Biomarkers of Technical Success After Embolectomy for Acute Stroke

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Abstract

Purpose of the Review
Stent retrievers and large-bore aspiration catheters have doubled substantial reperfusion rates compared to first-generation devices. This has been accompanied by a 3-fold reduction in procedural time to revascularization. To measure future thrombectomy improvements, new benchmarks for technical efficacy are needed. This review summarizes the recent literature concerning biomarkers of procedural success and harm and highlights future directions.

Recent Findings
Expanded Treatment in Cerebral Ischemia (eTICI), which incorporates scores for greater levels of reperfusion, improves outcome prediction. Core laboratory–adjudicated studies show that outcomes following eTICI 2c (90%–99% reperfusion) are superior to eTICI 2b50 and nearly equivalent to eTICI 3. Moreover, eTICI 2c improves scale reliability. Studies also confirm the importance of rapid revascularization, whether measured as first pass effect or procedural duration under 30 minutes. Distal embolization is a complication that impedes the extent and speed of revascularization, but few studies have reported its per-pass occurrence. Distal embolization and emboli to new territory should be measured after each thrombectomy maneuver. Collaterals have been shown to be an important modifier of thrombectomy benefit. A drawback of the currently accepted collateral grading scale is that it does not discriminate among the broad spectrum of partial collateralization. Important questions that require investigation include reasons for failed revascularization, the utility of a global Treatment in Cerebral Ischemia scale, and the optimal grading system for vertebrobasilar occlusions.

Summary
Emerging data support a lead technical efficacy endpoint that combines the extent and speed of reperfusion. Efforts are needed to better characterize angiographic measures of treatment harm and of collateralization.

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Since the publication of the consensus statement on angiographic revascularization grading in 2013, major strides have been made in the field of intraarterial stroke therapy (IAT). Stent retrievers and large-bore aspiration catheters have doubled the rate of substantial reperfusion (modified Treatment in Cerebral Ischemia [mTICI] score 2b/3, defined as at least 50% or greater reperfusion of the ischemic territory) compared to the first-generation Merci device. By virtue of these tools, recent pivotal trials demonstrated the benefit of mechanical thrombectomy for improving disability in patients with acute ischemic stroke presenting with anterior circulation large vessel occlusions.

With greater clinical experience and the emergence of newer devices and techniques, published rates of mTICI 2b/3 have steadily increased up to 90%, and have been accompanied by faster times to reperfusion. Accordingly, mTICI 2b/3 has become an outdated measure of technical success, and a new benchmark is needed to capture improvements in stroke intervention. This narrative review summarizes recent data concerning the 2 principal determinants of effective intraarterial treatment: the extent of tissue reperfusion and the speed of revascularization. Subsequently, angiographic measures of treatment harm and collateral circulation are discussed, followed by a closing section on future directions.

**Extent of Reperfusion: TICI Grading**

Revascularization consists of 2 closely related measures: recanalization of the target arterial occlusion and reperfusion of the target downstream territory. Recanalization is necessary for reperfusion, but it is not sufficient. If a device clears the target vessel occlusion but causes thrombus fragmentation and distal embolization, downstream regions of ischemia will persist. For this reason, the extent of tissue reperfusion is the primary measure of device and treatment efficacy.

Initial endovascular studies utilized the Thrombolysis in Myocardial Ischemia (TIMI) scale to grade reperfusion, but it was inconsistently applied, including in some cases to measure recanalization. The main limitation of TIMI for grading cerebral reperfusion is its emphasis on the speed of antegrade flow rather than the extent of reperfusion. The preferred Treatment in Cerebral Ischemia (TICI) scale was first described in 2003 and assigned scores based on the percentage of the target downstream ischemic territory that was reperfused. In its original formulation, TICI 2b (oTICI 2b) was defined as >67% but less than complete reperfusion. It was later modified (mTICI) by the Interventional Management of Stroke (IMS) trial investigators so that mTICI 2b constituted ≥50%–99% reperfusion. The modified 2b/3 threshold was endorsed by the 2013 consensus statement due to more evidence supporting the clinical benefit of achieving mTICI 2b/3 compared to oTICI 2b/3. Increasingly, studies are reporting TICI 2c to indicate near-complete or ≥90%–99% reperfusion. To avoid confusion regarding TICI nomenclature, the expanded TICI (eTICI) scale was created to incorporate all the previously reported reperfusion thresholds along with explicit threshold criteria (Table 1). Figures 1–4 illustrate examples of partial reperfusion scoring in the eTICI scale.

**Operational Definitions**

Standardized TICI grading is critical for establishing high-quality endovascular registries, for benchmarking endovascular care across comprehensive stroke centers, and for ensuring comparability between studies of devices and procedural techniques, the latter being particularly important when prospective device registration studies are designed based on a historical comparator. The 2013 consensus statement sought to standardize the operational rules for grading reperfusion.

Operationally, reperfusion is the restoration of antegrade blood flow that results in a capillary or parenchymal blush on
angiography. For grading reperfusion extent, angiography in the lateral projection is critical because it provides a clear view of the entire middle cerebral artery (MCA) territory. The anterior-posterior projection alone cannot be used to assign a TICI score due to the superimposition of the MCA branches distal to the limen insulae (point where the MCA enters the sylvian fissure).

There has been confusion around the choice of the target downstream territory (i.e., the denominator for calculating percent reperfusion). Some authors have argued that TICI grading is defined based on the perfusion status of the entire MCA territory. Accordingly, TICI scoring would be suitable only for grading reperfusion of M1 or carotid terminus occlusions, and would be useless in more distal occlusions. As the same authors point out, in a patient with codominant M2 branches who presents with occlusion of one M2 division, the TICI grade would be 2b from the outset if the entire MCA territory were considered and would indicate a successful treatment whether or not the occlusion is recanalized. This interpretation of TICI grading is clearly suboptimal. For this reason, the consensus statement recommendations specify the target downstream territory as the ischemic territory distal to the arterial occlusion. Therefore, in the above example, the territory supplied by the occluded M2 artery should be the denominator when calculating the percentage of tissue reperfusion (Figure 5).

With the inclusion of TICI 2c scores into eTICI grading, it is important to distinguish distal perfusion defects due to downstream emboli (true TICI 2c score) from unopacified watershed regions in which the pial collateral vessels have not returned to their baseline (premorbid) position (TICI 3 score, or complete reperfusion). Typically, true distal occlusions manifest as fixed vessel cutoffs whereas a watershed region will display a dynamic to-and-fro appearance of the contrast column secondary to competing antegrade and retrograde flow. If there is diagnostic uncertainty, repeat angiography.

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Figure 1 Example of Expanded Treatment in Cerebral Ischemia 2a Reperfusion

(A) Baseline lateral projection angiography of a right middle cerebral artery M1 occlusion. Dashed black oval circumscribes the target downstream territory (TDT). (B) Posttreatment lateral projection angiography. White lines indicate reperfusion in the nondominant inferior division, accounting for <50% of the TDT.

Figure 2 Example of Expanded Treatment in Cerebral Ischemia 2b50 Reperfusion

(A) Baseline lateral projection angiography of a right middle cerebral artery M1 occlusion. Dashed black oval circumscribes the target downstream territory (TDT). (B) Posttreatment lateral projection angiography. White lines indicate reperfusion in the temporal, parietal, and posterior frontal regions, accounting for between 50% and 66% of the TDT.
angiography after several minutes will reveal whether there is shifting of the watershed back to its normal position.

**Optimal Extent of Reperfusion**

The optimal reperfusion target has evolved over the past several years, reflecting improvements in thrombectomy devices and techniques. Initial IAT trials using primarily the Merci device counted final TICI 2a/3 (any partial to complete reperfusion) as the primary angiographic efficacy endpoint. Despite relatively high rates of TICI 2a/3 (70%–75%), these trials failed to demonstrate the efficacy of IAT. Subsequent studies explained this discrepancy by showing that procedure-end mTICI 2b/3 (substantial reperfusion) provided better prediction of good clinical outcome. The recent pivotal trials utilizing stent retrievers confirmed the concordance between substantial reperfusion and clinical efficacy. Based on accumulating data of TICI scores inclusive of 2c, there is already strong evidence in support of using final TICI 2c/3 (excellent reperfusion) as a new definition of procedure-end success. In a retrospective, single-center cohort of 129 patients with M1 or intracranial internal carotid artery (ICA) occlusions, there were significantly higher rates of early neurologic improvement and better 90-day modified Rankin Scale (mRS) scores among patients achieving TICI 2c compared to 2b. There were minimal differences in clinical outcomes between 2c and 3. These findings were confirmed in an ancillary analysis of the ASTER (Contact Aspiration vs Stent Retriever for Successful Revascularization) trial. Among 290 participants meeting study entry criteria, the center-adjusted odds of achieving 90-day mRS 0–2 were nearly identical between TICI 2c (odds ratio [OR], 1.71 [0.98–3.00]) and TICI 3 (OR, 1.73 [0.88–3.41]) relative to 2b. Subjects with combined TICI 2c/3 reperfusion had significantly higher odds of 90-day functional independence and early neurologic improvement (24-hour National Institutes of Health Stroke Scale score 0–1 or improvement of ≥8 points) and lower 90-day mortality compared to TICI 2b patients.

The prevalence of TICI 2c/3 scores in real-world practice is uncertain owing to only recent reporting of 2c scores.

**Figure 3** Example of Expanded Treatment in Cerebral Ischemia 2b67 Reperfusion

(A) Baseline lateral projection angiography of a left middle cerebral artery M1 occlusion. Dashed black oval circumscribes the target downstream territory (TDT). (B) Posttreatment lateral projection angiography. White lines indicate reperfusion in the temporal, parietal, and the majority of the frontal regions, accounting for between 67% and 89% of the TDT.

**Figure 4** Example of Expanded Treatment in Cerebral Ischemia 2b67 Reperfusion

(A) Baseline lateral projection angiography of a left middle cerebral artery M1 occlusion. Dashed black oval circumscribes the target downstream territory (TDT). (B) Posttreatment lateral projection angiography. White lines indicate near-complete reperfusion in the MCA territory, accounting for between 90% and 99% of the TDT.
However, it is likely increasing in parallel with the rise in TICI 2b rates. Core laboratory–adjudicated TICI 2c/3 rates at procedure end were 56.1% in COMPASS (Comparison of Direct Aspiration vs Stent Retriever as a First Approach trial; combined arms), 59.8% in ASTER (combined arms), and 75.8% in ARISE II (Analysis of Revascularization in Ischemic Stroke with EmboTrap II study) (Table 2). Few studies have evaluated the TICI 2b/67 threshold. A recent angiographic analysis of 729 evaluable participants in the HERMES collaboration found that about 30% achieved TICI 2b/67 (67%–89% reperfusion), which comprised 45% of the mTICI 2b (50%–89%) population. Outcomes between TICI 2b/67 and 2c were almost identical with a common OR of favorable mRS shift of 1.02 (0.70–1.46; p = 0.934) for 2c.

![Figure 5 Target Downstream Territory for M2 Occlusion](image)

(A) Baseline anteroposterior projection angiography of a left middle cerebral artery inferior division dominant M2 occlusion (arrow). (B) Baseline lateral projection angiography of the M2 occlusion. The solid white oval delineates the target downstream territory (TDT) of the M2 occlusion, which should be used as the denominator in calculating the percent reperfusion. The dashed black line outlines the remainder of the M1 territory that should not be included in the TDT.

### Table 2 Angiographic Results Including TICI 2c and First-Pass Effect in Recent Studies

<table>
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<tr>
<th>Study</th>
<th>Device</th>
<th>Multicenter</th>
<th>Core laboratory or blinded adjudication</th>
<th>Final TICI 2b/50/3</th>
<th>Final TICI 2c/3</th>
<th>Final TICI 3</th>
<th>First pass TICI 2c/3</th>
<th>First pass TICI 3</th>
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<td>NASA* (n = 354)</td>
<td>Solitaire</td>
<td>Yes</td>
<td>No</td>
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<td>NR</td>
<td>40.2</td>
<td>NR</td>
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<td>ARISE II (n = 227)</td>
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<td>Yes</td>
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<td>75.8</td>
<td>52.0</td>
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<td>Solitaire (with or without aspiration)</td>
<td>Yes</td>
<td>Yes</td>
<td>89.8</td>
<td>NR</td>
<td>13.1</td>
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<td>NR</td>
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<td>ASTERc (n = 336; combined arms)</td>
<td>Multiple (SR or aspiration)</td>
<td>Yes</td>
<td>Yes</td>
<td>86.3</td>
<td>59.8</td>
<td>41.4</td>
<td>28.9</td>
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<td>COMPASS (n = 269; combined arms)</td>
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<td>Yes</td>
<td>90.3</td>
<td>56.1</td>
<td>33.1</td>
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<td>Kang et al. (n = 429)*24</td>
<td>ADAPT using various catheters</td>
<td>Yes</td>
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<td>30.0</td>
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<td>15.4</td>
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<td>No</td>
<td>92.0</td>
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<td>NR</td>
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<td>Jindal et al.26 (n = 205)</td>
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<td>No</td>
<td>Yes</td>
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<td>22.0</td>
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<td>Garcia-Tornel et al.27 (n = 542)</td>
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<td>84.5</td>
<td>42.3</td>
<td>NR</td>
<td>24.9</td>
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**Abbreviations:** ADAPT = A Direct Aspiration First-Pass Technique; ARISE II = Analysis of Revascularization in Ischemic Stroke with EmboTrap II study; ASTER = Contact Aspiration vs Stent Retriever for Successful Revascularization trial; COMPASS = Comparison of Direct Aspiration vs Stent Retriever as a First Approach trial; NASA = North American Solitaire Acute Stroke registry; NR = not reported; SR = stent retriever; STRATIS = Systemic Evaluation of Patients Treated with Neurothrombectomy Devices for Acute Ischemic Stroke registry; TICI = Treatment in Cerebral Ischemia score.

Values are percentages.

* Data from primary NASA article24 and NASA first-pass effect analysis.21 TICI 2c results were not uniformly reported by the participating centers. Available 2c scores were assigned TICI 3.

* Subgroup analysis excluded posterior circulation strokes, tandem occlusions, intracranial atherosclerotic lesions, and primary approach using distal catheter with balloon guide catheter.

* Data from ASTER TICI 2c/3 analysis16 and ASTER first-pass effect analysis.22 TICI 2c scores were included into the TICI 3 category.
relative to 2b. If additional studies confirm this result, then TICI 2b may also be counted as technical success.

**Reliability of Reperfusion Grading**

The addition of the TICI 2c category into reperfusion scoring improves interrater reliability. In one study, categorizing results using a combined 2c/3 category yielded the highest agreement among various TICI grading schemes (kappa 0.755 vs 0.618 for mTICI).15 The probable explanation is that the 2c classification resolves the dilemma of grading near-complete reperfusion with the mTICI scale, where some neurointerventionists may upgrade the result to a TICI 3 score, while a more rigorous approach would assign mTICI 2b. This was a salient issue in an angiographic analysis of the MR CLEAN Registry. In 252 (33%) of 763 patients, the core laboratory scored partial reperfusion, whereas the local interventionists scored TICI 3.17 Overall, there was no difference in prediction of 90-day mRS between core laboratory and local reads, underscoring the similar outcomes between TICI 2c and 3.

**Speed of Reperfusion: First Pass Effect and Procedure Time**

In-hospital delays to reperfusion are associated with worse outcomes after IAT.18 Reducing the time from imaging selection to reperfusion in particular appears important for improving outcomes.19 Workflow optimization of the stroke, emergency, and neurointerventional teams is critical to minimize the delay from imaging to vessel puncture. Equally important are efforts to improve the technical speed of thrombus retrieval. There are 2 closely related yet complementary metrics for measuring intraprocedural delay: the number of thrombectomy attempts and the time from vessel puncture to reperfusion.

**Number of Thrombectomy Attempts and the First Pass Effect**

The number of thrombectomy attempts is a surrogate for procedure duration that provides practical advantages for evaluating technical efficacy. Foremost, it is easy to account for. Second, it is a direct measure of device effectiveness because it disregards the time required for guide catheterization and microcatheter access to the target vessel, which is variable and can be time consuming.20 Third, it may provide a potential marker of treatment harm, as risk necessarily accrues with each thrombectomy pass. Treatment risks include vessel injury, such as perforation, dissection, or severe vasospasm, and thrombus fragmentation in the form of distal embolization or non-target embolization.

The first pass effect (FPE) was initially described by the NASA (North American Solitaire Acute Stroke) Registry investigators and defined as complete reperfusion achieved with the first thrombectomy pass.21 Patients with FPE had significantly better functional outcome (90-day mRS ≤2 in 61.3% vs 35.3%), lower mortality at 90 days (16.3% vs 36.5%), and fewer procedural adverse effects compared to non-FPE patients. Similar results according to first pass TICI 2c/3 were reported by the ASTER investigators, who demonstrated significantly lower rates of any hemorrhagic transformation and parenchymal hematoma type 2.22 These findings persist when restricting the comparison to only those patients who achieved final complete or near-complete reperfusion, confirming the deleterious effect directly associated with additional thrombectomy maneuvers.21,23

Studies of primary contact aspiration thrombectomy have shown similar benefits of first attempt complete or near-complete reperfusion.22,25 To avoid ambiguity concerning what constitutes an aspiration pass, any withdrawal of the aspiration catheter, even partial, should be counted as a pass.22

Table 2 summarizes the FPE results in recent studies. FPE has been variably reported as first pass TICI 2c/3 or first pass TICI 3.21-25 The similar outcomes between procedure end TICI 2c and TICI 3 support the more inclusive formulation (first pass TICI 2c/3). First pass mTICI 2b/3, termed modified FPE, has also been reported as an outcome measure.21 The primary drawback of this endpoint is that mTICI 2b/3 represents a broad range of reperfusion (50%–100%) including results that are no longer optimal in the current era. Although decision-making should be tailored to the individual circumstances of each case, eTICI 2b/3 (50%–66%) is probably insufficient to declare success in most cases, and the risk–benefit ratio likely favors pursuing additional attempts. In this regard, first pass eTICI 2b/50 may be considered an unwelcome marker of thrombus fragmentation.

**Beyond the First Pass: When to Stop**

Given the exceedingly high rate of good outcomes associated with first pass excellent reperfusion (TICI 2c/3), FPE has become a leading marker of treatment success. Nevertheless, good outcomes are frequently observed when reperfusion is achieved even after the first pass. Numerous studies have shown that when full reperfusion is attained, the adverse effect of reperfusion delay is less pronounced.26,27 Among patients with final TICI 2c or 3 reperfusion, Jindal et al.26 reported functional independence rates of 64%, 65%, and 50% between passes 1, 2, and 3, respectively (p = 0.43). Likewise, other studies have shown that good outcome rates between first- and second-pass revascularization are equivalent.27,28 Mortality also appears to be similar within the first 2 passes. Future investigations should explore whether FPE should be replaced by 2-pass excellent reperfusion as the marker of top-level efficacy.

Although FPE is the technical goal of IAT, it occurs in fewer than half of cases (Table 2). With additional passes particularly beyond the second pass, the likelihood of revascularization decreases, outcomes following reperfusion become progressively worse, and treatment risks increase.26-31 As such, 2 related questions that neurointerventionists often struggle with is how many thrombectomy maneuvers to perform (1) before switching to another thrombectomy
modality and (2) before stopping. Concerning the first question, a study of 384 patients who underwent successful revascularization using stent retrievers found an exponential decrease in the mTICI 2b/3 rate with each subsequent pass, with rates below 10% after the third pass, supporting a strategy of switching after 3 passes.31 Regarding when to stop, a recent study of stent retriever thrombectomy found a very low rate of good outcomes beyond 3 passes (7.4% rate of 90-day mRS 0–2 for passes 4 through 8).30 On the contrary, 2 studies (involving 100% and 95% stent retriever usage) showed that patients who achieved substantial reperfusion on the fourth pass had a significantly higher rate of good outcomes compared to nonreperfusers.27,31 In both studies, there was a signal of benefit for reperfusion achieved on the fifth pass, particularly when there is near-complete/complete reperfusion or when the patient has minimal ischemic damage on baseline imaging.

There is conflicting evidence regarding the safety of pursuing additional thrombectomy attempts. In a secondary analysis of reperfused patients in the ASTER trial, patients treated primarily with stent retrievers had a significantly higher rate of parenchymal hematoma in multivariable analysis when receiving more than 3 thrombectomy passes.29 There was no such relationship in the primary contact aspiration group (interaction = 0.042). Conversely, a single-center study found no association of stent retriever passes with hemorrhagic transformation, either in total or divided into symptomatic vs asymptomatic.32

Further work is needed to characterize the evolving risk–benefit ratio associated with each additional thrombectomy attempt. To this end, revascularization results should be reported for every thrombectomy maneuver performed in a stroke interventional case including the devices and techniques used. Future studies should employ large datasets to examine the number of passes that should be performed prior to aborting the procedure, the clinical and imaging factors that modify this number, and when strategies should be changed.

Per-pass data collection is resource intensive and might be best reserved for research databases and clinical trials. This level of detail may not be suitable for real-world registries and quality metrics. Instead, key data elements should include time from puncture to first pass, first-pass eTICI result, final eTICI result, and pass number/elapsed time for reaching eTICI 2b/3. Moreover, until data suggest otherwise, eTICI reporting may be simplified to combine eTICI 2b50 and 2b67 into a single eTICI 2b score. eTICI 2c is an important reperfusion category and should be scored in quality improvement databases.

**Procedural Time to Reperfusion**

All delays from stroke onset to reperfusion negatively affect clinical outcome.18 However, among patients who undergo IAT, studies have shown that the duration from brain imaging to reperfusion has a greater clinical effect than onset-to-imaging time.19 This counterintuitive finding is a consequence of patient selection. The deleterious effect of preimaging delays is underestimated because patients who have extensive ischemic injury from such delays are selected away from treatment and therefore not considered when examining IAT outcomes. As recent studies have shown, imaging “resets the clock” for patients who present late but have good collaterals.33,34 As such, imaging-to-reperfusion time is a key workflow metric for IAT patients. Procedure time (PT), or the duration from initial arterial access (femoral or radial puncture) to intracranial revascularization, represents a substantial and highly variable portion of this delay.

Several studies have demonstrated that shorter PT is associated with better outcomes and is an independent predictor of 90-day functional independence.35,36 The correlate of FPE in terms of PT appears to be reperfusion within 30 minutes of puncture. In a multicenter study of 1,359 patients, there was a substantial decline in good outcome rates after 30 minutes of procedure time.35 For PT <30 minutes, 30–60 minutes, and >60 minutes, rates of 90-day mRS 0–2 were 45%, 33%, and 27% (p < 0.01); 90-day mortality was 17%, 22%, and 39% (p < 0.01); and symptomatic intracranial hemorrhage or PH2 rate was 2.3%, 6%, and 6% (p < 0.01), respectively. The authors also reported an exponential rise in procedural complications with longer PT, with a doubling time of 50 minutes. An important confounder was that TICI 2c/3 rates were higher with faster revascularization: 61%, 37%, and 18% for PT <30 minutes, 30–60 minutes, and >60 minutes (p < 0.01). Similar findings were seen in a pooled analysis of the SWIFT (Solitaire With the Intention For Thrombectomy), STAR (Solitaire Flow Restoration Thrombectomy for Acute Revascularization), and SWIFT PRIME (Solitaire With the Intention For Thrombectomy as Primary Endovascular Treatment) studies.36 Among 301 patients who achieved substantial reperfusion (final mTICI 2b/3), patients with longer procedure times (≥60 minutes) had worse outcomes but also lower TICI 3 rates (48% vs 74% in PT <60 minutes). Neither study evaluated the effect of PT only in patients with final TICI 2c/3 or TICI 3 reperfusion.

There are important differences between the number of thrombectomy attempts and procedure duration that can potentially affect outcomes. On the one hand, PT is a more physiologically relevant measure because it also incorporates the delay related to vessel tortuosity and difficult guide catheter placement in the neck. In one study, 25% of patients had 30-minute or longer delays to guide catheterization, and such patients had significantly worse outcomes (90-day mRS 0–2 13.6% vs 41.3%; p = 0.04).20 Nevertheless, many of the potential treatment risks are related to the actual thrombectomy pass, regardless of how long it takes to get to the thrombus. In the study by Alawieh et al.,35 among patients with PT <30 minutes or 30–60 minutes, fewer attempts were an independent predictor of good outcome, not shorter procedure time.

With better devices and greater technical experience, times to reperfusion have decreased substantially over the past several years (Figure 6). To further improve these times, it will be
bene
tifical to document and report the time required for individual procedural steps: vessel access to guide catheter in the neck, guide catheterization to first pass, and between-pass delays. This will help to identify process points that might be further optimized. Research efforts should characterize predictors of intraprocedural delay that might alter the initial treatment approach such as tortuous vascular anatomy and signs of refractory thrombus. Finally, future studies should further examine whether the number of thrombectomy passes provides additional prognostic information beyond its role as a proxy for procedure time.

Angiographic Measures of Harm: Distal Embolization and Emboli in New Territory

Thrombus fragmentation can produce 2 types of procedural complication: distal embolization to the downstream territory and emboli in a new, previously uninvolved territory (ENT) (Figure 7A).

Figure 7 Thrombus Fragmentation Resulting in Distal Embolization and Emboli to New Territory

Images from a patient presenting with tandem occlusion of the left cervical internal carotid artery and middle cerebral artery (MCA) M1 segment. (A) Lateral projection angiography after cervical angioplasty and stenting with embolic protection shows distal embolization involving multiple MCA branches (white arrows) and an embolus to new territory (ENT) involving the anterior cerebral artery distal A2 segment (black arrow). (B) Posttreatment lateral projection angiography demonstrates recanalization of the ENT. There has been some proximal recanalization of the MCA occlusions with residual distal embolus (white arrows).
Distal Embolization

Rates of distal embolization are infrequently reported in the thrombectomy literature. In 2 studies, it was seen in about 10% and 34% of cases.37,38 Quantifying distal embolization is challenging owing to the uncertainty of whether a distal occlusion visualized after a thrombectomy pass was present at baseline. MRI data suggest that this phenomenon is rare. In a large single-center study, 347 patients with occlusions of the anterior or posterior circulation were imaged with whole brain susceptibility-weighted MRI.39 The authors reported that only 24 (7.4%) patients had multiple thrombi, with all fragments seen distal to the primary occluding thrombus. Accordingly, it is reasonable to count all downstream occlusions after a thrombectomy maneuver as treatment-related distal emboli.

If distal emboli are numerous and peripherally located, the likelihood of achieving final TICI 2c/3 reperfusion is diminished (Figure 7B). So long as these emboli are not successfully recanalized during the procedure, the final TICI score will account for the effect of distal embolization. However, the availability of smaller, less traumatic stent retrievers and aspiration catheters has resulted in a growing confidence and ability to treat occlusions involving distal second- and third-order branches.40 Consequently, the incidence as well as the effect of distal embolization may be underestimated by the final reperfusion score. Treatment of distal emboli, regardless of whether they are recanalized, takes time and carries risk. Therefore, it remains important to document the per-pass occurrence of distal embolization and report the cumulative per-pass rate.

Emboli to New Territory

ENT rates range from 1% to 7% in recent core laboratory–adjudicated thrombectomy studies.5,14,33,41 Contrary to distal embolization, ENT may potentially worsen the natural history of the initial stroke. For instance, a thrombectomy pass for an MCA M1 occlusion that does not open the target vessel but results in ENT into the anterior cerebral artery (ACA) branches not only places a new territory at risk (the ACA) but also impairs ACA-to-MCA pial collaterals that sustain the target downstream territory. As a result, infarct growth is accelerated, and the final MCA infarct may be larger than if ENT did not occur. In a subset analysis of intracranial ICA and M1 occlusions that underwent thrombectomy in the IMS-III trial, ENT were identified in 26 (14.8%) of 175 evaluable patients, and 90-day mRS 0–2 outcomes were numerically lower in the patients with ENT (19.2%) vs without (32.2%).43

Determination of ENT depends on the site of target vessel occlusion, the circle of Willis anatomy, and the presence of coexistent occlusions. This determination is straightforward for MCA lesions, where any treatment-related ACA embolus represents ENT. However, the target downstream territory (area at risk for infarction) is variable for ICA occlusions depending on the presence of the contralateral A1 segment and the anterior communicating artery. If both are intact, the ipsilateral ACA territory should not be included in the target downstream territory of an ICA occlusion because there is antegrade supply from the contralateral ICA, provided there is no coexistent occlusion in the ipsilateral A2 segment or beyond. In this scenario, a treatment-related ACA embolus would be counted as ENT.

Conversely, if the anterior communicating artery is absent, both the ipsilateral ACA and MCA territories are included in the target downstream territory, and a treatment-related ACA embolus would be categorized as distal embolization. If the contralateral A1 segment is absent, both ACA territories and the ipsilateral MCA territory are involved. The status of the circle of Willis can be readily determined on pretreatment CT angiogram. Nevertheless, it is typically correct to assume that the ipsilateral ACA territory is spared from the target downstream territory during an ICA occlusion if there is not a large infarct on baseline imaging because patients with absent flow into the ACA will almost invariably present with extensive infarcts owing to the absence of pial collaterals.

The angiographic definition of ENT should be distinguished from the recently proposed classification of infarct in new territory (INT), which utilizes noninvasive imaging criteria.44 The INT classification is intended to evaluate whether an infarct is likely to be clinically significant based on size and also whether it is likely to be related to thrombectomy vs secondary to an embolic source. On the other hand, ENT is an angiographically documented complication of IAT, and the criteria are meant to distinguish ENT from distal embolization because of their differential effect on the collateral circulation and thus the natural history of the target occlusion.

Unmet Needs

Collateral Grading

During proximal artery occlusion, the collateral circulation supports tissue viability in the ischemic bed until the vessel can be recanalized. In a secondary analysis of the MR CLEAN trial, the benefit of thrombectomy was modified by the robustness of the baseline collaterals.45 Treatment benefit was diminished and potentially absent in patients with poor or nonexistent collaterals on pretreatment CT angiography.

Catheter angiography enables the evaluation of both the extent and speed of the pial collaterals. As with reperfusion grading, biplane angiography carried through the venous phase is necessary to fully assess the quality of the collateral circulation. The collateral score that has been most widely adopted and endorsed by stroke and neurointerventional societies is the American Society of Interventional and Therapeutic Neuroradiology (ASITN)/Society of Interventional Radiology (SIR) collateral grading system1,46–48 (Table 3). Based on this score, stronger collaterals have been associated with improved revascularization and better tissue and clinical outcomes following IAT.46–48 In an analysis of 160 patients with proximal MCA occlusion in the ENDO-STROKE (International Multicenter Registry for Mechanical
Recanalization Procedures in Acute Stroke registry, core laboratory–determined ASITN/SIR grades of 0–1, 2, and 3–4 were significantly associated with TICI 2b/2c reperfusion rates of 21%, 48%, and 77% and with good clinical outcomes (mRS 0–2) in 11%, 35%, and 49%, respectively.46

The strength of the pial collaterals is regionally variable (Figures 8 and 8). Collateralization may be strong in all or part of one MCA division but absent in the other. A major limitation of the ASITN/SIR classification is that the extent of the pial collaterals is coarsely graded as partial vs complete. Partial or grade 2 collaterals constitute the largest ASITN category in most studies, representing about 40% of cases.46-48

The conspicuous problem is that “partial” encompasses an overly broad range of tissue volume, from 1% to 99% of the ischemic territory. Further dividing partial collaterals into <50% vs 50%–99% of the target downstream territory would likely enhance prognostication. Moreover, the speed of collateralization matters little if the collaterals supply only a small fraction of the ischemic territory. The rapidity of collateral flow might be better reserved for stratifying cases with complete collaterals. A proposed expanded ASITN (eASITN) classification is provided in Table 4. Figures 8–11 illustrate examples of eASITN grades 2 to 4.

Intracranial ICA occlusions pose another challenge for collateral grading because the collateral vessels are not visualized when the target vessel is injected. Performing diagnostic angiography in the contralateral ICA is undesirable because it delays treatment. However, the collaterals may become evaluable if partial recanalization results in an M1 occlusion on intermediate runs. The collateral score should then be evaluated at this stage. Absent this scenario, it is reasonable to impute collateral information from noninvasive imaging such as CT angiography, although the correlation between these modalities is uncertain.1

Reasons for Failed Revascularization
Most studies examine only cases where a thrombectomy was performed, neglecting to report the instances of failed target vessel access. This underreporting represents a missed opportunity for understanding the limitations of IAT. To address this need, 2 large, single-center studies recently characterized the reasons for failed reperfusion (eTICI 0–1) using intention-to-treat cohorts.49,50 In one study, 72 (11%) of 648 patients had no reperfusion.49 The thrombus could not be reached in 15 (21%) cases owing to vessel tortuosity, stenosis, or failed femoral access. The thrombus could be reached but not passed in another 15 (21%) patients due to

<table>
<thead>
<tr>
<th>Table 3 ASITN/SIR Collateral Scoring</th>
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<tr>
<td>ASITN/SIR grade</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
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<td>3</td>
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<td>4</td>
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Abbreviations: ASITN = American Society of Interventional and Therapeutic Neuroradiology; SIR = Society of Interventional Radiology.

Figure 8 Example of Proposed Expanded American Society of Interventional and Therapeutic Neuroradiology Grade 2– Collaterals

(A) Baseline lateral projection angiography of a right middle cerebral artery M1 occlusion (early arterial phase). (B) Baseline lateral projection angiography (parenchymal phase). Dashed white oval outlines retrograde collaterals in a portion of the inferior division, accounting for <50% of the ischemic territory.
hard clot or underlying atherosclerotic lesion. In 42 (58%) cases, the thrombus was crossed but there was failure of one or more thrombectomy attempts. In the second study, 63 (10.6%) of 592 patients had a final eTICI 0–1 score. In 56 (89%) cases, the failure was a result of technical difficulties. The thrombus could not be reached due to vessel tortuosity or stenosis in 20 (32%) patients. In the remaining 36 (57%) cases, the thrombus could not be crossed or opened by thrombectomy devices. Additional studies based on intent-to-treat populations are needed to further identify potential opportunities for improving thrombectomy procedures.

Global TICI Scale
As previously mentioned, reperfusion must be graded based on the territory downstream to the target occlusion in order to properly capture the effect of the intervention. However, 80% reperfusion of an M3 occlusion represents far less tissue salvage and accordingly less clinical benefit than 80% reperfusion of an M1 occlusion. This clinical limitation of TICI scoring argues for a secondary global TICI scale that is independent of occlusion level. Global TICI would better capture the clinical significance of residual nonreperfused regions and would help inform the decision whether to pursue additional thrombectomy maneuvers or terminate the procedure. If global TICI scoring is based on the combined ACA and MCA territories, it would also incorporate the effects of ENT. Future studies should investigate the utility and reliability of such a scoring system.

Posterior Circulation/Basilar Strokes
Revascularization of vertebrobasilar occlusions is typically graded using TICI scoring. However, it is unclear whether this is appropriate. Unlike the anterior circulation, where eloquence is more evenly distributed, the critical functions of the posterior circulation are concentrated in the brainstem and thalami, which are supplied solely by perforators. These tiny vessels are difficult to quantify, and therefore successful revascularization must incorporate recanalization as well as reperfusion. TICI scoring, on the other hand, measures only reperfusion. Moreover, the lack of operational

### Table 4 eASITN Collateral Scoring

<table>
<thead>
<tr>
<th>eASITN grade</th>
<th>Description</th>
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<tr>
<td>0</td>
<td>No collateral vessels visible to the ischemic site</td>
</tr>
<tr>
<td>1</td>
<td>Single collateral vessel to the ischemic site with persistence of almost all the defect</td>
</tr>
<tr>
<td>2-</td>
<td>Collateral vessels to the ischemic site that result in retrograde capillary opacification or parenchymal blush in &lt;50% of the ischemic territory</td>
</tr>
<tr>
<td>2+</td>
<td>Collateral vessels to the ischemic site that result in retrograde capillary opacification or parenchymal blush in 50%–99% of the ischemic territory</td>
</tr>
<tr>
<td>3</td>
<td>Collateral vessels with complete retrograde angiographic blood flow to the ischemic bed by the late venous phase</td>
</tr>
<tr>
<td>4</td>
<td>Complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory during the arterial or early parenchymal phase</td>
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</table>

Abbreviation: eASITN = expanded American Society of Interventional and Therapeutic Neuroradiology.
criteria for grading TICI in the posterior circulation limits its reliability. A recent study reported less than substantial agreement among 3 experienced neurointerventionists using the mTICI scale. Further work is necessary to develop an effective revascularization grading system that is tailored to vertebrobasilar occlusions. Table 5 presents an overview of future recommendations and recommendations.

Figure 10  Example of Proposed Expanded American Society of Interventional and Therapeutic Neuroradiology Grade 3 Collaterals

(A) Baseline lateral projection angiography of a left middle cerebral artery M1 occlusion (early arterial phase). (B) Baseline lateral projection angiography (late parenchymal/early venous phase). There is slow collateral filling of the ischemic territory. (C) Baseline lateral projection angiography (venous phase). There is slow but complete collateralization of the ischemic territory.

Figure 11  Example of Proposed Expanded American Society of Interventional and Therapeutic Neuroradiology Grade 4 Collaterals

(A) Baseline lateral projection angiography of a left middle cerebral artery M1 occlusion (early arterial phase). (B) Baseline lateral projection angiography (late arterial phase). There is rapid collateral filling of the ischemic territory. (C) Baseline lateral projection angiography (parenchymal phase) and (D) (venous phase). There is complete collateralization of the ischemic territory.
1. eTICI should be used as the standard scale for grading endovascular reperfusion.

2. Future studies should evaluate clinical and safety outcomes after TICI 2b/7 reperfusion to determine whether this threshold should be counted as treatment success.

3. New angiographic benchmarks should combine the optimal extent and speed of reperfusion.

4. Revascularization results should be reported for every thrombectomy maneuver performed in a stroke interventional case including the devices and techniques used.

5. Future studies should employ large datasets to examine the number of passes that should be performed prior to aborting the procedure, the clinical and imaging factors that modify this number, and when strategies should be changed.

6. Standard timepoints during IAT should be recorded: vessel access, guide catheter placement, stent retriever deployment or contact aspiration start, stent retriever removal or contact aspiration end, and time to eTICI 2c/3.

7. Data suggest that the number of passes may affect prognosis independent of time delay (e.g., situations where tortuosity prevents easy catheter access, but there is rapid recanalization of the thrombus once access is obtained). Whether there is incremental prognostic information provided by pass number adjusting for procedure time should be determined.

8. Distal embolization and ENT after each thrombectomy pass should be assessed and the overall per-pass rate reported. This will aid in identifying determinants of thrombus fragmentation.

Abbreviations: eTICI = expanded Treatment in Cerebral Ischemia scale; ENT = emboli to new territory; IAT = intraarterial stroke therapy.

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<tr>
<th>Name</th>
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<tbody>
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</tr>
<tr>
<td>Albert J. Yoo, MD, PhD</td>
<td>Texas Stroke Institute, Dallas-Fort Worth</td>
<td>Drafted the manuscript for intellectual content</td>
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References


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Norman Ajiboye and Albert J. Yoo
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