Original research

Rescue intracranial permanent stenting for refractory occlusion following thrombectomy: a propensity matched analysis

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ABSTRACT

Background Rescue intracranial stenting (RIS) can be used in refractory large vessel occlusion (LVO) after mechanical thrombectomy (MT). We aimed to assess the safety and efficacy of RIS versus a propensity matched sample of patients with persistent LVO.

Methods We retrospectively analysed a multicenter retrospective pooled cohort of patients with anterior LVO (2015–2021) treated with MT, and identified patients with at least three passes and a modified Thrombolysis In Cerebral Infarction (mTICI) score of 0 to 2a. Propensity score matching was used to account for determinants of outcome in patients with or without RIS. The study outcomes included 3 months modified Rankin Scale (mRS) and symptomatic hemorrhagic transformation (HT).

Results 420 patients with a refractory anterior occlusion were included, of which 101 were treated with RIS (mean age 69 years). Favorable outcome (mRS 0–2) was more frequent in patients with a patent stent at day 1 (53% vs 6%, P<0.001), which was independently associated with an early dual antiplatelet regimen (P<0.05). In the propensity matched sample, patients treated with RIS versus without RIS had similar rates of favorable outcomes (36.8% vs 30.3%, P=0.606). Patients with RIS showed a favorable shift in the overall mRS distributions (common adjusted OR 0.74, 95% CI 0.60 to 0.91, P=0.006). Symptomatic HT was marginally more frequent in the RIS group (9% vs 3%, P=0.07), and there was no difference in 3-month mortality.

Conclusion In selected patients with a refractory intracranial occlusion despite at least three thrombectomy passes, RIS may be associated with an overall shift towards more favorable clinical outcome, and no significant increase in the odds of symptomatic HT or death.

INTRODUCTION

Mechanical thrombectomy (MT) has a compelling efficacy to improve the outcome of patients with acute ischemic stroke (AIS) due to emergent large vessel occlusion (LVO). The efficacy of MT to improve functional outcome is strongly linked to the completeness and swiftness of revascularization. A successful revascularization is commonly defined as a modified Thrombolysis In Cerebral Infarction (mTICI) score of 2b or above, corresponding to a partial filling of at least 50% of the target territory. Yet, 12–34% of patients treated with MT are not adequately revascularized, frequently due to the failure to reach the clot, and in 3–9% no modification of the occlusion configuration is obtained after clot retrieving maneuvers. These ‘refractory’ occlusions can result from inadequate device selection or technical considerations, clot composition, or underlying vessel wall conditions, most notably intracranial atherosclerosis.

WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ Rescue intracranial stenting (RIS) can be used for obtaining or maintaining vessel permeability in refractory large vessel occlusion after thrombectomy for acute ischemic stroke.

WHAT THIS STUDY ADDS
⇒ Using a propensity matched sample of patients with persistent occlusion, we showed that RIS was associated with a significantly more favorable functional outcome, and with no increase of symptomatic hemorrhagic transformation. Functional independence was significantly higher in patients with patent stents at day 1, and patients under dual antiplatelet therapy had notably higher rates of stent patency at day 1.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ These results call for the consideration of RIS as a possible strategy in selected patients with refractory occlusion after mechanical thrombectomy, and for the conduct of a randomized trial.
Ischemic stroke

Patients with refractory occlusions harbor a very severe prognosis, in terms of functional outcome and mortality. Intracranial stenting is increasingly reported in acute conditions as a rescue technique for maintaining vessel permeability. Rescue intracranial stenting (RIS) poses several challenges in the context of AIS, most notably for the management of antithrombotic regimens. Indeed, the risk of hemorrhagic transformation (HT) is likely increased by the initiation of acute antithrombotics and may offset the benefits of sustained adequate revascularization following stent placement.

Among patients with refractory LVO, defined as mTICI 0 to 2a, despite at least three passes of clot retrieving maneuvers, we aimed to assess the safety and efficacy of RIS versus no RIS in propensity matched samples.

PATIENTS AND METHODS
Study design, inclusion, and exclusion criteria
Sample identification
We used data from a multicenter retrospective pooled cohort of patients with proximal vessel occlusion of the anterior circulation treated between 2015 and 2021 with MT. Patients were identified in two ways. Patients who received RIS were retrospectively identified in the prospective MT stroke databases at 14 university hospitals in France, using the trainee-led research network Jeunes en Neuroangiologie Interventionnelle (JENI). The control population was constituted by retrospectively querying the Endovascular Treatment of Ischemic Stroke (ETIS) registry for patients with TICI 0 to 2a following MT. ETIS, described in detail previously, is a nationally representative, prospective registry of patients treated with MT.

Inclusion and exclusion criteria
We included consecutive adult patients with AIS, a proximal vessel occlusion of the anterior circulation, defined as an internal carotid or an M1 segment of the middle cerebral artery (MCA) occlusion, that met the following criteria: (1) at least three passes of clot retrieving maneuvers, using a stent retriever, an aspiration catheter or combined; and (2) an mTICI score of 2a, 1 or 0 following these passes in the RIS population, or an mTICI score of 2a, 1 or 0 at the end of the procedure in the control population. Tandem occlusions, isolated internal carotid artery (ICA) occlusions, and posterior circulation LVO were excluded.

Endpoints
Primary and secondary outcomes were assessed in the propensity matched samples. The primary endpoint was the proportion of patients with a favorable functional outcome at 3 months using the modified Rankin Scale (mRS), a favorable outcome being defined as an mRS of 0–2.

The secondary outcomes were: (1) ordinal shift in mRS in RIS versus no RIS patients; (2) symptomatic HT, defined as the association of any type of intracerebral hemorrhage (ICH) on brain imaging with a National Institutes of Health Stroke Scale (NIHSS) score >4 points from the value at baseline or the lowest value in the first 7 days, or that led to death or was identified as the predominant cause of the neurological deterioration according to the European Cooperative Acute Stroke Study II (ECASS II) criteria; and (3) target vessel patency at day 1.

This report was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Baseline and procedural data
Baseline, demographics, procedural and follow-up data were retrieved from electronic health records at each site by co-investigators.

The type of MT or thromboaspiration device, and utilization of a balloon catheter, as the first tools were at the operator’s discretion in each center. Similarly, due to the retrospective nature of data acquisition, the decision to proceed to RIS as well as the acute initiation of antithrombotics, and their postoperative management, was done on a case-by-case basis at the treating team’s decision.

The following data were collected in each participating center: mTICI before MT, anesthetic management, number of passes before stenting, angiographic evaluation of the vessel patency when and if a stentriever was deployed, mTICI before stent implantation, type (name and size) of implanted stent used, stent location, intraoperative antithrombotic regimen, follow-up antithrombotic regimen, acute stent thrombosis (intraoperative) and delay until this event, and stent patency at day 1.

Post-procedure follow-up outcomes
For safety assessment, HT and symptomatic intracranial hemorrhage according to ECASS-II, delay between stenting and control imaging, modality for control imaging, stent patency at control imaging, delayed (postoperative) stent thrombosis, neurological deterioration due to delayed stent thrombosis, delay until deterioration, 24-hour NIHSS, NIHSS at discharge, and mRS at 3 months were recorded. The stroke etiology was determined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, at each contributing center.

Standard protocol approvals, registrations, and patient consent
As for all non-interventional retrospective studies of de-identified data, written informed consent was waived and a commitment to compliance (Reference Methodology CPMR-4) was filed to the French data protection authority (CNIL) before data centralization, in respect of the General Data Protection Regulation. Patients and proxies were informed they could oppose the use of their data for research purposes.

Statistical analysis
Continuous variables were summarized using means (SDs) or medians (IQRs) where appropriate, and discrete variables were summarized using counts (percentages). The χ² test, Fisher’s exact test, t-test, and Mann-Whitney test were used as appropriate for the univariate analysis, with a P value <0.05 (two-tailed) as the threshold for statistical significance.

In the entire sample of patients treated with RIS, multivariable regression models were used to determine factors that were independently associated with study endpoints. Variables associated with the outcome in univariate analysis (P<0.1) were entered into nominal and ordinal models and backward elimination was then used to remove non-significant variables (P>0.05).

To control all potential bias introduced by confounding factors between patients treated by RIS and the controls, a propensity score matching generated by logistic regression was conducted. Patients were matched by using a ratio of 1:1 with a nearest neighbor-matching algorithm without replacement. A caliper of width equal to 0.2 of the SD of the propensity score logit was used. Clinical variables included as contributors to the propensity score were pre-stroke mRS, age, baseline NIHSS, baseline
Alberta Stroke Program Early CT Score (ASPECTS), and the delay between onset or last seen well (LSW) and groin puncture. In the matched subset we analyzed variables associated with symptomatic HT and a favorable functional outcome (dichotomous), and mRS by an ordinal shift analysis using the same framework as in the unmatched RIS sample (uni- then multivariable models).

A sensitivity analysis was performed using the same approach, after excluding patients with a TICI 2a reperfusion to assess only those with a TICI 0 or a TICI 1.

Analyses were done using JMP Pro 14 (SAS Institute Inc, Cary, NC) software.

RESULTS
Study population and subgroups
During the study period, through the trainee-led research network JENI, 101 patients treated with RIS at 14 centers for a refractory anterior LVO despite at least three intracranial passes were retrospectively identified. Among the 10 738 screened patients in the ETIS registry, 10 419 were excluded, mostly (7189, 69%) due to adequate revascularization, leaving 319 patients with a persistent occlusion at the end of the thrombectomy procedure, despite at least three passes. A total of 420 patients were therefore included in the unmatched study samples, including 101 with RIS. See the flowchart for patient selection details in figure 1.

Analysis of patients in the unmatched RIS subgroup
The characteristics of all 101 patients with RIS analyzed are described in online supplemental table A. Patients were median 69 years old (IQR 57.5–76) and 44% were females. The median NIHSS at baseline was 12 (IQR 8–17) and 72% had an occlusion of the M1 segment of the MCA. There was a median of 3 passes before permanent stenting (IQR 3–4), which was performed under general anesthesia in 57 patients (56.4%).

The median number of individual technique passes before RIS was 1 (IQR 1–2) with a stent, 2 (IQR 1–2) with contact aspiration alone, and 2 (IQR 2–4) with a combined (stent+distal aspiration) technique.

Vessel patency during stent retriever deployment was assessed in 77 patients, of which 74/77 (96.1%) showed antegrade flow. Dual antiplatelet therapy (DAPT) was acutely initiated in 34.7% of patients, and 4% of patients received heparin. The list of implanted stents is provided in online supplemental table B.

Nineteen patients showed perioperative intra-stent thrombosis (18.8%), an event that was similarly frequent in patients with or without acute DAPT (19% vs 19%, P=1.00). At the end of the procedure, 62% of patients with RIS had a modified TICI score of 2b–2c or 3 online supplemental file 1.

Outcomes in the unmatched RIS group
Day 1 vessel patency, and hemorrhagic transformation
Vessel patency was assessed at day 1 in the entire sample, and 68 stents (67.3 %) were patent. Delayed stent thrombosis had occurred in 22 of 95 patients with a patent stent at the end of the procedure, and five occluded stents at the end of the procedure were patent at day 1. Variables associated with day 1 stent patency are detailed in table 1.

Female sex, absence of intravenous thrombolysis, and immediate postoperative or perioperative initiation of a DAPT regimen were more frequent in patients with a patent stent at day 1 (all P<0.05). There were similar rates of HT, whether symptomatic (P=0.304) or not (P=0.437), in patients with an occluded or patent stent at day 1. Although non-significantly different from the single antiplatelet regimen, all symptomatic HTs occurred in patients receiving DAPT (100% vs 0%; P=0.451). There was major heterogeneity in the antiplatelet regimen used at the acute phase of RIS (see online supplemental figure 1), and we identified 29 different strategies for antiplatelet agent (APA) management, including 17 different APA combinations at the acute phase and

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Table 1  Day 1 vessel patency in the RIS group, and univariate associations

<table>
<thead>
<tr>
<th>Variable</th>
<th>D1 stent occluded (n=33)</th>
<th>D1 stent patent (n=68)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>70.3±13.9</td>
<td>64.9±15.4</td>
<td>0.082</td>
</tr>
<tr>
<td>Female sex</td>
<td>19 (57.6%)</td>
<td>25 (36.8%)</td>
<td>0.056</td>
</tr>
<tr>
<td>Current smoking (Y)</td>
<td>5 (15.2%)</td>
<td>21 (30.9%)</td>
<td>0.185</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (30.3%)</td>
<td>16 (23.5%)</td>
<td>0.763</td>
</tr>
<tr>
<td>Hypertension (Y)</td>
<td>13 (39.4%)</td>
<td>32 (47.1%)</td>
<td>0.537</td>
</tr>
<tr>
<td>Baseline NIHSS</td>
<td>13±5.8</td>
<td>12.3±6.2</td>
<td>0.590</td>
</tr>
<tr>
<td>IV thrombolysis (Y)</td>
<td>17 (51.5%)</td>
<td>19 (27.9%)</td>
<td>0.027</td>
</tr>
<tr>
<td>Occlusion site (MCA)</td>
<td>27 (81.8%)</td>
<td>46 (67.6%)</td>
<td>0.103</td>
</tr>
<tr>
<td>Vessel patent on SR deployment (Y)</td>
<td>28 (84.8%)</td>
<td>46 (67.6%)</td>
<td>0.081</td>
</tr>
<tr>
<td>Acute DAPT (Y)</td>
<td>9 (27.3%)</td>
<td>26 (38.2%)</td>
<td>0.369</td>
</tr>
<tr>
<td>Acute heparin</td>
<td>1 (3%)</td>
<td>3 (4.4%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Follow-up DAPT (Y)</td>
<td>21 (63.6%)</td>
<td>63 (92.6%)</td>
<td>0.013</td>
</tr>
<tr>
<td>Favorable outcome (Y)</td>
<td>2 (6.1%)</td>
<td>36 (52.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any HT</td>
<td>8 (24.2%)</td>
<td>12 (17.6%)</td>
<td>0.437</td>
</tr>
<tr>
<td>Symptomatic HT (Y)</td>
<td>0 (0%)</td>
<td>4 (5.9%)</td>
<td>0.304</td>
</tr>
<tr>
<td>DAPT, dual antiplatelet therapy; HT, hemorrhagic transformation; IV, intravenous; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; RIS, rescue intracranial stenting; SR, stent retriever; Y, yes.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
seven differing strategies for follow-up antithrombotic regimens (single to double APA, single P2Y12 inhibitor to double non-P2Y12, etc).

Functional outcome
In the unmatched samples, the overall proportion of favorable outcome was 24.7%, and favorable outcome was more frequent in patients with RIS (38% vs 20%, P < 0.001).

In the RIS group, patients had significantly higher rates of favorable outcome with a patent stent at day 1 (53% vs 6%, P < 0.001). Favorable outcome was associated with less frequent acute or delayed stent thrombosis (5% vs 36% in patients with unfavorable outcome, P < 0.001), younger age (59 ± 15 vs 70 ± 14, P < 0.001), lower baseline NIHSS (P = 0.009), longer onset or LSW to imaging, and acute initiation of DAPT (50% vs 27%, P = 0.029). After multivariable adjustment, age, baseline NIHSS, delay until imaging as well as delayed thrombosis (adjusted odds ratio (aOR) 9.7, 95% confidence interval (95% CI) 1.9 to 50.2, P < 0.001) remained significantly associated with clinical outcome. The antiplatelet regimen did not.

The stroke etiology was dominated by large artery atherosclerosis (44%), followed by intracranial atherosclerotic disease (24%) and undetermined etiology (12%), not associated with outcome or stent patency (see details in online supplemental figure 4).

Propensity score matching and outcome comparisons
After propensity score matching using pre-stroke mRS status, age at ictus, baseline NIHSS and ASPECTS, and delay since onset or last known well for unwitnessed strokes as score contributors, the matched sample comprised 152 patients, with 76 patients in the RIS arm and 76 in the persistent occlusion arm. Detailed patient characteristics in each arm are presented in table 2. There were no baseline differences between each propensity arm, except for a more frequent history of diabetes (26.3% vs 11.8%, P = 0.003), as well as a history of stroke or transient ischemic attack (33% vs 17%, P = 0.035), in the RIS arm.

Hemorrhagic transformation
An HT occurred in 45% of patients and was more frequent in patients with no RIS (37% vs 22%, P = 0.049). Symptomatic HT occurred in nine patients and was marginally more frequent in patients with no RIS (9% vs 3%, P = 0.07). Due to the low number of occurrences of symptomatic HT, we did not perform a multivariable adjustment to assess determinants. Neither HT nor symptomatic HT were significantly associated with clinical outcome.

Clinical outcome
A total of 51 (33.6%) patients achieved a favorable functional outcome, with no differences across matched groups (P = 0.606) using this dichotomous outcome.

In univariable analysis, favorable outcome was associated with younger age (P < 0.001) and a smaller baseline NIHSS (P = 0.006). Other variables did not influence the outcome, including RIS (32.4% favorable outcome vs 36.8% in the no RIS group, P = 0.606). In a multivariable nominal model, with forced adjustment for RIS, there was no independent association between RIS and favorable outcome (aOR 1.26, 95% CI 0.60 to 2.62, P = 0.534).

Using an ordinal shift analysis in the entire matched sample, RIS had a favorable shift in the overall mRS distributions (common aOR 0.74, 95% CI 0.60 to 0.91, P = 0.006) along with lower NIHSS (P < 0.001) and lower age (P = 0.007).

When comparing the subgroup of RIS patients with a patent stent at day 1 (49/76, 64%) to those with no RIS, patients in the RIS group had a significantly higher rate of favorable outcome (55.1% vs 32.4%, P = 0.01). The association between RIS and a favorable functional outcome remained significant after adjustment for age and NIHSS (aOR 1.42, 95% CI 1.17 to 3.68, P = 0.004).

There were no differences in 3-month mortality in matched RIS and no RIS groups (27% vs 23%, P = 1.000). The mRS of matched and unmatched groups are presented in figure 2. A post-hoc subgroup analysis was performed by stratifying per baseline occlusion (MCA or ICA), and is presented in details in online supplemental figure 2. There was a significantly better outcome in patients treated with RIS in both matched and unmatched samples in patients with ICA occlusions, and a similar association was also found in the unmatched sample of patients with MCA occlusions (all P < 0.05). In the matched sample of patients with MCA occlusions, there was no association between RIS and a better outcome (P = 0.75), but mortality was significantly higher in the no RIS group (24% vs 16%, P = 0.03).

All results were similar (effect, significance) after excluding patients with TICI 2a from the RIS sample.

<table>
<thead>
<tr>
<th>Table 2 Univariate comparison of propensity matched arms</th>
<th>No RIS (n=76)</th>
<th>RIS (n=76)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>68.0±16.2</td>
<td>67.4±13.7</td>
<td>0.817</td>
</tr>
<tr>
<td>Female sex</td>
<td>40 (52.6%)</td>
<td>33 (43.4%)</td>
<td>0.330</td>
</tr>
<tr>
<td>Past medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>49 (64.5%)</td>
<td>45 (59.2%)</td>
<td>0.445</td>
</tr>
<tr>
<td>Current smoking</td>
<td>18 (23.7%)</td>
<td>18 (23.7%)</td>
<td>0.900</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (11.8%)</td>
<td>20 (26.3%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Prior stroke or TIA</td>
<td>13 (17.1%)</td>
<td>25 (32.9%)</td>
<td>0.035</td>
</tr>
<tr>
<td>Prior mRS</td>
<td>0.3±0.6</td>
<td>0.3±0.7</td>
<td>0.807</td>
</tr>
<tr>
<td>Index stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline NIHSS</td>
<td>12.5±6.9</td>
<td>12.6±6.1</td>
<td>0.873</td>
</tr>
<tr>
<td>Baseline ASPECTS</td>
<td>8.2±1.6</td>
<td>8.2±1.5</td>
<td>1.000</td>
</tr>
<tr>
<td>Occlusion level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>14 (18.4%)</td>
<td>20 (26.3%)</td>
<td>0.331</td>
</tr>
<tr>
<td>MCA</td>
<td>62 (81.6%)</td>
<td>56 (73.7%)</td>
<td>0.062</td>
</tr>
<tr>
<td>Known symptoms onset</td>
<td>43 (56.6%)</td>
<td>55 (72.4%)</td>
<td>0.062</td>
</tr>
<tr>
<td>LSW or onset to imaging (mins)</td>
<td>190.9±140.5</td>
<td>183.8±127.9</td>
<td>0.744</td>
</tr>
<tr>
<td>Imaging to groin (mins)</td>
<td>127.7±77.4</td>
<td>136.6±106.1</td>
<td>0.567</td>
</tr>
<tr>
<td>IV thrombolysis before MT</td>
<td>34 (44.7%)</td>
<td>30 (39.5%)</td>
<td>0.622</td>
</tr>
<tr>
<td>Number of SR passes</td>
<td>3.9±1</td>
<td>3.8±1.6</td>
<td>0.791</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1 vessel patency</td>
<td>??</td>
<td>??</td>
<td>??</td>
</tr>
<tr>
<td>Any HT</td>
<td>28 (36.8%)</td>
<td>17 (22.4%)</td>
<td>0.049</td>
</tr>
<tr>
<td>Symptomatic HT</td>
<td>7 (9.2%)</td>
<td>2 (2.6%)</td>
<td>0.071</td>
</tr>
<tr>
<td>Favorable outcome</td>
<td>23 (30.3%)</td>
<td>28 (36.8%)</td>
<td>0.606</td>
</tr>
</tbody>
</table>
| ASPECTS, Alberta Stroke Program Early CT Score; HT, hemorrhagic transformation; ICA, internal carotid artery; IV, intravenous; LSW, last seen well; MCA, middle cerebral artery; mRS, modified Rankin Scale; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; SR, stent retriever; TIA, transient ischemic attack.

Ischemic stroke
DISCUSSION

In this large propensity matched sample of patients treated with RIS for a refractory anterior LVO following failed MT despite at least three passes, we found (1) that a notable proportion of patients treated with RIS achieved a favorable functional outcome, (2) that RIS was associated with better functional outcomes in shift analyses when compared with matched controls, and (3) that RIS was associated with fewer symptomatic ICHs (despite a large proportion of patients being treated with an acute DAPT regimen). These findings shed light on the safety and relevance of RIS for refractory mechanical occlusion.

Among plausible issues to improve the outcome of patients treated for an AIS due to LVO, RIS has been increasingly used and reported to increase the rates of recanalization after standard MT failure or early recurrences,3-6,12 and several dedicated trials are underway.31

Recent works have reported RIS safety and efficacy in approaching settings. Yet, the main difference between previous publications and the present analysis was that we aimed to match our large group of patients with RIS with the most relevant group of patients that were treated with MT, and with a true refractory occlusion (that is, not the failure to reach the clot). For this purpose, we chose a minimum of three clot retrieving maneuvers in the control group, using the definition of refractory thrombectomy already employed14,15; in practice, rescue maneuvers are rarely performed before two or three attempts to remove the clot.1,16-18 That led to the exclusion of 436 patients for which the main reason for failure was not a refractory occlusion but failure to reach the clot (eg, 0 number of passes). Indeed, we believe that in patients for which the clot is not reached, the question of RIS is irrelevant. Further, stenting for refractory occlusion may not yield similar results to that of stenting for a presumed underlying stenosis. Although there is likely a strong interplay between both entities, we chose to restrict our analyses to true refractory cases.

This pragmatic choice may explain the main differences between our work and previous studies. Indeed, in an aggregate level meta-analysis, Premat et al found RIS to be associated with improved clinical outcome at 90 days and lower mortality compared with no recanalization,7 which was not the case in our matched sample using mRS 0–2 as a dichotomous outcome measure. Similarly, in a more recent work by Mohammad et al,8 that used propensity matching, the authors found RIS to be significantly associated with higher rates of functional independence and lower rates of mortality at 3 months. It is likely that in these works, the comparator group (failed revascularization) was slightly biased towards worse outcomes, in that patients for which the clot was not reached or for which fewer than three passes of MT were attempted may have had less favorable baseline or anatomical characteristics that impeached or discouraged the operator to pursue the procedure further. This bias is inherent to retrospective works investigating procedures with yet unconfirmed nefarious or beneficial effects, for which the operator’s decision to proceed is likely influenced by confounders that are poorly evaluated a posteriori.

Importantly, we found that patients with a patent stent at day 1 had significantly higher rates of functional independence, when compared with both patients with occluded stents, and patients for which RIS was not attempted. This result is among the most stable findings in previous studies3,6,19-21 highlighting the critical importance of antithrombotic management when an RIS is attempted to maintain stent patency, and the necessary trade-off with hemorrhagic risk in patients with a particularly high risk of HT. This endpoint does not appear in other recent studies on the subject,48 and appears to be a determining factor in the patient’s clinical evolution.

In that regard, our results do provide additional insight on the association between antithrombotic management and the risks of acute or delayed stent occlusion following RIS and the risk of symptomatic HT. First, among the 95 patients with a patent stent at the end of the procedure, a delayed thrombosis occurred in 22 patients (23.2%) and was almost three times more frequent in patients with a single antiplatelet follow-up regimen, intuitively pleading for the acute initiation of DAPT. Further, while all symptomatic HT occurred in patients with a DAPT regimen, this finding was not statistically more frequent than in patients with a single antiplatelet. Premat et al found that an aggressive antiplatelet regimen did not seem to result in increased rates of symptomatic ICH with low heterogeneity (OR 0.68, 95% CI 0.37 to 1.27, P=0%).3 Of note, the rates of symptomatic ICH in previous works investigating RIS were of similar magnitude, though slightly higher than that found in our analysis (6%). Wareham et al found22 symptomatic ICH to be 12% (95% CI 8% to 17%), while Stracke and colleagues19 and Forbrig et al23 found rates of 11% and 12%, respectively. These works have not linked DAPT with higher rates of symptomatic ICH in the context of RIS. In a recent work by Back et al,24 in which almost 80% of patients were treated with tirofiban infusion (a glycoprotein IIb/IIIa inhibitor), and above 95% with follow-up DAPT, authors reported only 3% of symptomatic HT, in line with the low rates of clinically relevant hemorrhage despite the aggressive antithrombotic regimen.

An important consideration when analyzing these rates of symptomatic HT, and the counterintuitive absence of higher symptomatic HT in the group of patients for which no RIS was attempted, is that the core ischemic volume is a very strong determinant of the risk of HT. In turn, failure to revascularize being associated with larger final ischemic volumes, it is expected that patients with refractory occlusions will have high risks of HT, and that in patients with RIS, the additional risk bore by DAPT initiation may be partly counterbalanced by an ischemic core reduction volume.

Expectedly, there was an important variability in the use of antiplatelet drugs in our series (online supplemental figure 1). There was an equal use (44%) of single and dual antiplatelet acute treatment, and acetylsalicylic acid (ASA) alone or abciximab alone were the most frequent treatment regimens at the
acute phase (21% both). This heterogeneity in antithrombotic management has recently been reported on a national scale in France by Caroff and colleagues, and is a major lead for improvement in such complex neurointerventional procedures. Interestingly, four patients received cangrelor, a promising agent in RIS due to its immediate action, and reversibility.

Of note, the results of Gao et al in a recent randomized clinical trial may not be transposable to the acute setting described therein. The authors indeed showed in a sample of patients with symptomatic severe intracranial atherosclerotic stenosis that the addition of percutaneous transluminal angioplasty and stenting to medical therapy, compared with medical therapy alone, resulted in no significant difference in the risk of stroke or death. Indeed, their results only included patients with atheromatous stenoses, low volumes of ischemia since transient ischemic attack or non-disabling, non-perforator (defined as non-brainstem or non-basal ganglia end artery) territory ischemic stroke, and in elective patients with ideal APA medication.

These patients differ in many ways from those included in our sample, with emergent symptomatic LVO, and likely differing etiologies for the refractory nature of their occlusions. Similarly, our work differs from that of Al Kasab and colleagues, by the fact that the authors investigated the role of RIS in LVO for patients with underlying intracranial atherosclerosis, while our sample comprised less than a quarter of patients with confirmed intracranial atherosclerosis. In that sense, our results are complementary to that of Al Kasab et al, that showed the benefit of RIS for patients with reocclusion or residual stenosis following successful thrombectomy, while we showed similar results in a population of patients with refractory occlusion.

Importantly, the etiology is most often unknown during thrombectomy and, except for cases of identified stenosis, the exact physiopathology of refractory occlusion is commonly unknown. The underlying causes are likely probably diverse, including vessel condition (dissection, atherosclerosis), clot characteristics of varying compositions, and technical strategy or operative.

The understanding of the underlying cause for the failure to revascularize was not our objective and the study was in turn not designed to address this question. Yet it is likely that these varying mechanisms may also explain the varying outcomes following stenting than that found in a more homogenous sample of mostly Asian patients with almost exclusively intracranial atherosclerosis.

Finally, as the field evolves, it can also be assumed that other therapeutic alternatives may become widely available in the future, such as devices for fibrin-rich tough clots recently evaluated in the Post Marketing Study of Patients to Evaluate NIMBUS Revascularization Effectiveness With Challenging Occlusions (SPERO) Study.

Our study has several limitations. First, as a retrospective analysis of prospectively collected, cross-sectional hospital-based cohorts it is subject to the important limitations inherent in such a design. Most importantly, the risk of selection bias for the group of patients that underwent RIS is hard to assess and may have biased the sample towards more favorable patient profiles, that were deemed more likely to benefit from a more aggressive therapeutic approach. We aimed at limiting this bias by using a propensity matched analysis based on strong determinants of poorer outcome (age, NIHSS, treatment delays, etc). Second, this analysis was restricted to patients who had benefited from at least three intracranial passes, leading to uncontrolled confounders. There is not an agreed number of passes before stenting, and some interventionalists may stent after a failed first pass, but we choose to follow a more accepted definition of refractory occlusion. Third, patients with posterior circulation occlusions were excluded to prevent confounding our endpoint (functional outcome) with basilar occlusions that have distinctly worse outcomes, and for which the pathophysiology for refractory occlusion may differ due to varying anatomy and etiological considerations. Fourth, the constitution of the RIS group was based on the retrospective query of local databases, with a risk of memory bias and lack of exhaustivity. We also were unable to read all imaging centrally, and relied on local interpretation, likely introducing heterogeneity in the outcome assessment, despite the experience of all co-investigators. Similarly, we were not able to collect precise procedural information regarding the method for stenting, and the need for presenting angioplasty.

Among important strengths is the number of RIS cases reported in our analysis, and the use of carefully conducted propensity matching to compare RIS cases against a relevant subgroup of controls. To our knowledge this is indeed the first study to conduct this comparison against patients for which the clot was reached, and in which attempts at retrieving the clot were performed.

**CONCLUSION**

In selected patients with a refractory intracranial occlusion despite at least three MT passes, rescue intracranial stenting may be associated with an overall shift towards more favorable outcome, and no significant increase in the odds of symptomatic HT. The optimal antithrombotic regimen in this situation remains undetermined, but patients receiving DAPT had notably higher rates of stent patency at day 1, and functional independence rates were significantly higher in patients with patent stents. A pragmatically designed randomized trial, investigating RIS after failed MT, is in order.

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Ischemic stroke

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