating arteries is important for distal confirmation in ICA or basilar artery occlusion. On the contrary, in MCA occlusion, leptomeningeal collateral flow, which shows greater individual differences, is important. Thus, CTA can misclassify truncal-type MCA occlusion as BSO if a patient has poor leptomeningeal collaterals to the MCA area. In fact, about 3.2% of CTA-determined BSOs were actually found to be TTOs on DSA (**Table 3**). Expectedly, all of these cases were MCA occlusions.

Given this, CTA-determined occlusion type, which showed a higher sensitivity for detecting the BSO compared to TTO, might be slightly biased toward identifying BSO. This limitation could be overcome by using multiphase CTA, which can allow for sufficient time for retrograde filling of contrast media into the distal part of the artery.

CONCLUSIONS

Among only a few identification methods, the ICAS-LVO can be feasibly identified by angiographical findings. The identification of ICAS-LVO based on based on occlusion type, is a reliable and practical identification method for ICAS-LVO. Procedural details by occlusion type and its predictability to endovascular results were reported. Furthermore, occlusion type can be determined before or in the early stages of the procedure, which may be most helpful in setting up an optimal endovascular treatment strategy.

AUTHOR CONTRIBUTIONS

J-HB established the study idea, designed the manuscript structure, acquired and analyzed the data, and wrote the manuscript. BMK established the study idea, designed the manuscript structure, and made critical revisions to the manuscript with substantive intellectual content.

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REFERENCES

1. Powers WJ, Derdeyn CP, Biller J, Coffey CS, Hoh BL, Jauch EC, et al. American heart association/american stroke association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke.* (2015) 46:3020–35. doi: 10.1161/STR.0000000000000074
2. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke.* (2018) 49:e46–110. doi: 10.1161/STR.0000000000000158
3. Hong KS, Ko SB, Yu KH, Jung C, Park SQ, Kim BM, et al. Update of the Korean clinical practice guidelines for endovascular recanalization therapy in patients with acute ischemic stroke. *J Stroke.* (2016) 18:102–13. doi: 10.5853/jos.2015.01655
4. Linfante I, Cipolla MJ. Improving reperfusion therapies in the era of mechanical thrombectomy. *Trans Stroke Res.* (2016) 7:294–302. doi: 10.1007/s12975-016-0469-3
5. Hong KS, Ko SB, Lee JS, Yu KH, Rha JH. Endovascular recanalization therapy in acute ischemic stroke: updated meta-analysis of randomized controlled trials. *J Stroke.* (2015) 17:268–81. doi: 10.5853/jos.2015.17.3.268
6. Lapergue B, Blanc R, Gory B, Labreuche J, Duhamel A, Marnat G, et al. Effect of endovascular contact aspiration vs. stent retriever on revascularization in patients with acute ischemic stroke and large vessel occlusion: the ASTER randomized Clinical trial. *JAMA.* (2017) 318:443–52. doi: 10.1001/jama.2017.9644
7. Linfante I, Starosciak AK, Walker GR, Dabus G, Castonguay AC, Gupta R, et al. Predictors of poor outcome despite recanalization: a multiple regression analysis of the NASA registry. *J Neurointerv Surg.* (2016) 8:224–9. doi: 10.1136/neurintsurg-2014-011525
8. Song D, Cho AH. Previous and recent evidence of endovascular therapy in acute ischemic stroke. *Neurointervention.* (2015) 10:51–9. doi: 10.5469/neuroint.2015.10.2.51
9. Yoo AJ, Andersson T. Thrombectomy in acute ischemic stroke: challenges to procedural success. *J Stroke.* (2017) 19:121–30. doi: 10.5853/jos.2017.00752
10. Campbell BC, Hill MD, Rubiera M, Menon BK, Demchuk A, Donnan GA, et al. Safety and efficacy of solitaire stent thrombectomy: individual patient data meta-analysis of randomized trials. *Stroke.* (2016) 47:798–806. doi: 10.1161/STROKEAHA.115.012360
11. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet.* (2016) 387:1723–31. doi: 10.1016/S0140-6736(16)00163-X
12. Goyal M, Jadhav AP, Bonafe A, Diener H, Mendes Pereira V, Levy E, et al. Analysis of workflow and time to treatment and the effects on outcome in endovascular treatment of acute ischemic stroke: results from the SWIFT PRIME randomized controlled trial. *Radiology.* (2016) 279:888–97. doi: 10.1148/radiol.2016160204
13. Menon BK, Sajobi TT, Zhang Y, Rempel JL, Shuaib A, Thornton J, et al. Analysis of workflow and time to treatment on thrombectomy outcome in the endovascular treatment for small core and proximal occlusion ischemic stroke (ESCAPE) randomized, controlled trial. *Circulation.* (2016) 133:2279–86. doi: 10.1161/CIRCULATIONAHA.115.019983
14. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA.* (2016) 316:1279–88. doi: 10.1001/jama.2016.13647
15. Bang, OY. Considerations when subtyping ischemic stroke in Asian patients. *J Clin Neurol.* (2016) 12:129–36. doi: 10.3988/jcn.2016.12.2.129
16. Al Kasab S, Almadidy Z, Spiotta AM, Turk AS, Chaudry MI, Hungerford JP, et al. Endovascular treatment for AIS with underlying ICAD. *J Neurointerv Surg.* (2017) 9:948–51. doi: 10.1136/neurintsurg-2016-012529
17. Baek JH, Kim BM, Kim DJ, Heo JH, Nam HS, Song D, et al. Importance of truncal-type occlusion in stentriever-based thrombectomy for acute stroke. *Neurology.* (2016) 87:1542–50. doi: 10.1212/WNL.0000000000003202
18. Baek JH, Kim BM, Yoo J, Nam HS, Kim YD, Kim DJ, et al. Predictive value of computed tomography angiography-determined occlusion type in stent retriever thrombectomy. *Stroke.* (2017) 48:2746–52. doi: 10.1161/STROKEAHA.117.018096
19. Gascou G, Lobotesis K, Machi P, Maldonado I, Vendrell JF, Riquelme C, et al. Stent retrievers in acute ischemic stroke: complications and failures during the perioperative period. *AJNR Am J Neuroradiol.* (2014) 35:734–40. doi: 10.3174/ajnr.A3746
20. Jia B, Feng L, Liebeskind DS, Huo X, Gao F, Ma N, et al. Mechanical thrombectomy and rescue therapy for intracranial large artery occlusion with underlying atherosclerosis. *J Neurointerv Surg.* (2018) 10:746–50. doi: 10.1136/neurintsurg-2017-013489
21. Kang DH, Kim YW, Hwang YH, Park SP, Kim YS, Baik SK. Instant reocclusion following mechanical thrombectomy of *in situ* thromboocclusion and the role of low-dose intra-arterial tirofiban. *Cerebrovasc Dis.* (2014) 37:350–5. doi: 10.1159/000362435
22. Kim YW, Hong JM, Park DG, Choi JW, Kang DH, Kim YS, et al. Effect of intracranial atherosclerotic disease on endovascular treatment for patients with acute vertebrobasilar occlusion. *AJNR Am J Neuroradiol.* (2016) 37:2072–8. doi: 10.3174/ajnr.A4844
23. Lee JS, Hong JM, Lee KS, Suh HI, Choi JW, Kim SY. Primary stent retrieval for acute intracranial large artery occlusion due to atherosclerotic disease. *J Stroke.* (2016) 18:96–101. doi: 10.5853/jos.2015.01347
24. Lee JS, Hong JM, Lee KS, Suh HI, Demchuk AM, Hwang YH, et al. Endovascular therapy of cerebral arterial occlusions: intracranial atherosclerosis versus embolism. *J Stroke Cerebrovasc Dis.* (2015) 24:2074–80. doi: 10.1016/j.jstrokecerebrovasdis.2015.05.003
25. Lee YY, Yoon W, Kim SK, Baek BH, Kim GS, Kim JT, et al. Acute basilar artery occlusion: differences in characteristics and outcomes after endovascular therapy between patients with and without underlying severe atherosclerotic stenosis. *AJNR Am J Neuroradiol.* (2017) 38:1600–4. doi: 10.3174/ajnr.A5233
26. Yi TY, Chen WH, Wu YM, Zhang MF, Chen YH, Wu ZZ, et al. Special endovascular treatment for acute large artery occlusion resulting from atherosclerotic disease. *World Neurosurg.* (2017) 103:65–72. doi: 10.1016/j.wneu.2017.03.108
27. Yi TY, Chen WH, Wu YM, Zhang MF, Zhan AL, Chen YH, et al. Microcatheter "first-pass effect" predicts acute intracranial artery atherosclerotic disease-related occlusion. *Neurosurgery.* (2018). doi: 10.1093/neuros/nyy183. [Epub ahead of print].
28. Yoon W, Kim SK, Park MS, Kim BC, Kang HK. Endovascular treatment and the outcomes of atherosclerotic intracranial stenosis in patients with hyperacute stroke. *Neurosurgery.* (2015) 76:680–6. doi: 10.1227/NEU.0000000000000694

29. Matias-Guiu JA, Serna-Candel C, Matias-Guiu J. Stroke etiology determines effectiveness of retrievable stents. *J Neurointerv Surg.* (2014) 6:e11. doi: 10.1136/neurintsurg-2012–010395
30. Kang DH, Yoon W, Kim SK, Baek BH, Lee YY, Kim YW, et al. Endovascular treatment for emergent large vessel occlusion due to severe intracranial atherosclerotic stenosis. *J Neurosurg.* (2018) 22:1–8. doi: 10.3171/2018.1.JNS172350
31. Baek JH, Kim BM, Kim DJ, Heo JH, Nam HS, Yoo J. Stenting as a rescue treatment after failure of mechanical thrombectomy for anterior circulation large artery occlusion. *Stroke.* (2016) 47:2360–3. doi: 10.1161/STROKEAHA.116.014073
32. Lee JS, Hong JM, Kim JS. Diagnostic and therapeutic strategies for acute intracranial atherosclerosis-related occlusions. *J Stroke.* (2017) 19:143–51. doi: 10.5853/jos.2017.00626
33. Chang Y, Kim BM, Bang OY, Baek JH, Heo JH, Nam HS, et al. Rescue stenting for failed mechanical thrombectomy in acute ischemic stroke: a multicenter experience. *Stroke.* (2018) 49:958–64. doi: 10.1161/STROKEAHA.117.020072
34. Fiehler J. Failed thrombectomy in acute ischemic stroke: return of the stent? *Stroke.* (2018) 49:811–2. doi: 10.1161/STROKEAHA.118.020541
35. Kim BM. Causes and solutions of endovascular treatment failure. *J Stroke.* (2017) 19:131–42. doi: 10.5853/jos.2017.00283
36. Yang D, Lin M, Wang S, Wang H, Hao Y, Zi W, et al. Primary angioplasty and stenting may be superior to thrombectomy for acute atherosclerotic large-artery occlusion. *Interv Neuroradiol.* (2018) 24:412–20. doi: 10.1177/1591019918763380
37. Cho KH, Yoon Y, Sohn SI, Kim JS. Susceptibility vessel signs on T2*-weighted gradient echo images in patients with cerebral atherosclerosis. *Int J Stroke.* (2014) 9:E32. doi: 10.1111/ijs.12318
38. Kim SK, Baek BH, Lee YY, Yoon W. Clinical implications of CT hyperdense artery sign in patients with acute middle cerebral artery occlusion in the era of modern mechanical thrombectomy. *J Neurol.* (2017) 264:2450–6. doi: 10.1007/s00415-017-8655-0
39. Kim SK, Yoon W, Kim TS, Kim HS, Heo TW, Park MS. Histologic analysis of retrieved clots in acute ischemic stroke: correlation with stroke etiology and gradient-echo MRI. *AJNR Am J Neuroradiol.* (2015) 36:1756–62. doi: 10.3174/ajnr.A4402
40. Hwang YH, Kim YW, Kang DH, Kim YS, Liebeskind DS. Impact of target arterial residual stenosis on outcome after endovascular revascularization. *Stroke.* (2016). 47:1850–7. doi: 10.1161/STROKEAHA.116.013046
41. Suh HI, Hong JM, Lee KS, Han M, Choi JW, Kim JS, et al. Imaging predictors for atherosclerosis-related intracranial large artery occlusions in acute anterior circulation stroke. *J Stroke.* (2016) 18:352–4. doi: 10.5853/jos.2016.00283
42. Baek JH, Kim BM, Heo JH, Kim DJ, Nam HS, Kim YD. Outcomes of endovascular treatment for acute intracranial atherosclerosis–related large vessel occlusion. *Stroke.* (2018) 49:2699–705. doi: 10.1161/STROKEAHA.118.022327

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