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# Refractory Stroke Thrombectomy: Prevalence, Etiology, and Adjunctive Treatment in a North American Cohort

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## ABSTRACT

**BACKGROUND AND PURPOSE:** Acute stroke intervention refractory to mechanical thrombectomy may be due to underlying vessel wall pathology including intracranial atherosclerotic disease and intracranial arterial dissection or recalcitrant emboli. We studied the prevalence and etiology of refractory thrombectomy, the safety and efficacy of adjunctive interventions in a North American-based cohort.

**MATERIALS AND METHODS:** We performed a multicenter, retrospective study of refractory thrombectomy, defined as unsuccessful recanalization, vessel reocclusion in <72 hours, or required adjunctive antiplatelet glycoprotein IIb/IIIa inhibitors, intracranial angioplasty and/or stenting to achieve and maintain reperfusion. Clinical and imaging criteria differentiated etiologies for refractory thrombectomy. Baseline demographics, cerebrovascular risk factors, technical/clinical outcomes, and procedural safety/complications were compared between refractory and standard thrombectomy groups. Multivariable logistic regression analysis was performed to determine independent predictors of refractory thrombectomy.

**RESULTS:** Refractory thrombectomy was identified in 25/302 cases (8.3%), correlated with diabetes (44% versus 22%,  $P = .02$ ) as an independent predictor with OR = 2.72 (95% CI, 1.05–7.09;  $P = .04$ ) and inversely correlated with atrial fibrillation (16% versus 45.7%,  $P = .005$ ). Refractory etiologies were secondary to recalcitrant emboli (20%), intracranial atherosclerotic disease (60%), and/or intracranial arterial dissection (44%). Four (16%) patients were diagnosed with early vessel reocclusion, and 21 patients underwent adjunctive salvage interventions with glycoprotein IIb/IIIa inhibitor infusion alone (32%) or intracranial angioplasty and/or stenting (52%). There were no significant differences in TICI 2b/3 reperfusion efficacy (85.7% versus 90.9%,  $P = .48$ ), symptomatic intracranial hemorrhage rates (0% versus 9%,  $P = .24$ ), favorable clinical outcomes (39.1% versus 48.3%,  $P = .51$ ), or mortality (13% versus 28.3%,  $P = .14$ ) versus standard thrombectomy.

**CONCLUSIONS:** Refractory stroke thrombectomy is encountered in <10% of cases, independently associated with diabetes, and related to underlying vessel wall pathology (intracranial atherosclerotic disease and/or intracranial arterial dissection) or, less commonly, recalcitrant emboli. Emergent salvage interventions with glycoprotein IIb/IIIa inhibitors or intracranial angioplasty and/or stenting are safe and effective adjunctive treatments.

**ABBREVIATIONS:** AIS = acute ischemic stroke; DAC = distal access catheter; ELVO = emergent large-vessel occlusion; GPI = glycoprotein IIb/IIIa inhibitors; IAD = intracranial arterial dissection; ICAD = intracranial atherosclerotic disease; sICH = symptomatic intracranial hemorrhage

Multiple randomized controlled trials have established mechanical thrombectomy as the standard of care treatment for acute ischemic stroke (AIS), secondary to an emergent large-vessel occlusion (ELVO).<sup>1</sup> Successful recanalization has been shown to be an independent predictor of favorable functional outcomes, with studies emphasizing near-complete reperfusion for

optimal outcomes.<sup>2,3</sup> However, in the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) meta-analysis of 5 randomized controlled trials constituting 634 endovascular cases, successful thrombectomy was achieved in 71% of cases with nearly 30% of cases failing to achieve successful revascularization.<sup>1</sup>


Several causes have been postulated for the failure of thrombectomy, including anatomic difficulty, suboptimal devices, clot

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burden or composition, and underlying vessel wall pathology.<sup>4</sup> The mechanism of vessel occlusion (embolic-versus-thrombotic) and underlying vascular pathology determines the response to mechanical thrombectomy.<sup>5</sup> Multiple studies from Asia have described intracranial atherosclerotic disease (ICAD) as an important underlying etiology of refractory thrombectomy encountered in 15%–20% of cases,<sup>6–8</sup> with fewer studies describing spontaneous intracranial arterial dissection (IAD) or recalcitrant emboli as other causes.<sup>9–11</sup> In refractory cases, in which there is a failure of recanalization or progressive reocclusion after mechanical thrombectomy, the use of adjunctive medical treatment with antiplatelet glycoprotein IIb/IIIa inhibitors (GPI) and endovascular interventions with intracranial angioplasty and/or stenting have been described.<sup>7,12</sup>

To our knowledge, no studies have characterized the prevalence of refractory stroke thrombectomy and its underlying etiologies in a North American-based population. In our study, we aimed to investigate the predictors of refractory thrombectomy in patients presenting with AIS secondary to ELVO. We also describe clinical and imaging features used to differentiate etiologies of underlying vessel wall pathology (ICAD and/or IAD) or recalcitrant emboli. Finally, we assess the safety and efficacy of adjunctive medical and endovascular treatment techniques in our refractory thrombectomy cohort relative to patients undergoing standard thrombectomy.

## MATERIALS AND METHODS

### Patient Population

Between January 2015 and December 2019, we identified consecutive patients with AIS who underwent endovascular mechanical thrombectomy for an ELVO at 3 Northwestern University affiliated comprehensive stroke centers. An institutional review board (IRB) approved retrospective study was conducted via a prospectively maintained multi-institutional neurointerventional database. Emergent off-label use of Humanitarian Device Exemption (HDE) intracranial stents were reported to the IRB and device manufacturers as required.

Patient and imaging criteria for mechanical thrombectomy were the following: age >18 years; prestroke mRS score of <2; presenting NIHSS score of  $\geq 6$  within 24 hours from last known well; ASPECTS  $\geq 6$ ; and CTA/MRA demonstrating anterior or posterior circulation ELVO including the ICA, M1–M2 MCA, basilar artery, or the P1 segment of the posterior cerebral artery. Patients presenting within 6–24 hours with anterior circulation occlusions were treated if they fulfilled CTP/MRI and DWI-PWI criteria (measured by RAPID post-processing software; iSchemaView) as per the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo (DAWN) and/or Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 (DEFUSE) 3 trials.<sup>13,14</sup>

### Mechanical Thrombectomy Procedures and Adjunctive Treatment of Refractory Cases

All procedures were attempted initially via transfemoral puncture using 6F, 80- to 100-cm-long guide sheaths placed in the cervical ICA or vertebral artery. Nearly all used a triaxial system with coaxial advancement of large-bore (0.054- to 0.072-inch inner diameter) distal access catheters (DACs) and 0.021- to 0.027-inch

microcatheters using 0.014- to 0.016-inch microwires to cross the thromboembolus for stent retriever deployment. Mechanical thrombectomy was performed with DAC advancement to the proximal aspect of the clot under continuous vacuum aspiration during stent retriever deployment across the thromboembolus. Next, the stent-delivery microcatheter was removed to maximize the DAC vacuum aspiration force and stent retriever engagement of the clot for ~5 minutes, and the combined stent retriever–DAC aspiration complex was retracted into the cervical or distal guide sheath under manual syringe aspiration. In a minority of cases, mechanical thrombectomy was performed with a large-bore DAC reperfusion catheter under vacuum aspiration without stent retriever use.

Refractory thrombectomy was defined as unsuccessful recanalization (TICI 0–1 reperfusion) after at least 3 passes or vessel reocclusion identified within 72 hours of presumed successful thrombectomy. In addition, residual or recalcitrant emboli or underlying intracranial vessel wall pathology (atherosclerotic plaque and/or an unstable dissection flap) that resulted in severe flow-limiting stenoses with impending or progressive reocclusion on immediate postthrombectomy angiograms were characterized as refractory thrombectomy. In these refractory thrombectomy cases, adjunctive rescue treatment was attempted with either GPI (eptifibatide 180 mcg/kg or abciximab 0.25 mg/kg in a single patient) intracranial angioplasty and/or stenting at the discretion of the neurointerventionalist. Following IV GPI infusion, serial cerebral angiography assessed interval improvement in vessel stability and patency for at least 15 minutes. In cases of persisting flow limitation or reocclusion despite GPI treatment, further salvage with intracranial angioplasty and/or stenting was performed. If intracranial stenting was the primary intervention, it was performed with either concomitant GPI infusion, antiplatelet loading, or in the setting of pre-existing dual-antiplatelet therapy.<sup>15</sup>

All patients having experienced refractory thrombectomy and adjunctive interventions were placed on at least aspirin >300 mg daily (300 mg rectal or 325 mg oral, depending on the patient's ability to swallow or the presence of a nasogastric tube) antiplatelet therapy postprocedure. If intracranial stenting required dual-antiplatelet loading, a 600-mg loading bolus of clopidogrel was provided (Siemens) with 75-mg daily therapy after an intraprocedural cone beam CT or postprocedure CT head study excluded intracranial hemorrhage complications. Patients receiving clopidogrel for intracranial stenting were followed with P2Y<sub>12</sub> assays (VerifyNow, Acumetrics, San Diego, CA) within 12 hours to ensure an adequate antiplatelet response. All standard and refractory thrombectomy cases had early (<72 hours) CTA and/or MR imaging/MRA follow-up available to identify early vessel reocclusion or stable vessel patency.

### Etiology Assessment of Refractory Thrombectomy Cases

We developed criteria to differentiate 3 potential etiologies for refractory thrombectomy: 1) ICAD, 2) IAD, or 3) recalcitrant embolus (Table). We used demographics (age), presentations (headache/neck pain, trauma, recent cardiac surgery), type and number of vascular risk factors (atrial fibrillation versus hypertension, diabetes mellitus, hyperlipidemia, prior stroke/TIA, and smoking), cross-sectional (CT/MR imaging) and angiographic (CTA/MRA/DSA) imaging findings (multivessel disease/peripheral vascular calcifications, intimal flap/subintimal contrast, double lumen,

## Clinical and Imaging Diagnostic Criteria to Differentiate Etiologies of Refractory Thrombectomy

	ICAD	IAD	Recalcitrant Embolus
Demographics	Age $\geq$ 65 Years	Age $\leq$ 55 Years	Any age
Presentations/Risk Factors	$\geq$ 3 Vascular risk factors: hypertension, diabetes mellitus, hyperlipidemia, prior stroke/TIA, smoking	Trauma, acute headache, neck pain	Atrial fibrillation Embolus infarcts: >1 Vascular territory Cardiac surgery Calcified embolus
Imaging Findings	Multivessel disease Peripheral vascular calcifications (extracranial and intracranial ICA)	Intimal flap Double lumen	
Interventional Findings	No stent normalization Residual stenosis >50%	Stent normalization Residual stenosis <50%	No stent normalization Residual stenosis >50% >3 Passes

calcified embolus, embolic distribution of infarcts >1 vascular territory), interventional angiographic findings following stent retriever deployment for thrombectomy, GPI infusion, intracranial angioplasty and/or stenting (>3 passes, stent normalization, degree of residual stenosis). Two independent neurointerventionalists classified each refractory thrombectomy case into at least 1 of the 3 underlying etiologies using this preset criteria (patients did not need to meet all criteria to be classified into 1 category). IAD cases were further classified into spontaneous/iatrogenic dissections versus superimposed IAD related to underlying ICAD pathology (if patients satisfied crossover criteria of both categories). Consensus was achieved in all cases.

### Data and Outcome Analysis

We analyzed patient demographics (age, sex, race/ethnicity), NIHSS presentations, vascular risk factors, ASPECTS, and ELVO locations in the anterior (ICA and/or MCA) versus posterior (basilar artery/PI segment of the PCA) circulation. Interventions were studied with respect to, IV tPA utilization, endovascular times to treatment (last known well to puncture or successful reperfusion), procedural times (puncture to reperfusion), angiographic outcomes (reperfusion grade, device passes, first pass reperfusion), major (neurovascular) or minor complications, and symptomatic intracranial hemorrhage (sICH) as per the European Cooperative Acute Stroke Study (ECASS-3) criteria on 1- to 3-day follow-up CT/MR imaging.<sup>16</sup> Clinical outcomes were assessed using the mRS and mortality at 90 days.

We adjudicated both angiographic and clinical outcomes to assess procedural efficacy. Reported angiographic outcomes were regraded using the modified TICI score and confirmed by a neurointerventionalist blinded to the interventions.<sup>17</sup> Successful reperfusion efficacy was defined as modified TICI  $\geq$ 2b, and complete reperfusion was defined as modified TICI 2c/3. Favorable clinical outcomes were defined as mRS  $\leq$  2, consistent with an independent or functional neurologic status requiring concordance of separate assessments by both stroke neurology and neurointerventional surgery practitioners at 90-day follow-up in the outpatient clinic and/or by telephone. In cases of disagreement, the lower modified TICI and higher mRS scores were used to record angiographic and clinical outcomes, respectively. Safety was assessed by comparing major procedural complications, sICH, and mortality at 90 days in the refractory thrombectomy cohort relative to the standard thrombectomy control group.

### Statistical Analysis

All statistical analyses were performed using SPSS software (Version 24.0, IBM). Continuous variables are presented as medians (minimum-maximum) except for the number of thrombectomy passes that are presented as mean (SD), while discrete and categorical variables are presented as counts and percentages. Continuous variables were compared using the Mann-Whitney test, while categorical and binary variables were compared using the Fisher exact or the  $\chi^2$  test. Univariate analyses compared baseline demographics and procedural, angiographic, and clinical outcomes between standard and refractory thrombectomy groups. Multivariate analysis was performed to identify independent predictors of refractory thrombectomy with the patient's age and vascular risk factors used as variables for a logistic regression model. A *P* value of <.05 was considered statistically significant.

## RESULTS

Mechanical stroke thrombectomy for an anterior or posterior circulation ELVO was performed in 302 consecutive patients (median age, 70 years; range, 20–98 years; 162 women and 140 men), with 25/302 (8.3%) meeting defined criteria for refractory thrombectomy. The Online Supplemental Data provides details on baseline demographics, vascular risk factors, presentations, technical and clinical outcomes of the refractory thrombectomy cohort in comparison with the standard thrombectomy group (*n* = 277/302).

Although there were presentation trends toward younger age (66 versus 71 years, *P* = .09) and lower NIHSS scores (15 versus 17, *P* = .11) in patients experiencing refractory thrombectomy, these did not reach statistical significance. There were no significant differences in presentation times, IV tPA use, ELVO locations, or anterior-versus-posterior circulation occlusions. With respect to vascular risk factors, diabetes was significantly associated with refractory thrombectomy (44% versus 22%; *P* = .02) and the only independent predictor on logistic regression analysis (OR = 2.72; 95% CI, 1.05–7.09; *P* = .04). Conversely, atrial fibrillation was inversely correlated with refractory thrombectomy (16% versus 45.7%; *P* = .005), accounting for the predominant etiology of intracranial vessel wall pathology (ICAD and/or IAD) over recalcitrant/calcified emboli.

Two independent observers classified underlying etiologies for refractory thrombectomy and achieved consensus as per the predefined criteria (Table). ICAD was the most common vessel

wall pathology associated with refractory thrombectomy in 15/25 (60%) patients, an isolated finding in 9 patients, and with superimposed IAD pathology in 6 patients. Five separate spontaneous or iatrogenic intracranial dissections (5/25 or 20%) were identified for a total of 11/25 (44%) IAD etiologies. A minority of refractory cases were determined to be secondary to recalcitrant/calcified emboli in 5/25 (20%).

In the refractory cohort, 4 of 25 (16%) patients were diagnosed with vessel reocclusion within 72 hours after presumed successful thrombectomy without an opportunity for vessel salvage. Despite adjunctive interventions in only 21/25 patients, with GPI in 8/25 (32%), intracranial angioplasty and/or stenting in 13/25 (54%), there were no significant differences in procedural times, successful reperfusion (87.5% versus 90.9%,  $P = .48$ ), complete or first-pass reperfusion, complications, sICH (0% versus 9%,  $P = .24$ ), favorable clinical outcomes (39% versus 48%,  $P = .51$ ), or mortality (13% versus 28.3%,  $P = .14$ ) at 90 days in comparison with the standard thrombectomy group, respectively (Online Supplemental Data). Only 1 patient receiving GPI and rescue intracranial stenting for a recalcitrant embolus developed a minor groin hematoma complication that resolved with conservative management.

In refractory thrombectomy cases that underwent adjunctive interventions, 5 of 8 (62%) patients with isolated ICAD were treated with intracranial angioplasty and/or stenting including 3 patients treated initially with angioplasty alone (2 of whom required rescue stenting for reocclusions either immediately or post-operatively at 2 months). In relatively equivalent proportions, 5/9 (56%) patients with IAD were adequately managed with GPI without intracranial stenting, including 4/6 (67%) IAD patients with underlying ICAD (Online Supplemental Data). However, all 4/4 (100%) patients with recalcitrant/calcified emboli that were eligible for salvage interventions required intracranial stenting, including 1 rescue stent placement after a failed attempt with GPI. At early CTA/MRA follow-up, most adjunctive interventions maintained vessel patency, except for 2/21 (9.5%) patients that were treated with intracranial stenting, but suffered vessel reocclusion or in-stent thrombosis.

## DISCUSSION

Our study indicates that refractory stroke thrombectomy occurs in approximately 8–9% of cases of a representative North American population, a lower prevalence than in previously reported Asian studies.<sup>4</sup> Patients with cerebrovascular risk factors including diabetes and hyperlipidemia may be prone to refractory thrombectomy due to underlying vessel wall pathology such as ICAD and/or IAD versus the less common etiology of recalcitrant emboli.<sup>5</sup> Antiplatelet GPI, intracranial angioplasty and/or stenting are safe and effective adjunctive treatments for vessel salvage, resulting in equivalent clinical outcomes compared with patients undergoing standard thrombectomy.<sup>8,18</sup>

ICAD is a common cause of AIS, accounting for nearly 15%–20% of ELVOs in Asian populations, and it often requires adjunctive treatment to obtain successful recanalization or maintain vessel patency in cases refractory to mechanical thrombectomy.<sup>8,19,20</sup> Lee et al<sup>5</sup> reported a series of patients having undergone thrombectomy, including 24 patients with underlying ICAD, and

identified independent predictors of male sex, hypercholesterolemia, and posterior circulation occlusions. In a smaller series of 14 patients with ELVO related to ICAD, Suh et al<sup>20</sup> also showed a predilection for younger patients, male sex, smoking, and involvement of the M1 segment of the MCA in 93% of cases. Our study supports these statistical trends for younger patients; cerebrovascular risk factors, especially diabetes as an independent predictor of refractory thrombectomy; and an inverse correlation with atrial fibrillation consistent with the nonembolic stroke etiology of in situ vessel wall pathologies (ICAD or IAD). Although there were no significant differences in the prevalence of anterior-versus-posterior circulation occlusions, the MCA remained the most commonly affected vessel in 76% of refractory cases.

Despite extracranial cervical dissections being responsible for 10%–25% of strokes in young and middle-aged patients,<sup>21</sup> IAD is a rare diagnosis accounting for <2% of all AIS.<sup>22,23</sup> However, IAD is an important consideration in cases of refractory thrombectomy secondary to spontaneous or iatrogenic/traumatic etiologies and is probably under-recognized when superimposed in the setting of an acutely ruptured atherosclerotic plaque. Differentiating IAD from ICAD is not always possible during emergent thrombectomy, with significant imaging overlap of both vessel wall pathologies. In a French study, spontaneous IAD was observed in 3% of all mechanical thrombectomy cases; the authors described complete normalization of vessel caliber after stent retriever deployment without irregular clot visualization or extraction as an imaging feature suggestive of IAD pathology.<sup>9</sup> In contrast, Suh et al<sup>20</sup> reported the need for angioplasty and/or stent placement to achieve vessel recanalization, persistent residual stenosis (>70%), and the absence of a dissection (intimal flap on final angiography as imaging criteria indicative of ICAD). While these paradigms may differentiate uncomplicated cases, not all refractory thrombectomy cases conform to a binary classification. In our study, we developed comprehensive criteria, including patient demographics, clinical risk factors, and additional imaging criteria, to improve the assessment and diagnosis of refractory thrombectomy etiologies, including recalcitrant emboli. Cases with overlapping findings were deemed superimposed IAD in the setting of ICAD. Twenty of 25 (80%) refractory thrombectomy cases were attributable to either IAD or ICAD; 6 were diagnosed as combined IAD/ICAD pathology.

Two large cohort Korean studies by Baek et al<sup>18</sup> and Kang et al<sup>24</sup> studied the management of refractory thrombectomy secondary to ICAD, demonstrating that >70% of patients initially fail stent retriever thrombectomy and require adjunctive treatment. Both antiplatelet GPI and intracranial angioplasty/stenting were shown to be safe and effective with equivalent rates of successful reperfusion, functional clinical outcomes, sICH, and mortality in comparison with patients negative for ICAD undergoing standard thrombectomy. Patients treated with GPI required rescue stenting in 9%–46% of cases, and angioplasty and/or stenting groups underwent permanent stenting in 64%–94% of cases. Balloon angioplasty alone in the treatment of symptomatic ICAD is controversial, with some studies suggesting that it is a safe and effective alternative that obviates the need for dual-antiplatelet therapy in the immediate postthrombectomy period of intracranial hemorrhage risk.<sup>25,26</sup> Other studies compared the durability



of endovascular treatment strategies for symptomatic ICAD and identified higher rates of immediate lesion recoil, delayed restenosis (50% versus 7.5%), and iatrogenic dissections with angioplasty alone versus angioplasty in conjunction with stenting.<sup>27</sup> In our cohort, 14 patients experiencing refractory thrombectomy with underlying ICAD (including 6 patients with superimposed IAD) were equivocally salvaged with either GPI or angioplasty and/or stenting. However, in 3 patients who underwent angioplasty alone, 2 required rescue stent placement for immediate or delayed restenosis/occlusion.

Few studies have evaluated treatment options for spontaneous IAD in the setting of ELVO, and suggest the superiority of intracranial stenting over mechanical thrombectomy alone.<sup>9,28,29</sup> Labeyrie et al<sup>9</sup> demonstrated improved recanalization rates and lower rates of residual dissection-related stenosis with intracranial stenting, but >50% rescue recanalization in patients managed conservatively. In our study, 9 patients with IAD (6 with underlying ICAD, 2 iatrogenic, and 1 spontaneous) were managed equivocally with antiplatelet GPI or intracranial stenting and no patients treated with GPI required rescue stenting.

Another less common cause of intracranial ELVO and refractory thrombectomy is recalcitrant/calcified emboli that may be spontaneous or iatrogenic with increasing cardiovascular catheterization procedures in patients with calcified aortic/cervical atherosclerotic plaques or cardiac valves.<sup>30</sup> In a large multicenter European retrospective study, Maurer et al<sup>31</sup> reported a 1.3% (40/2969) prevalence for calcified emboli and noted worse angiographic  $\text{TICI} \geq 2\text{b}$  reperfusion rates (57.5%), functional outcomes (mRS 0–2, 26.5%), and mortality (55.9%) at 90 days. These recalcitrant/calcified emboli are less likely to respond to standard mechanical thrombectomy techniques and often require adjunctive intracranial stenting for successful revascularization.<sup>10,11</sup> In fact, all 4 patients who were eligible for salvage interventions in our cohort of 5 patients with recalcitrant emboli etiologies required intracranial stenting. We suspect that the prevalence of recalcitrant emboli causing refractory thrombectomy may continue to decline with advancements in the technology of flexible distal guide sheaths, large-bore aspiration catheters, and clot-retrieval devices.<sup>32</sup>

Using GPI or thienopyridine P2Y<sub>12</sub> inhibitors during or after stroke thrombolysis/thrombectomy is concerning, with a risk of intracranial hemorrhagic complications from reperfusion or core infarct transformation. However, single (aspirin) and often dual-antiplatelet loading (for intracranial stenting) are mandatory after adjunctive interventions for refractory thrombectomy to maintain vessel recanalization and prevent in-stent thrombosis or reocclusion via platelet aggregation across an acutely ruptured atherosclerotic plaque or dissection flap. In our study, 2/12 patients treated with intracranial stents reoccluded, possibly due to in-stent thrombosis complications from inadequate or delayed antiplatelet loading. This is consistent with previously published literature suggesting an 87% patency rate for rescue stenting after failed mechanical thrombectomy.<sup>33</sup> Immediate and adequate antiplatelet loading should be initiated in refractory thrombectomy interventions, with early P2Y<sub>12</sub> testing recommended to confirm antiplatelet efficacy. Furthermore, novel intravenous P2Y<sub>12</sub> inhibitors such as cangrelor may offer improved therapeutic transition to oral

antiplatelet loading agents and safety over GPI. Several studies have shown no increased incidence of sICH after intracranial stenting and suggest that the benefit of recanalization outweighs the risk of hemorrhage.<sup>8,12,34</sup> Although no patients in our refractory thrombectomy cohort developed sICH complications, the risk should not be underestimated. This may have been partly due to our patient or imaging selection of small-core infarct volumes, intraprocedural cone beam CT scanning to exclude hemorrhagic complications prior to adjunctive interventions with GPI or intracranial angioplasty and/or stenting, and strict hemodynamic control afterwards to limit reperfusion complications.

Our study had several limitations, due to the inherent methodologic weaknesses of retrospective and small sample size studies, to assess rare pathologies such as ICAD, IAD, and recalcitrant/calcified emboli presenting with ELVO. Furthermore, patients experiencing refractory thrombectomy were managed at the discretion of treating neurointerventionalists without a formal protocol or randomization to adjunctive interventions of GPI versus intracranial angioplasty and/or stenting. Hence, we deferred direct comparisons of either underlying etiologies or treatment protocols for refractory thrombectomy. We limited our aims to assessing the prevalence of refractory thrombectomy in a North American population not previously described in the literature and identifying specific etiologies using a comprehensive diagnostic clinical and imaging evaluation. Finally, we compared the safety and efficacy of adjunctive interventions for vessel salvage in patients experiencing refractory thrombectomy with the standard thrombectomy cohort.

## CONCLUSIONS

Refractory stroke thrombectomy occurs with a prevalence of ~8–9% in a North American population, less than in reported Asian populations. Various cerebrovascular risk factors have been associated with refractory thrombectomy. In the current study, diabetes mellitus was shown to be associated with and an independent predictor of refractory thrombectomy and its underlying vessel wall pathologies. ICAD and/or IAD are presumably the most common etiologies for ELVO presentations refractory to mechanical thrombectomy and, less commonly, recalcitrant/calcified emboli. Both antiplatelet GPI and intracranial angioplasty/stenting are safe and effective adjunctive interventions for vessel salvage in the refractory thrombectomy setting, with equivalent clinical outcomes to standard thrombectomy.

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